Monograph

20 August 2002

Tritosulfuron

Volume 1

Report and
Proposed Decision

Rapporteur Member State: Germany

Contents

Level 1

Tritosulfuron

Statement of Subject Matter and
Purpose of Monograph

1 Statement of subject matter and purpose for which the monograph was prepared

1.1 Purpose for which the monograph was prepared (Dossier Document A)

1.2 Summary and assessment of information relating to collective provision of dossiers (Dossier Document B)

As BASF is the only notifier, this point is not relevant.

1.3 Identity of the active substance (Annex IIA 1) (Dossier Documents J, K-II and L-II)

1.3.1 Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)

Applicant:

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Agricultural Center
Product Registration Management
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1.3.2 Common name and synonyms (Annex IIA 1.3)

Tritosulfuron (ISO, accepted)

1.3.3 Chemical name (Annex IIA 1.4)

IUPAC: 1-(4-methoxy-6-trifluoromethyl-1,3,5-triazin-2-yl)-3-(2-trifluoromethylbenzenesulfonyl)urea

CAS: N-[[[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino]carbonyl]-2-(trifluoromethyl)benzenesulfonamide

1.3.4 Manufacturer's development code number (Annex IIA 1.5)

BAS 635 H, LAB 271272, Reg.-No. 271272, PS 271272

1.3.5 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

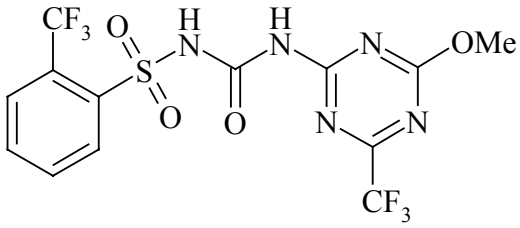
CAS: 142469-14-5
CIPAC: 735
EEC: not assigned
EINECS: not assigned

1.3.6 Molecular and structural formulae, molecular mass (Annex IIA 1.7)

Molecular formular: $C_{13}H_9F_6N_5O_4S$

Molecular mass: 445.3 g/mol

Structural formula:



1.3.7 Manufacturer or manufacturers of the active substance (Annex IIA 1.2)

Manufacturer:
BASF Aktiengesellschaft
Crop Protection Division
P.O. Box 120
D-67114 Limburgerhof

Person to contact: Dr. Wolfgang Türk
Production Crop Protection
Telephone: +49 (0) 621 60-79145
Telefax: +49 (0) 621 60-79519

Manufacturing site:
Pilot plant at BASF AG, Ludwigshafen

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C.

1.3.9 Specification of purity of the active substance (Annex IIA 1. 9)

950 g/kg (minimum purity)
0.2 g/kg AMTT (maximum content)

1.3.10 Identity of isomers, impurities and additives (Annex IIA 1.10)

Confidential information, see Annex C.

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C.

1.4 Identity of the plant protection product (Annex IIA 3.1; Annex IIIA 1) (Dossier Documents J, K-II, L-II, K-III, and L- III) (to be included for each preparation for which an Annex III dossier was submitted)

1.4.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name:	BAS 635 00 H, preliminary designator (country specific alternatives are under consideration)	
Code number:	Plant protection product:	BAS 635 00 H
	Adjuvant:	BAS 152 00 S (Citowett 2000, Citowett New)
	Active Substance:	BAS 635 H (Tritosulfuron)
	BASF internal No.:	Reg.-No. 271272

1.4.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

BASF Aktiengesellschaft
Crop Protection Division
P.O. Box 1 20
67114 Limburgerhof
Germany

Contact person: Dr. Karl Zoller
Production Crop Protection
Tel. No.: (0)6 21/ 60-7 91 46
Fax No.: (0)6 21/ 60-7 95 19

1.4.3 Type of the preparation and code (Annex IIIA 1.5)

Combi-pack solid (WG) / liquid (SL): KK

1.4.4 Function (Annex IIA 3.1; Annex IIIA 1.6)

Herbicide

1.4.5 Composition of the preparation (Annex IIIA 1.4)

Confidential information, see Annex C.

1.5 Use of the plant protection product (Annex IIA 3.2 to 3.4; Annex IIIA 3.1 to 3.7, 3.9, 12.1) (Dossier Documents C, D, and E) (to be included for each preparation for which an Annex III dossier was submitted)

1.5.1 Field of use (Annex IIA 3.3; Annex IIIA 3.1)

Tritosulfuron (BAS 635 H) is a new active substance developed by BASF Aktiengesellschaft. The chemical family is sulfonylurea. The formulated product BAS 635 00 H is a water dispersible granules (WG) containing 714 g/kg tritosulfuron. It is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in cereals (winter and spring wheat, winter and spring barley, winter rye, oats, triticale) and maize. It will be applied as well as a solo product as well as in combination with other herbicidal active substances. Up to now the following combination and solo products are under development:

BAS-code	Content of tritosulfuron g/kg	Formulation type	Other active substance g/kg
BAS 635 00 H*	714	WG	
BAS 641 01 H**	400	WG	cinidon-ethyl, 240
BAS 655 00 H**	250	WG	dicamba, 500
BAS 655 01 H**	125	WG	dicamba, 600

* representative formulation of EU Dossier
** further formulated product under development

1.5.2 Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Only weeds which have emerged at the time of application will be controlled. Optimum timing is when weeds are still small and have not begun to compete with the crop.
The herbicidal action is mainly over the leaves. Upon uptake by the leaves, tritosulfuron, is to a limited extent, systemically translocated in the plant (i.e. acropetally and basipetally). The application of the sulfonylurea tritosulfuron results in the blockage of the enzyme acetolactate-synthase (ALS) also referred to as acetohydroxy acid synthase. The inhibition of ALS activity leads to amino acid starvation and to the accumulation of toxic precursors. The primary effect of the herbicide is the restraint of new growth and cell development of susceptible weeds. The product is most effective if applied on young growing dicotyledonous

weeds. Tritosulfuron at the recommended application rates is well tolerated in all tested cereals and maize varieties.

1.5.3 Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3. 7, 3.9)

Tritosulfuron is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in cereals (winter and spring wheat, winter and spring barley, winter rye, oats, triticale) and maize. The product **must** be used as a mixture with an additive (e.g. Citowett New) at a rate of 70 g/ha BAS 635 00 H (containing 50 g as/ha tritosulfuron) and 1.25 l/ha Citowett New. The product is applied as single application at BBCH 21-39 in winter cereals (TRZAW, HORVW), at BBCH 13-39 in summer cereals (TRZAS, TRZDU, HORVS, AVESA, SECCE, TTLSS) and at BBCH 12-18 in maize. The recommended water volumes are 150 to 400 l/ha, resulting in a maximum concentration of the active substance of 0.33 g/l in the spray liquid.

For the list of uses supported by available data see 2.8.3.1, Appendix III.1

1.5.4 Information on authorisations in EU Member States (Annex IIIA 12.1)

Tritosulfuron is a new active substance developed by BASF Aktiengesellschaft, which is contained in herbicidal plant protection products. This dossier is the application of BASF Aktiengesellschaft for first inclusion of tritosulfuron in Annex I of EU Directive 91/414/EEC. Therefore no registrations or authorisations are existent in EU Member States or elsewhere.

Level 2

Tritosulfuron

Overall Conclusions

2 Reasoned statement of the overall conclusions

2.1 Identity

2.1.1 Identity

All points (Annex II and III) have been addressed and the information supplied is acceptable.

1.1.2 Physical and chemical properties

Tritosulfuron (pure and technical active substance) is a white solid. A melting point of approx. 168 °C was determined for PAS. Decomposition of the as was observed at 340 °C. The vapour pressure (< $1 \cdot 10^{-7}$ hPa) and volatility (< $1.012 \cdot 10^{-4}$ Pa m^3 mol^{-1}, 20 °C) of tritosulfuron are very low. Tritosulfuron is hydrolytical and photolytical stable under environmental conditions. The water solubility and the log $P_{o/w}$ depends on the pH value (approx. 1 to 78 g/l, 20 °C and approx. 2.9 to –2.4, respectively). The test substance is soluble in acetone (> 250 g/l), dichloromethane (25 g/l), ethyl acetate (83 g/l), methanol (23 g/l). Lowest solubility are observed in toluene (< 10 g/l). The substances is insoluble in *n*-heptane. The substance is not highly flammable or autoflammable, not explosive and without oxidising properties.

BAS 635 00 H is a brown, free flowing water dispersible granule with a faint aromatic odour. It has neither explosive nor oxidising properties and it is not highly flammable. Its pH-value of 5.25 ± 0.05 lies within the naturally occurring in the acidic range. The results of the accelerated storage test and the shelf life test confirm its stability at least for two years under practical and commercial conditions. Its technical properties indicate no particular problems when used as recommended.
For the purpose of better efficacy BAS 635 00 H is applied together with Citowett 2000 (BAS 152 00 S). The compatibility study according to ASTM method E 1518-93 shows that the tank mixture is applicable without any problems as recommended.

2.1.3 Details of uses and further information

2.1.3.1 Details of uses

Tritosulfuron is intended to be used in cereals (autumn and spring sown) and in maize. It is a post-emergence herbicide with systemic action. The product must be used as a mixture with an additive (e.g. Citowett New) at a rate of 70 g/ha BAS 635 00 H (containing 50 g as/ha tritosulfuron) and 1.25 l/ha Citowett New. The recommended spray (water) volume is from 150 to 400 l/ha. At the field rate of 50 g as/ha tritosulfuron the concentration is between 0.33 g/l to 0.13 g/l tritosulfuron in the spray liquid. The maximum number of applications is one. The timing is between BBCH 13-39 in cereals (spring-sown cereals from BBCH 13-39; autumn-sown cereals from BBCH 21-39) and between BBCH 12-18 in maize. Application is confined to the spring season.

2.1.3.2 Further information

Information on handling, storage, transport or fire, destruction or decontamination, and emergency measures for the active substance as manufactured and information on packaging, cleaning procedures, handling, storage, transport or fire, emergency measures, and procedures for destruction or decontamination for the plant protection product have been supplied and are acceptable.

2.1.4 Classification and labelling

The following is proposed in accordance with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC):

Tritosulfuron (AMTT content ≤ 0.02 %)

Hazard symbol:	Xi	
	N	dangerous for the environment
Indication of danger:	Irritating	
Risk phrase:	R43	May cause sensitisation by skin contact
	R50/53	very toxic for aquatic species/can cause long-term concerns in water ecosystems

Reasons for classification
For justification of R 43 see B.6.2.6 Skin sensitisation.
For justification of R50/53 see Vol. 1, point 2.6.2 and Vol. 3, point B.9.2 Effects on aquatic species

The following is proposed in accordance with Directive 78/631/EEC in combination with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC):

BAS 635 00 H

Hazard symbol:	N	dangerous for the environment
Indication of danger:	None	
Risk phrase:	None	
	R50/53	very toxic for aquatic species/can cause long-term concerns in water ecosystems

Reasons for classification
For justification see B.6.11: Acute toxicity including irritancy and skin sensitisation of preparations.

For justification of R50/53 see Vol. 1, 2.6.2 and Vol. 3, point B.9.2 Effects on aquatic species

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

Analytical methodology is available for the determination of active substance and impurities in the technical material as manufactured

Tritosulfuron in the active substance as manufactured is determined by a HPLC external standard method on a reversed phase column with UV detection.

Organic impurities in the active substance as manufactured are determined by a HPLC external standard method on a reversed phase column with UV detection.

Tritosulfuron and one impurity in the formulation are determined by HPLC external standard methods on reversed phase columns with UV detection

The methods are fully validated.

2.2.2 Analytical methods for formulation analysis

Analytical methodology is available for the determination of the active substance and one impurity in the formulation.

Tritosulfuron and one impurity in the formulation are determined by HPLC external standard methods on reversed phase columns with UV detection.

The methods are fully validated.

2.2.3 Analytical methods for residue analysis

For the assessment of the analytical methods for the determination of tritosulfuron residues the following criteria were used:

- The submitted methods enable the enforcement of the following relevant residue limits (at the time of evaluation):

plants and plant products	0.01	mg/kg	proposed MRL for cereal and maize grain and other food of plant origin
soil	1.0	µg/kg	phytotoxic concentration of tritosulfuron to rape seed
drinking water	0.1	µg/l	EU drinking water limit
surface water	25.5	µg/l	higher aquatic plant
air	225	µg/m³	based on a proposed $AOEL_{systemic}$ of 0.75 mg/kg bw/d

- Mean recovery rates at each fortification level in the range of 70 to 110 % with a relative standard deviation of ≤ 20 %
- No interfering blanks (< 30 % of the LOQ)
- Methods must employ the simplest approach, involve the minimum cost, and require commonly available equipment.
- The enforcement method for food must be suitable for the determination of all compounds included in the residue definition (see 2.4.1), using an additional confirmatory method if appropriate.
- The enforcement methods for environmental matrices must be able to analyse for all compounds of toxicological and/or ecotoxicological significance in soil, water and air (see 2.5.1), using an additional confirmatory method if appropriate.

According to these criteria adequate analytical methods are available for the determination of tritosulfuron in plant material, soil, drinking water and air (for a summary see Table 2.2-1).

Table 2.2-1: Methods for the determination of residues

	Matrix	Method	Limit of quantification		Reference
crops	wheat: grain, plant, straw maize: grain, plant, straw	HPLC-UV	0.01	mg/kg	Sasturain et al, 2001
	corn, grain	LC-MS/MS	0.001	mg/kg	Stewart, 2001
	wheat: grain, middlings		0.001	mg/kg	
	wheat: straw, forage, hay		0.01	mg/kg	
	metabolite AMTT				
	wheat corn	GC-MS	0.001	mg/kg	Jordan and Malinsky, 2001
animal matrices	milk, muscle, fat, kidney, liver egg	HPLC-UV	0.01	mg/kg	Grosshans, 1998
	metabolite AMTT				
	milk, muscle, fat, kidney, liver	GC-MS	0.001	mg/kg	Jordan and Malinsky, 2001

	Matrix	Method	Limit of quantification		Reference
soil	as + M01, 02, 03	LC-MS/MS	0.001	mg/kg	Richter, 2001a
	as + M01, 02, 03, AMTT	LC-MS/MS	0.001	mg/kg	Smith and Clouser-Rouche, 2001
	as	GC-ECD	0.001	mg/kg	Keller, 1998
	M01, 02, 03		0.01	mg/kg	
water	drinking/surface				Richter, 2001b
	as + M01, 03	LC-MS/MS	0.05	µg/l	
	M02 + AMTT	GC-MS	0.05	µg/l	
	drinking/leachate as + M01, 02, 03	GC-MS	0.05	µg/l	Ziegler, 1998
air		HPLC-UV	2.8	µg/m^3	Zangmeister, 1998

2.3 Impact on human and animal health

Preamble

In the course of toxicity testing for tritosulfuron different batches containing different impurities were used. In the long-term and the 2-generation studies which were conducted with batch no. N24 severe effects were observed, including mammary gland tumors and a high pup mortality in rats, respectively. Further studies with the same batch were conducted in order to obtain a NOAEL for these effects. Upon checking differences between the batches, it was shown that batch no. N24 contained an impurity – AMTT – in higher quantities than batches nos. N34, N42, N53 and N59 (see Table 2.3-1). Two long-term rat studies were conducted with these batches and a 2-generation study in rats was performed with batch no. N34. These new studies did not show the effects observed before, with regard to mammary gland tumors and pup mortality. Therefore, it might be considered that AMTT was responsible for these effects. In order to understand the mechanism that is behind the mode of action of AMTT, and keeping in mind that AMTT is also a metabolite in soil and water, a variety of additional studies with AMTT were conducted.

The toxicological evaluation is only supporting an Annex I inclusion of technical tritosulfuron specified with an AMTT content ≤ 0.02 % (as impurity). Anyhow, the derivation of an ADI and an ARfD for AMTT is considered necessary because of residues in soil, water and plants.

Table 2.3-1: Overview on the content of AMTT and purity of different batches of tritosulfuron

Batch No.	Purity	Study	Content AMTT
N12	95.6 %	Acute oral/dermal/inhalation toxicity (rat), dermal/eye irritation (rabbit), skin sensitisation (guinea pig), prenatal toxicity in Wistar Rats/gavage	0.24 %
N12	96.1 %	*Salmonella typhimurium*/*E. coli* reverse mutation assay	0.16 %
N14	96.4 %	28-day oral (rat+mouse), 90-day oral (rat+mouse), prenatal toxicity in Himalayan rabbits/gavage	0.05 %
N24	96.8 %	28-day dermal (rat), 90-day + 12-month oral (dog), Ames-Test, *in vitro* gene mutation test in CHO cells, *in vitro* chromosome aberration assay in V79 cells, *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, *in vivo* mouse micronucleus test, 24-month feeding (rat), supplementary 24-month feeding (rat), 18-month feeding (mouse), 2-gen. reproduction study (rat), supplementary 2-gen. reproduction study (rat), acute and subchronic oral neurotoxicity study (rat)	2.45 %
N24	95.9 %	28-day dermal, rat	2.45 %
N34	99.1 %	24-month feeding (rat), supplementary 24-month feeding (rat), 2-gen. reproduction study (rat)	0.024 %
N42	98.7 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat)	0.02 %
N53	99.8 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat)	0.012 %
N59	98.2 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat), developmental neurotoxicity study (rat)	0.006 %

Table 2.3-2: Overview on study type and batches of tritosulfuron

Study type	Batch No. / Purity
Absorption, distribution, excretion; oral/ intravenous, rat	Triazine-14C labelled tritosulfuron: 437-32: radiochemical/chemical purity > 99 % 537-01; radiochemical purity > 99 %, chemical purity > 98 %. Phenyl-14C labelled tritosulfuron: 436-23: radiochemical purity > 97 %, chemical purity > 96 % 538-01: radiochemical purity > 99 %, chemical purity > 98 %. Phenyl-13C labelled tritosulfuron: 481-05; chemical purity > 99 %. Non radiolabelled tritosulfuron: N14; chemical purity > 96 %
Metabolism	Triazine-14C labelled tritosulfuron: 437-32: radiochemical purity 99.2 % Phenyl-14C labelled tritosulfuron: 436-23: radiochemical purity 97.0 % Phenyl-13C labelled tritosulfuron: 481-05: radiochemical purity > 99 % 691-33-1 (unlabelled): 99.8 % (chemical)
Metabolism	Triazine-14C labelled tritosulfuron: 437-1406 (triazin-2,4-14C): radiochemical purity: > 99 %, chemical purity 97 %
Acute oral toxicity, rat	N12: 95.6 %
Acute dermal toxicity, rat	N12: 95.6 %
Acute inhalation toxicity, rat	N12: 95.6 %
Dermal irritation, rabbit	N12: 95.6 %
Eye irritation, rabbit	N12: 95.6 %
Skin sensitisation, guinea pig	N12: 95.6 %
28-day oral, rat	N14: 96.4 %
28-day oral, mouse	N14: 96.4 %
28-day dermal, rat	N24: 95.9 %
90-day, rat	N14: 96.4 %
90-day, mouse	N14: 96.4 %
90-day, dog	N24: 96.8 %
12-month, dog	N24: 96.8 %
Ames Test	N24: 96.8 %
Ames test	N12: 96.1 %
CHO	N24: 96.8 %
V79, Chinese hamster	N24: 96.8 %
UDS, Rat hepatocytes	N24: 96.8 %
Micronucleus test, mouse	N24: 96.8 %
12-month, rat	N42: 98.7 %; N53: 99.8 %; N59: 98.2 %
24-month, rat	N34: 99.1 %; N42: 98.7 %; N53: 99.8 %; N59: 98.2 %
24-month, rat	N24: 96.8 %
24-month, mice	N24: 96.8 %
2-generation, rat	N34: 99.1 %
2-generation, rat	N24: 96.8 %
2-generation, rat	N24: 96.8 %
Developmental toxicity, rat	N12: 95.6 %
Developmental toxicity, rabbit	N14: 96.4 %
Acute neurotoxicity, rat	N24: 96.8 %
Subchronic neurotoxicity, rat	N24: 96.8 %
Developmental neurotoxicity, rat	N59: 98.2 %

2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products

2.3.1.1 Metabolism / Toxicokinetics

Tritosulfuron was rapidly and almost completely absorbed after oral administration to male and female rats at dose levels of 50 and 500 mg/kg bw. The radioactivity was preferably excreted via the renal route (approx. 70 – 80 % within 48 hours). The bioavailability was in the range of 90-100 %. The initial plasma half-life was short at both dose levels (5 - 6 hours). At the low dose level a slower terminal phase (19 - 24 hours) followed. Highest tissue concentrations were found in the gastro-intestinal tract and the excretion organs. There was no indication of accumulation of radioactivity in fat or other tissues. The test substance was metabolised to the sulfonamide 635M02 of the trifluoromethyl-phenyl ring and its sulfonic acid 635M23. After hydroxylation at the 4-position of the phenyl ring this compound was further conjugated with glucuronic acid or sulfate. No significant amounts of AMTT were produced in the rat by transformation of tritosulfuron.

2.3.1.2 Dermal absorption

The *in vivo* dermal absorption of tritosulfuron in rats is approximately 3 % or less depending on the duration of exposure and concentration. The initial rate of absorption through rat epidermal membranes was at least 2.27 fold greater relative to human epidermal membranes. Therefore, it can be assumed that human dermal penetration is in the order of 1 %.

2.3.1.3 Acute toxicity studies, local irritation and skin sensitising properties

Tritosulfuron (batch no. N12) is characterised by a low acute oral, dermal and inhalation toxicity. The substance is neither irritating to the skin nor to the eyes. It is a skin sensitiser in the Maximisation Test. The results of the acute toxicity studies with tritosulfuron are summarised in the table below.

Table 2.3-3: Acute toxicity of tritosulfuron

Test	Species	Result
LD_{50} oral (Limit test)	Rat	4700 mg/kg bw
LD_{50} dermal (Limit test)	Rat	> 2000 mg/kg bw
LC_{50} inhalation (head/nose, 4h, dust aerosol)	Rat	> 5,4 mg/l air
Skin irritation	Rabbit	Non irritant
Eye irritation	Rabbit	Non irritant
Skin sensitisation (Magnusson/Kligman Test)	Guinea pig	Sensitising

2.3.1.4 Short-term toxicity

The short-term toxicity of tritosulfuron was investigated in dietary 4-week studies in rats and mice, 3-month studies in rats, mice and dogs and in a 12-month study in dogs. In addition, the short-term toxicity following dermal exposure was determined in a 28-day study in rats.

The 3-month and 12-month dog studies as well as the 28-day dermal study in rats were conducted with tritosulfuron containing high amounts of AMTT (batch no. N24). The dietary 4-week and 3-month studies in rats and mice were performed with batch no. N14 (purity 96.4 %). See Table 2.3-1 and Table 2.3-2.
The signs of toxicity in the mouse were minor and consisted mainly of some clinical chemical changes (after 3 months: increased urea and decreased serum triglyceride levels in males), as well as decreased body weights and increased water consumption. In the 3-month toxicity study cystitis was noted in 3/10 female mice and in one male mouse as well as decreased adrenal weights in females. Both, in the 28-day study and in the 3-month study the NOAEL was found to be 3000 ppm (equal to 547 mg/kg bw/d in male mice/692 mg/kg bw/d in female mice and 770 mg/kg bw/d in male mice/938 mg/kg bw/d in female mice).

The main target organs in the rat were liver and kidney. After 28 days of tritosulfuron administration the signs of toxicity consisted of decreased body weight gain, increased water consumption and urinary volume with decreased urinary specific gravity, altered clinical-chemical parameters, i.e. decreases in glucose, triiodthyronine and triglycerides and an increase in total bilirubin levels. Histopathological evaluation revealed papillary necrosis and nephropathies. The NOAEL was found to be 3000 ppm (equal to 296 mg/kg bw/d in males, 313 mg/kg bw/d in females).
After 3 months of administration to rats, increased liver weights, centrilobular hypertrophy in hepatocytes as well as altered clinical-chemical and hematological parameters and altered enzyme activities were noted in addition to the results obtained after the 4-week administration. At the dose level of 15000 ppm, premature deaths were noted in female rats, most likely due to the occurrence of severe nephropathies. The NOAEL was found to be 1000 ppm (equal to 75 mg/kg bw/d in males, 85 mg/kg bw/d in females).

Overall, the signs of toxicity observed in the dogs were similar to rats and mainly consisted of centrilobular hypertrophy of liver hepatocytes and single cell necrosis accompanied by increased organ weights and altered clinical-chemical parameters, i.e. higher platelet counts, shorter partial thromboplastin times, higher activities of alkaline phosphatase and alanine aminotransferase, lower levels of triglycerides, cholesterol, creatinine, potassium, calcium, lower concentrations of total proteins, mainly due to lower albumin levels and higher levels of inorganic phosphate. In the kidneys, a degeneration of renal tubular epithelium was noted after the 3-month administration period. Weights of adrenal and thyroid glands were increased. The NOAEL was found to be 500 ppm (equal to 15 mg/kg bw/d in males, 17 mg/kg bw/d in females).
Feeding of tritosulfuron to dogs for one year resulted in clinical chemical changes mainly at the high dose level of 5000 ppm. At this dose level and to a lesser extent at 1000 ppm there was decreased body weight gain at the beginning of the study. Functional and/or morphological changes of the liver consisted of decreased urea levels and increased activities of alkaline phosphatase in female dogs, increased organ weights together with necrosis of hepatocytes in two males and inflammatory reactions in the liver of females. The NOAEL in this 12-month dog study was 200 ppm (equal to 6 mg/kg bw/d).
The overall NOAEL in dogs was considered to be 500 ppm (equal to 15 mg/kg bw/d from the 90-day study) based on the LOAEL from the 12-month study.

In a 4-week dermal toxicity study in rats no substance-related systemic adverse effects were detected up to the highest dose level tested of 1000 mg/kg bw. There were no signs of local irritation in this study.
A summary of short-term toxicity studies is given in Table 2.3-4.

Table 2.3-4: Summary of short-term toxicity studies

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
28-day feeding Chbb:THOM Wistar rat 0, 3000, 8000, 15000 (m) / 20000 (f) ppm N14	3000 ppm [296]	8000 ppm: Increased water consumption and urinary volume, lower sodium, chloride and triglyceride values. At 15000 ppm (m): Reduced bw, bw gain and food consumption. 20000 ppm (f): Papillary necrosis, multifocal vacuolar degeneration of renal tubules in one female, altered hematological parameters.
28-day feeding B6C3F1 CrlBr mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [547]	8000 ppm: Increased water consumption
28-day dermal Chbb:THOM Wistar rat 0, 50, 200, 1000 mg/kg bw/d N24	[1000]	No systemic adverse effects. No signs of local irritation.
90-day feeding study Chbb:THOM Wistar rat 0, 1000, 5000, 15000 ppm N14	1000 ppm [75]	5000 ppm: Increased water consumption, slightly lower red blood cell parameters; centrilobular hypertrophy in hepatocytes; increased liver weights, nephropathies (slight). 15000 ppm: Premature deaths (5/10 f), reduced bw and bw gain, altered clinical-chemical and hematological parameters; altered enzyme activities; papillary necrosis; nephropathies (severe)
90-day feeding study B6C3F1 CrlBR mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [770]	8000 ppm: Increased water consumption, reduced bw and bw gain (m), increased urea/decreased triglyceride levels (m), increased adrenal gland weights and cystitis (f)
90-day feeding study Beagle dogs 0, 500, 3000, 9000 ppm N24	500 ppm [15]	3000 ppm: Increased platelet count (f day 41); decreased albumin concentration (f day 41); increased alkaline phosphatase activity (m day 91), increased rel. adrenal gland weights (f), centrilobular hypertrophy (m) 9000 ppm: Decreased bw and bw gain, altered clinical chemical and hematological parameters (increase in alkaline phosphatase and alanine aminotransferase activity, decreased albumin conc.), increased weights of liver, kidney, adrenal and thyroid glands, centrilobular hypertrophy and degeneration of hepatocytes; focal and multifocal lesions in kidneys; degenerative changes of tubular epithelium with reactive inflammatory response in cortical region of kidneys.
12-month feeding study Beagle dogs 0, 200, 1000, 5000 ppm N24	200 ppm [6]	1000 ppm: Initial bw loss (m), increased activity of alkaline phosphatase (f), decreased urea concentrations (f) 5000 ppm: Initial bw loss (m), retarded bw development (f), altered clinical chemical and hematological parameters, increased liver weights, centrilobular necrosis of hepatocytes (m), inflammatory reactions in livers (f), increased adrenal gland weights (m)

m: male; f: female; bw: body weight; d: day

2.3.1.5 Genotoxicity studies

The potential genotoxicity of tritosulfuron (batch no. N24) was investigated in a series of both *in vitro* and *in vivo* studies. Batch no. N12 was additionally tested in a bacterial mutagenicity test. All regular end points for genetic damage (point mutations, chromosome damage and DNA-damage and repair) were assessed. Tritosulfuron was evaluated for its potential

genotoxicity *in vitro* using bacterial and mammalian cell mutagenicity tests, a chromosome damage (clastogenicity) test and an unscheduled DNA synthesis test. There was no indication for genotoxic potential. *In vivo*, the test substance was assessed for the induction of micronuclei in mice. The results of this study showed that tritosulfuron (N24) has no chromosome-damaging potential. It is therefore concluded, that tritosulfuron of batches with a high content of AMTT has no mutagenic or genotoxic properties both *in vitro* and *in vivo.*

Table 2.3-5: Summary of mutagenicity studies

Study/strains/species/batch no.	Test conditions	Results
Ames mutagenicity test; TA 1535, 100, 1537, 98, E. coli WP2 uvrA N24	without S-9 mix with S-9 mix	Negative Negative
Ames mutagenicity test; TA 1535, 100, 1537, 98, E. coli WP2 uvrA N12	without S-9 mix with S-9 mix	Negative Negative
CHO/HPRT mutagenicity test N24	without S-9 mix with S-9 mix	Negative Negative
In vitro cytogenetics: chromosome aberration in Chinese hamster V79 cells N24	without S-9 mix with S-9 mix	Negative Negative
In vitro UDS, rat hepatocytes N24	-	Negative
In vivo chromosome aberration: Mouse micronucleus test N24	0, 125, 250 and 500 mg/kg bw (intraperitoneally)	Negative

2.3.1.6 Long-term toxicity / carcinogenicity studies

The 12-month chronic toxicity study (batches nos. N42, N53, N59) and two 24-month carcinogenicity studies in rats (batches nos. N34, N42, N53, N59) conducted with tritosulfuron containing low quantities of AMTT and the 18-month carcinogenicity study in mice which was conducted with tritosulfuron containing high quantities of AMTT (batch no. N24) did not show a carcinogenic potential.

In the 12-month chronic toxicity study in rats the administration of 7000 ppm of tritosulfuron resulted in an increase in water consumption in both sexes, a mild anemic process as well as clues to slight impairment of renal function in females which was evidenced by increases in urinary volume with decreased urinary specific gravity. Males at this dose level showed slightly increased incidence of chronic interstitial nephritis in the kidneys and slightly increased incidence of pericholangitis in the liver. Increased number of animals with ‘anogenital region smeared with urine’ and/or ‘inflammation in the anogenital region’ was seen at 7000 and 3500 ppm. These findings indicate that the kidney is the main target organ for tritosulfuron toxicity in chronic rat studies, which is in accordance with the subchronic rat toxicity studies. The NOAEL was found to be 1000 ppm (equal to 51.7 mg/kg bw/d in males and 68.4 mg/kg bw/d in females.

In a 24-month carcinogenicity study in rats conducted with tritosulfuron containing low quantities of AMTT the main findings consisted in an increase in water consumption and the clinical finding ‘anogenital region smeared with urine’ in both sexes at 3500 ppm. The NOAEL was found to be 1000 ppm (equal to 48 mg/kg bw/d in males and 64 mg/kg bw/d in females).

In a supplementary 24-month carcinogenicity study in rats conducted with doses of 0 ppm and 7000 ppm (equal to 327 mg/kg bw/day in males, 463 mg/kg bw/day in females) tritosulfuron

containing low quantities of AMTT the main changes consisted in the clinical observation "anogenital region smeared with urine" and/or "inflammation in the anogenital region", an increase in water consumption, as well as changes in certain red blood cell parameters (polychromasia, anisocytosis and microcytosis) in females. In the kidney, papillary necrosis was noted in either sex, pyelonephritis in males and angiectasis in renal papilla in females. In addition, male animals had cystitis and urothelial hyperplasia in the urinary bladder.
A carcinogenicity study in mice was conducted with tritosulfuron containing high quantities of AMTT. Animals of the high dose group (7500 ppm) were prematurely sacrificed after 16 months of treatment without further examinations. At 3750 ppm there was increased water consumption. Decreased body weight gain was seen at all dose levels. The NOAEL was found to be below 250 ppm (equal to < 36 mg/kg bw/d in males, < 44 mg/kg bw/d in females).
In 24-month carcinogenicity studies in rats conducted with a batch of tritosulfuron containing high levels of AMTT (N24: 2.45 %) neoplastic lesions were found in the mammary glands, i.e. adenocarcinomas and fibroadenomas. Non-neoplastic lesions consisted in effects on the testes (degeneration of the germinal epithelium, sperm stasis, focal calcification of seminiferous tubules), on the uterus and mammary gland (diffuse hyperplasia) and in increased haematopoiesis in the bone marrow at 3500 ppm. Rats of the high dose groups (7000 ppm) were prematurely sacrificed after 16 months of treatment without further examinations.
The main toxicological profile of tritosulfuron could also be confirmed in these long-term studies conducted with tritosulfuron containing high levels of AMTT. Water consumption was increased and body weight gain was decreased. Changes of white cell (leukocytosis, mainly lymphocytosis, increased numbers of polymorphonuclear granulocytes) and red cell parameters (anemia, increases in reticulocytes), distinct changes in clinico-chemical parameters (increases in alanine aminotransferase, calcium, cholesterol, decreases in triglycerides, alkaline phosphatase, increases or decreases of proteins, i.e. globulins and albumin) as well as urinary parameters (polyuria with decreased specific gravity, cloudy and/or discoloured urine samples, increased numbers of epithelial cells, granular casts and macrohematuria) were recorded.
It was concluded that tritosulfuron with a high AMTT content did show a carcinogenic potential in Wistar rats.
A summary of long-term toxicity and carcinogenicity studies with tritosulfuron is shown in Table 2.3-6.

Table 2.3-6: Summary of long-term toxicity and carcinogenicity studies with tritosulfuron

Study type / species / dose levels /batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
12-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500; 7000 ppm N42, N53, N59	1000 ppm [51.7]	3500 ppm: Anogenital region smeared with urine and/or "inflammation in the anogenital region. 7000 ppm: Increased water consumption and urinary volume (f), decreased urinary specific gravity (f), anemia (f), chronic interstitial nephritis in the kidneys (m), pericholangitis in liver (m)
24-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500 ppm N34, N42, N53, N59	1000 ppm [48]	3500 ppm: Anogenital region smeared with urine, increased water consumption; no carcinogenic properties.
Supplementary 24-month feeding study Wistar rats (Chbb: THOM) 0; 7000 ppm N34, N42, N53, N59	1000 ppm [48]	Anogenital region smeared with urine, inflammation in the anogenital region, increased water consumption, changes in red blood cell parameters (f), papillary necrosis in the kidney, pyelonephritis (m), cystitis and urothelial hyperplasia in urinary bladder (m), angiectasis in renal papilla (f), no carcinogenic properties.
24-month feeding study Wistar rats (Chbb: THOM) 0; 250; 1000; 3500; 7000 ppm N24	< 250 ppm [< 11.8]	250 ppm: Lower body weight, increased incidence of palpable masses in the skin 1000 ppm: Additionally increased water consumption, changes of hematological and clinico-chemical parameters. 3500 ppm: Additionally, increased mortality in females, abnormal clinical signs, changes of urinary parameters, effects on testes, uterus and mammary gland 7000 ppm: Premature sacrifice after 16 months. Mammary gland tumors at all dose levels.
24-month feeding study Wistar rats (Chbb: THOM) 0; 50; 100 ppm N24	100 ppm [5]	No effects
18-month feeding study B6C3F1 CrlBR mice 0; 250; 1000; 3750; 7500 ppm N24	< 250 ppm [< 36]	250 and 1000 ppm: Decreased bw and bw gain. 3750 ppm: Additionally increased water consumption. 7500 ppm: Premature sacrifice after 16 months No carcinogenic properties.

m: male; f: female; bw: body weight; d: day

2.3.1.7 Reproductive toxicity / developmental (teratogenicity) studies

The reproduction toxicity of tritosulfuron was investigated in a 2-generation reproduction study containing low quantities of AMTT (batch. no. N34) as well as in prenatal toxicity studies in rats (batch no. N12) and rabbits (batch no. N14). Two multigeneration studies on rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24).
In the 2-generation study in rats, tritosulfuron containing low quantities of AMTT had no adverse effects on reproductive performance or fertility of the F_0 and F_1 parental animals of all substance treated groups. Oestrus cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between the treated rats and the

corresponding controls. Slight signs of general toxicity occurred in both parental generations (F_0 and F_1) at 3600 ppm evidenced by an increased incidence of urine smeared fur. In the presence of slight maternal toxicity, $F_{1a/}$ F_{1b} and F_2 pups had minimally lower body weight gain and an increased incidence of dilated renal pelves at necropsy. No substance-related clinical, gross or histopathological findings were noted at 600 and 100 ppm. The NOAEL for parental and reproductive toxicity was found to be 600 ppm (equivalent to 40 mg/kg bw/d).

Two studies were carried out with tritosulfuron containing high levels of AMTT (batch no. N24) in rats. In these studies multiple effects on reproduction were seen, the most striking being the increased pup mortality also in the absence of maternal toxicity. Fertility was not affected at any dose level.
In summary, the main findings were: Reproductive performance was impaired in the mid and high dose group F_0 parental females and in the F_1 parental females of all treatment groups substantiated by an increased pup mortality of the F_{1a}/F_{1b} pups at 700 and 3500/2100 ppm, and of the F_2 pups at all dose levels, especially during early postnatal life. The number of stillborn pups was also increased at the high dose level. As a consequence, the viability index and the lactation index were reduced. The high pup mortality led to total litter losses in several dams. General toxicity occurred in both parental generations at 700 ppm and 3500/2100 ppm (increased number of animals with fur smeared with urine, reduced food consumption, reduced body weight and body weight gain, increased water consumption). Hematology showed mild adverse effects on the red blood cells of females at 3500 ppm (decreased red blood cell count and hematocrit). Concerning pathology, none of the altered organ weights could be correlated with a histopathological finding in these organs. A NOAEL for reproductive toxicity was not achieved. The NOAEL for parental toxicity was set at 100 ppm (equal to 10 mg/kg bw/d).
A supplementary study investigating dose levels of 25 and 50 ppm was performed. In this study F_2 pup mortality was increased at 50 ppm in the absence of parental toxicity. The NOAEL for parental toxicity was 50 ppm (eqivalent to 4.8 mg/kg bw/d), the NOAEL for reproductive toxicity was 25 ppm (equivalent to 2.4 mg/kg bw/d).

In the prenatal toxicity studies, different batches of tritosulfuron were administered to rats (batch. no. N12) and rabbits (batch no. N14). In the rat fetuses a slightly higher incidence of hydrourethers in combination with renal pelvis dilatations were noted at 360 mg/kg bw/d. Maternal toxicity was substantiated by decreases in body weight gain. The NOAEL for maternal and developmental toxicity was 120 mg/kg bw/d. Tritosulfuron was not teratogenic in rats.
In the prenatal toxicity study in Himalayan rabbits signs of developmental toxicity were observed at the highest dose level only (450 mg/kg bw/d) in the form of a slightly increased occurrence of one skeletal variation (accessory 13^{th} rib). At this dose level there was overt maternal toxicity (reduced food consumption, decreases in body weight gain, discoloured urine/hematuria). The NOAEL for maternal and developmental toxicity was found to be 150 mg/kg bw/d. Tritosulfuron was not teratogenic in rabbits.
The summary of reproduction toxicity studies with tritosulfuron are shown in Table 2.3-7.

Table 2.3-7: Summary of reproduction toxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
2-generation study Wistar rat (Chbb:THOM) 0, 100, 600, 3600 ppm N34	Parental and reproductive toxicity: 600 ppm [40]	3600 ppm: Parental toxicity: Clinical signs (urine smeared fur). Reproductive toxicity: Decreased bw gain, increased incidence of dilated renal pelves
2-generation study Wistar rats (Chbb: THOM) 0; 100; 700; 3500/2100 ppm N24	Parental toxicity: 100 ppm [10] Reproductive toxicity: < 100 ppm [< 10]	100 ppm: Increased pup mortality (F2 pups) 700 + 3500/2100 ppm: Parental toxicity: Abnormal clinical signs, increased water consumption, decreased bw, changes of hematological and clinico-chemical parameters. Reproductive toxicity: Increased number of stillborn pups and pup mortalities, decreased bw, delayed physical development
2-generation study Wistar rats (Chbb: THOM) 0; 25; 50 ppm N24	Parental toxicity: 50 ppm [4.8] Reproductive toxicity: 25 ppm [2.4]	50 ppm: Parental toxicity: None Reproductive toxicity: Increased F_2 pup mortality
Developmental toxicity Wistar rat (Chbb:THOM) 0, 40, 120, 360 mg/kg bw/d days 6-15 N12	Maternal toxicity: [120] Developmental toxicity: [120]	360 mg/kg bw/d: Maternal toxicity: Decreased bw gain. Developmental toxicity: Hydrourethers/renal pelves dilatation. Tritosulfuron is not teratogenic
Developmental toxicity Himalayan rabbit 0, 50, 150, 450 mg/kg bw/d days 7-19 N14	Maternal toxicity: [150] Developmental toxicity: [150]	450 mg/kg bw/d: Maternal toxicity: Decreased food intake (days 7-13 p.i.), decreased bw gain, discoloured urine/hematuria. Developmental toxicity: Slightly increased incidence of accessory $13t^h$ rib(s) Tritosulfuron is not teratogenic

m: male; f: female; bw: body weight; p.p. post partum

2.3.1.8 Neurotoxicity / Delayed neurotoxicity studies

The acute and subchronic neurotoxicity studies in rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24). The developmental neurotoxicity study in rats was conducted with tritosulfuron containing low quantities of AMTT (batch. no. N59).
In the acute neurotoxicity study, the only clinical sign of toxicity (urine-smeared anogenital region) was seen at the high dose level (2000 mg/kg bw). There were no other test substance related effects at any dose level. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 1000 mg/kg bw. The NOAEL for neurotoxicity was 2000 mg/kg bw.
In the 90-day neurotoxicity study in rats, increased water consumption at 3500 ppm and 500 ppm, reduced food consumption at 3500 ppm and a smeared anogenital region at 3500 ppm were the only test substance related findings. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 100 ppm (equal to 7 mg/kg bw/d). The NOAEL for neurotoxicity was 3500 ppm (equal to 243 mg/kg bw/d).
In a developmental neurotoxicity study the only effects that were observed were an urine-smeared anogenital region, body weight loss during first day of treatment, reduced body weight during gestation period and reduced food consumption during gestation in the dams as

well as slightly reduced mean body weight changes during the last week of lactation in the offspring at 8000 ppm. No signs of developmental neurotoxicity were noted up to the highest concentration. The NOAEL for maternal/neonatal toxicity was found to be 1000 ppm (equal to 65 mg/kg bw/d). The NOAEL for developmental neurotoxicity was 8000 ppm (equal to 509 mg/kg bw/d).
In conclusion, tritosulfuron is not neurotoxic to adult animals (batch no. N24) as well as to the developing animal (batch no. N59). A summary of the neurotoxicity studies is presented in Table 2.3-8.

Table 2.3-8: Summary of neurotoxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
Acute oral neurotoxicity study Wistar rat (Chbb:THOM) 0, 500, 1000, 2000 mg/kg bw single dose, gavage N24	Neurotoxicity: [2000] General toxicity: [1000]	2000 mg/kg bw: Clinical signs (urine smeared anogenital region). Neurotoxicity: None Tritosulfuron is not neurotoxic.
90-day subchronic neurotoxicity Wistar rat (Chbb:THOM) 0, 100, 500, 3500 ppm N24	Neurotoxicity: 3500 ppm [243] General toxicity: 100 ppm [7]	500 ppm: Increased water consumption 3500 ppm: reduced food consumption and bw, increased water consumption, urine smeared anogenital region Neurotoxicity: None Tritosulfuron is not neurotoxic.
Developmental neurotoxicity Wistar rats (Crl:CD(SD)IGS BR) 0, 200, 1000, 8000 ppm day 6 (p.c.)-21 (p.p.) N59	Developmental neurotoxicity: 8000 ppm [509] Maternal/neonatal toxicity: 1000 ppm [65]	Developmental neurotoxicity: None 8000 ppm - Maternal/neonatal toxicity: Clinical signs (urine smeared anogenital region), decreased bw gain Tritosulfuron is not neurotoxic to adult rats as well as to the developing rat

m: male; f: female; bw: body weight; p.c.: post coitum; p.p.: post partum

2.3.1.9 Further toxicological studies

635M02 (Reg.-No. 292 564; BH 635-2) is a soil metabolite and was detected in the rat metabolism study. It was tested in three mutagenicity assays as well as in acute oral tests. The metabolite was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. Two acute oral studies were conducted. The one with test substance preparation in 0.5 % Tylose and aqua bidest resulted in an oral LD_{50} of 1000 mg/kg bw, the other with test substance preparation in olive oil resulted in an oral LD_{50} of > 2000 mg/kg bw.

Table 2.3-9: Summary of toxicity studies of metabolite 635M02 (Reg.-No. 292 564)

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in rats Wistar rats (Chbb:THOM (SPF))	Batch No. 00831-201, purity: 98.2 %, Test substance preparation in 0.5 % Tylose CB 30.000 in aqua bidest	LD_{50}: 1000 mg/kg bw
Acute oral toxicity of TBSA in rats Wistar rats (Chbb:THOM (SPF))	Batch No. 26778/99; 26778/101, Purity: > 98.5 %, Test substance preparation in olive oil DAB 10	LD_{50}: > 2000 mg/kg bw
Salmonella typhimurium/ Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 00831-201, Purity: 98.2 %.	Not mutagenic
Gene mutation assay in Chinese hamster ovary (CHO) V79 cells *in vitro* (V79 / HPRT)	Batch No. 00831-201, Purity: 98.2 %.	Not mutagenic
In vitro chromosome aberration assay in V79 cells	Batch No. 00831-201, Purity: 98.2 %	Not mutagenic

635M03 (Reg.-No. 335 182; BH 635-3) is a soil metabolite. It was detected in the rat metabolism study as a transient metabolite. It was tested in three mutagenicity assays as well as in an acute oral test and a 90-day feeding study. 635M03 was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw. The NOAEL in a 90-day dietary rat study was 15000 ppm (equal to 1187 mg/kg bw).

Table 2.3-10: Summary of toxicity studies of metabolite 635M03 (Reg.-No. 335 182)

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in rats Wistar rats (Chbb:THOM (SPF))	Batch No. 00831-274, Purity: 98.7 %; Batch 01185-044, purity 99.4 %.	LD_{50}: > 5000 mg/kg bw
Subchronic toxicity study in Wistar rats [CRL:WI(GLX/BRL/HAN)IGS BR]. Administration in the diet for 3 months	Batch No. 01185-269, Purity: 99.2 %.	No substance related effects NOAEL: 15000 ppm (1187 mg/kg bw/d)
Salmonella typhimurium/Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 00831-274, Purity: 98.7 %.	Not mutagenic
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT)	Batch No. 01185-085, Purity: 99.8 %.	Not mutagenic
In vitro chromosome aberration assay in Chinese hamster V79 cells	Batch No. 01185-085, Purity: 99.8 %.	Not mutagenic

635M01 (Reg.-No. 335 184; BH 635-4) is a soil metabolite. It was detected in the rat metabolism study. It was tested in three mutagenicity assays as well as in an acute oral test. It was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw.

Table 2.3-11: Summary of toxicity studies of metabolite 635M01 (Reg.-No. 335 184)

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in Wistar rats (Chbb:THOM (SPF))	Batch No. 01185-088, Purity: 97.0 %	LD_{50}: > 5000 mg/kg bw
Salmonella typhimurium/Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 00831-277, Purity: 97.9 %	Not mutagenic
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT) Chinese hamster ovary (CHO) cells	Batch No. 01185-088, Purity: 97.0 %	Not mutagenic
In vitro chromosome aberration assay in V79 cells (cells derived Chinese hamster)	Batch No. 01185-088, Purity: 97.0 %	Not mutagenic

635M17 (Reg.-No. 373 906) is a plant metabolite. It was detected in the rat metabolism study in minor quantities. It was tested in three mutagenicity assays as well as in an acute oral test. It was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) *in vivo*. There were no indications of any impairment of chromosome distribution in the course of mitosis.
An acute oral toxicity study revealed an LD_{50} of > 2000 mg/kg bw.

Table 2.3-12: Summary of toxicity studies of metabolite 635M17 (Reg.-No. 373 906)

Study/strains/species	Test material/ conditions	Results
Acute oral toxicity study in Wistar rats Crl: WI(GLX/BRL/HAN)IGS BR (SPF)	Batch No. 01742-22, Purity: 98.3 %.	LD_{50}: >2000 mg/kg bw
Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 01742-22, Purity: 98.3 %.	Not mutagenic
In vitro gene mutation test in Chinese hamster ovary (CHO) cells (HPRT Locus Assay)	Batch No. 01742-22, Purity: 98.3 %.	Not mutagenic
Cytogenetic study *in vivo* in the mouse micronucleus test after two intraperitoneal administrations (NMRI mice)	Batch No. 01742-22, Purity: 98.3 %.	Not mutagenic

AMTT (635M04) was an impurity in the batch no. N24 (2.45 %). It is also a metabolite in the rat, soil and water. A separate metabolism study was conducted with AMTT, it was tested in an acute oral test, as well as in three mutagenicity tests. Furthermore, in order to prove that the effects seen in the 2-generation study using tritosulfuron batch no. N24 was due to high AMTT content, it was tested in a pre/postnatal toxicity study. In order to understand the mechanism by which AMTT exerts its effects it was subjected to two additional studies: a subchronic toxicity study with estrus cycle determination as well as hormone analysis and determination of the binding capacity to the estrogen receptor.
AMTT does not accumulate in rats, but is effectively excreted. The major metabolite AHTT is generated by demethylation and is detected as different tautomeric structures. The oral LD_{50} was found to be > 200 < 2000 mg/kg bw. Estrus cycle determination, hormone analysis as well as PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes in a subchronic toxicity study. AMTT is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the

CHO/HPRT mutation assay and did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse and therefore is considered to be non-mutagenic in this micronucleus assay. The oral application of AMTT induced severe maternal and developmental toxicity at 20 mg/kg bw/day and at 50 mg/kg bw/day in a pre/postnatal screening study. Therefore, AMTT might be responsible for the effects observed in the 2-generation study with tritosulfuron containing high levels of AMTT, with respect to pup mortality. In the presence of endogenous estrogens, the bonding capacity of tritosulfuron and AMTT to the estrogen receptor is regarded as extremely low. A biological effect of the substances, the activation of the receptor-mediated gene expression, is extremely unlikely.

Table 2.3-13: Summary of supplementary studies with AMTT (635M04) (CAS-Nr. 5311-05-07)

Study/strains/species	Test material/ conditions	Results
Study of the biokinetics and metabolism in Wistar rats Chbb:THOM (SPF)	14C-AMTT; Batch No. 687-1008, chemical purity > 98 %, radiochemical purity: > 95 %.	Rapid exceretion, major metabolite: AHTT
Study on the acute oral toxicity of AMTT in Wistar rats Chbb:THOM (SPF)	Batch No. 27 939/16, purity: 92.3 % - 94.2 %.	LD_{50}: > 200 < 2000 mg/kg bw
Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats (Chbb:THOM (SPF)) Administration in the diet up to 32 weeks 0, 40, 120 ppm	Batch No. 01185-097, purity: 99.9 %	LOAEL: 40 ppm (3.6 mg/kg bw/d): Estrus cycle determination, hormone analysis, PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes.
Ames Salmonella/mammalian-microsome mutagenicity test and Escherichia coli / mammalian microsome reverse mutation assay (standard plate test and preincubation test) S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 27 939/16, purity: 92.3 % - 94.2 %.	Not mutagenic
Gene mutation assay in Chinese hamster ovary (CHO) V79 cells *in vitro* (V79/HPRT) with AMTT	Batch No. 01185-097, purity: 99.9 %.	Not mutagenic
Micronucleus assay in bone marrow cells of the mouse (NMRI) after a single intraperitoneal administration	Batch No. 27939-141 CP031929, purity: 99.8 %.	Not mutagenic
AMTT and BisSH - Pre-/ postnatal screening toxicity study in Wistar rats [Chbb: THOM (SPF)] – Oral administration (gavage)	Batch No. CP031929, purity: 99.8 %, BisSH; batch No. CP 031930, purity: 99.7 %	Severe maternal and developmental toxicity at 20 mg/kg bw/d and at 50 mg/kg bw/d AMTT
Study of a possible bond of AMTT and tritosulfuron to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line	Endometrial RUCA-I-adenocarcinoma cell line of the rats	Extremely low bonding capacity of tritosulfuron and AMTT to the estrogen receptor in the presence of endogenous estrogens

2.3.1.10 Human Data

Since industrial production has not yet commenced no data on medical surveillance of the manufacturing personnel is available. The personnel who are handling developmental compounds are surveyed by regular medical examinations. This surveillance programme is not aimed to specifically identify tritosulfuron related symptoms or diseases. Poisoning incidents or clinical cases are not reported.

2.3.2 Acceptable Daily Intake (ADI)

2.3.2.1 ADI for tritosulfuron (AMTT max. 0.02 %)

From the studies conducted with tritosulfuron containing low concentrations of AMTT (batches nos. N34, N42, N53, N59) there is no evidence for carcinogenic, teratogenic or reproduction disturbing properties of the active substance. The overall NOAEL is approximately 50 mg/kg bw/d from the long-term and 2-generation studies in rats. The standard assessment factor of 100 is considered appropriate. This results in a proposed **ADI of 0.5 mg/kg bw**.

2.3.2.2 ADI for AMTT

From the studies conducted with tritosulfuron containing high concentrations of AMTT (batch no. N24) there is evidence for carcinogenic and reproduction disturbing properties. *In vitro* and *in vivo* mutagenicity studies which were conducted with this batch were negative. With regard to carcinogenic properties the lowest NOAEL is 5 mg/kg bw/d from the 24-month feeding study in rats. Calculated for an amount of 2.45 % AMTT the NOAEL is 0.123 mg/kg bw/d.
The NOAEL for reproductive toxicity was 25 ppm (equivalent to 2.4 mg/kg bw/d) based on increased F_2 pup mortality at 50 ppm. Calculated for the amount of AMTT the overall NOAEL is 0.06 mg/kg bw/d. A safety factor of 100 is considered appropriate. This results in a proposed **ADI of 0.0006 mg/kg bw.**

2.3.3 Acceptable Operator Exposure Level (AOEL)

2.3.3.1 Systemic AOEL for tritosulfuron (AMTT max. 0.02 %)

Tritosulfuron (batch no. N12) is of low acute oral, dermal and inhalation toxicity. Under the condition of following the rules of good agricultural practice the risk of an acute intoxication by tritosulfuron can be ruled out. Likewise, batches tested for chronic toxicity/carcinogenicity and reproductive toxicity in rats with a minimum purity of 98.2 % and a maximal AMTT content of 0.024 % proved to be devoid of carcinogenic and reproductive disturbing properties.
The AOEL is usually derived on the basis of so-called mid-term toxicity studies, i.e. the subacute/subchronic toxicity studies. The lowest NOAEL is 75 mg/kg bw/d from the 90-day feeding studies in rats (batch no. N14). Since the extent of absorption after oral administration is almost complete, correction from the oral AOEL to a systemic AOEL is not needed.

Applying the standard assessment factor of 100 in accordance with current EU assessment practice this results in a **systemic AOEL of 0.75 mg/kg bw/d**.

Note: The NOAELs from the 90-day and 12-month studies in dogs were lower than the NOAEL from the 90-day study in rats. The overall NOAEL in dogs was considered to be 500 ppm (equal to 15 mg/kg bw/d from the 90-day study). The conservative approach would be to derive the AOEL on the basis of this NOAEL but both short-term studies in dogs were conducted with tritosulfuron containing high levels of AMTT (batch no. N24). Since the rat was proved to be more sensitive against high AMTT levels it was considered more appropriate to derive the AOEL from the lowest NOAEL in rats treated with low AMTT levels.

2.3.3.2 Systemic AOEL for AMTT

The derivation of an AOEL for AMTT is not necessary because the Annex I inclusion is only supported for tritosulfuron specified with an AMTT content ≤ 0.02 %.

2.3.4 Acute Reference Dose (ARfD)

2.3.4.1 ARfD for tritosulfuron (AMTT max. 0.02 %)

On the basis of its toxicological profile, tritosulfuron containing low concentrations of AMTT is unlikely to present an acute hazard for consumers. The acute oral toxicity of tritosulfuron (batch no. N12) is low and there are no acute toxicological alerts seen in repeated dose toxicity studies.

2.3.4.2 ARfD for AMTT

FAO/WHO (2000) stated that there is a need to establish an ARfD if developmental/ reproductive effects are observed, except when these are clearly a consequence of maternal toxicity, and if hormonal or other biochemical alterations are observed in studies with repeated doses, which might conceivably be elicited also by a single dose. From the studies conducted with tritosulfuron containing high levels of AMTT there is evidence for carcinogenic as well as reproduction disturbing properties. Since the critical endpoint in the 2-generation reproduction toxicity study was pup mortality it is considered necessary to derive an ARfD especially for a sensitive sub-population (e.g. pregnant women) and the unborn offspring. It is proposed to derive an ARfD on the same basis as the ADI value applying a safety factor of 100. This results in an **ARfD of 0.0006 mg/kg bw (same as ADI).**

2.3.5 Drinking water limit

The determination of a MAC value is not necessary, because according to Directive 91/414/EC only the ADI and AOEL values have to be determined. Therefore, the establishment of a maximum admissible concentration for drinking water from an ADI value is not yet confirmed by a harmonized EU proposal. In addition to that, the maximum

admissible concentration of an active substance is 0.1 µg/l, as established by the Directive 89/778/EEC.

2.3.6 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

According to the toxicological properties of tritosulfuron containing low concentrations of AMTT as impurity (max. 0.02 %), harmful effects on the health of operators, bystanders, workers or consumers are not to be expected when the plant protection product is used in accordance with good plant protection practice.
The available data for tritosulfuron containing a maximum of 0.024 % AMTT do not support evidence of carcinogenic and the fertility or development damaging properties of the active substance. Likewise tritosulfuron containing high levels of AMTT (batch N24) is devoid of a genotoxic potential.
The potential operator exposure was estimated for the intended uses. The estimated systemic exposure to tritosulfuron accounts for 0.094 % (German model) or 1.31 % (UK-POEM) of the proposed systemic AOEL if no PPE is used. Thus, the estimated exposures does not present an undue risk.
In view of a single rather than a repeated scenario as it is the situation of field applicators, it is not likely that the potential exposure of bystanders will exceed the AOEL.

The active substance intake by consumers was estimated according to the BBA guideline. The theoretical maximum daily intake (TMDI) accounted for only a part of the ADI which represents a large margin of safety for consumers.

In view of the recommended uses and application techniques, harmful effects on the health of domestic or wild animals are not to be expected.

2.4 Residues

2.4.1 Definition of the residues relevant to MRLs

2.4.1.1 Plants

The metabolism and distribution of tritosulfuron was investigated in maize using phenyl and triazine labelled tritosulfuron. In most samples tritosulfuron was the main component. In addition, a range of metabolites were detected at low absolute concentrations. The metabolite AMTT (635M04) was not detected in the maize metabolism study. Therefore, parent only is included in the residue definition.

Residue definition plant: parent tritosulfuron

2.4.1.2 Animals

The metabolism of tritosulfuron has been investigated in lactating goats and laying hens using phenyl and triazine labelled tritosulfuron. After administration of an exaggerated dose

residues were found at very low levels consisting of unchanged parent compound and three major metabolites (635M02, 635M04, 635M09). With focus on the metabolite 635M04 (AMTT), it can be assumed that this compound would be present in animal matrices at levels below 0.001 mg/kg after feed up-take with realistic residues and therefore, it would not be detected by any residue analytical method.
The parent compound was detected at significant proportions in all matrices, even though it occurred at very little absolute residue levels.

Residue definition animal products: parent tritosulfuron

2.4.2 Residues relevant to consumer safety

Chronic dietary intake levels were estimated using the proposed MRL value derived from supervised residue trials. The results obtained on the basis of the German and WHO European regional diet were compared with the proposed ADI value of 0.5 mg/kg bw for tritosulfuron with a maximum content of 0.02 % AMTT. In case of this low AMTT content, a chronic dietary consumer risk is unlikely.

TMDI (WHO European diet 1998):	0.0002 mg/kg bw/day – 0.04 % of the ADI
TMDI (German diet):	0.0004 mg/kg bw/day – 0.07 % of the ADI

2.4.3 Residues relevant to worker safety

BAS 635 00 H is intended as a post emergence herbicide in cereals. Thus it is normally applied at times when it is not necessary to enter crops shortly after spraying. To assess cases where re-entry is not avoidable, the worker exposure has been calculated using a model proposed by the German BBA (Hoernicke et al., 1998).
Considering both the application regimen and the estimated operator and worker exposure data for the active ingredient in the product, re-entry operations does not present an undue risk to the worker.

2.4.4 Proposed EU MRLs and compliance with existing MRLs

The proposed MRL for plants is based on an assessment of the submitted residue data.

MRL proposal: 0.01 mg/kg for cereal and maize grain and other food of plant origin.

2.4.5 Proposed EU import tolerances and compliance with existing import tolerances

No import tolerances have been proposed in the EU or applied for in any EU Member State.

2.4.6 Basis for differences, if any, in conclusion reached having regard to established or proposed CAC MRLs

Not applicable since no Codex MRLs have been established yet.

2.5 Fate and behaviour in the environment

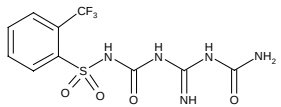
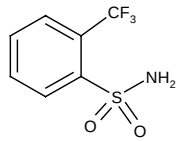
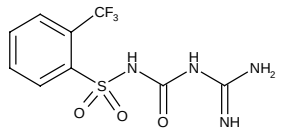
2.5.1 Definition of the residues relevant to the environment

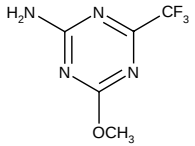
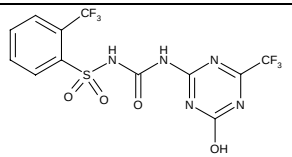
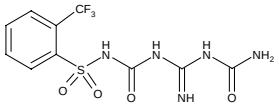
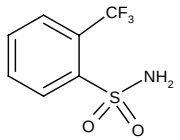
The major metabolites in soil are 635M01, 635M02 and 635M03. Metabolite 635M04 (AMTT) did not occur in soil degradation studies in the laboratory or in the field > 10 % and was not expected to occur in significant amounts in groundwater. The entry of the metabolites 635M01, 635M02 and 635M03 in ground water can not be excluded, because the concentrations exceeded 0.1 µg/l in lysimeter studies and model calculations. 635M01, 635M02 (both > 10 %) and 635M03 (< 10 %) can occur in surface water. In sediment metabolite 635M01 can be formed in significant amounts.

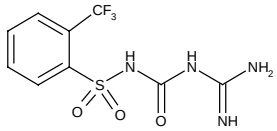
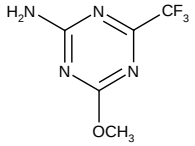
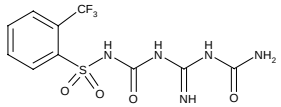
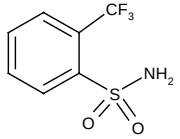
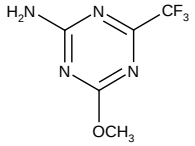
Therefore tritosulfuron and the metabolites 635M01, 635M02 and 635M03 should be included in the definition of the residues relevant to the environment.

The metabolites 635M01, 635M02 and 635M03 shows no biological activity, but the toxicological relevance in groundwater is open for metabolite 635M01 and 635M02. Ecotoxicological studies (chronic earthworm test) have to be submitted for 635M01, 635M02 and 635M03 for the risk assessment in soil. The ecotoxicological risk assessment of metabolite 635M01 in surface water is not yet finished (Lemna study required).

Table 2.5-1: Overview about metabolites

Code	Active substance	Soil		
BAS 635 H	tritosulfuron			
Metabolites		Occurrence	Risk assessment	
Code	Structural formula		Persistence, crop rotation	Ecotoxicology
635M01		soil aerobic (20 °C): lab: max. 56 % after 60 d $DT_{50,lab}$: 23 - 184 d (n = 7) $DT_{50,field}$: EU: 30 - 336 d, USA: 65 - >621 d	Effects on succeeding crops not relevant (see B 3.2.8). Maximum residues in wheat straw of 0.056 mg/kg after a plant back interval of 30 days are of no toxicological concern.	Earthworms: LC_{50} > 1000 mg/kg; no acute risk Data on long-term risk have to be submitted
635M02		soil aerobic (20 °C): lab: max. 23 % after 118 d $DT_{50,lab}$: 28 - 96 d (n = 4) $DT_{50,field}$: EU: 36 - 216 d, USA: 76 - >614 d	Effects on succeeding crops not relevant (see B 3.2.8). Maximum residues in wheat straw of 0.015, 0.02 and 0.035 mg/kg after plant back intervals of 30, 120 and 365 days, respectively are of no toxicological concern.	Earthworms: LC_{50} > 1000 mg/kg; no acute risk Data on long-term risk have to be submitted
635M03		soil aerobic (20 °C): lab: max. 15 % after 120 d $DT_{50,lab}$: 32 - ~1 a (n = 4) $DT_{50,field}$: USA: 53 - > 417 d	Effects on succeeding crops not relevant (see B 3.2.8). Maximum residues in wheat straw of 0.008 mg/kg after a plant back interval of 30 days are of no toxicological concern.	Earthworms: LC_{50} > 1000 mg/kg; no acute risk Data on long-term risk have to be submitted

Code	Active substance	Soil		
BAS 635 H	tritosulfuron			
Metabolites		Occurrence	Risk assessment	
Code	Structural formula		Persistence, crop rotation	Ecotoxicology
635M04		soil aerobic (20 °C): lab: max. 6 % after 90 d $DT_{50,lab}$: 98 (n = 1) $DT_{50,field}$: EU: 11 - 133 d, USA: 5 - 69 d	Effects on succeeding crops not relevant (see B 3.2.8) Maximum residues in bean plants of 0.011 mg/kg, in wheat forage of 0.013 mg/kg and in straw of 0.029 mg/kg after a plant back interval of 30 days are of no toxicological concern.	Earthworms: LC_{50} 671 mg/kg; no acute risk
635M19		soil anaerobic: lab: max. 16 % after 28 d DT_{50}: not available	The formation of metabolite 635M19 seemed to be no relevant process under realistic outdoor conditions (spring application). Therefore, this metabolite should be classified as non-relevant.	
		Ground water		
		Occurrence	Risk assessment	
			Pesticidal activity	Toxicology	Ecotoxicology
635M01		lysimeter (µg/l): max. annual av. conc.: 0.1-1.04 modelling (µg/l): max. annual av. conc.: 0.091	no herbicidal activity (see chapter B.9.11)	Relevance cannot be excluded on the base of limited data (only acute oral toxicicty and mutagenicity tests)	data have to be submitted for the most sensitive aquatic organism *Lemna gibba*.
635M02		lysimeter (µg/l): max. annual av. conc.: 0.02-0.11 modelling (µg/l): max. annual av. conc.: 0.347	no herbicidal activity (see chapter B.9.11)	Relevance cannot be excluded on the base of limited data (only acute oral toxicicty and mutagenicity tests)	not ecotoxicologically relevant

Code	Active substance	Soil			
BAS 635 H	tritosulfuron				
Metabolites		Occurrence	Risk assessment		
Code	Structural formula		Persistence, crop rotation		Ecotoxicology
635M03		lysimeter (µg/l): max. annual av. conc.: 0.07-0.57 modelling (µg/l): max. annual av. conc.: 0.240	no herbicidal activity (see chapter B.9.11)	Non-relevant metabolite	not ecotoxicologically relevant
635M04		lysimeter (µg/l): max. annual av. conc.: < 0.1 modelling (µg/l): max. annual av. conc.: 0.017	Not relevant	Relevant metabolite	not ecotoxicologically relevant
NIR		lysimeter (µg/l): max. annual av. conc.: 0.32-0.68		No data	
		Surface water and sediment			
		Occurrence	Risk assessment		
			Ecotoxicology		
635M01		water-sediment study: water: max. 28.1 % after 100 d sed.: max. 35 % after 100 d PEC calculation (drift): water: 0.149 µg/l	data have to be submitted for the most sensitive aquatic organism *Lemna gibba*		
635M02		water-sediment study: water: max. 15 % after 14 d PEC calculation (drift): water: 0.055 µg/l	not ecotoxicologically relevant		
635M04		PEC calculation (runoff): water: max. 0.039 µg/l	not ecotoxicologically relevant		

2.5.2 Fate and behaviour in soil

The degradation of tritosulfuron in aerobic soil studies is characterised by a rather low mineralization rate of the phenyl ring (0 % after 91 d, < 3 % after 358 d) and by a much higher mineralization of the triazine ring (5 % after 90 d, 21 % after 358 d). 17 up to 25 % of the radioactivity was not extractable after 90 days of incubation. The amounts of bound residues increased up to 28 % and 43 % on day 358 for triazine and phenyl labeled substance, respectively.
This reflects the basic metabolic degradation pathway of tritosulfuron. The major pathway starts with the opening of the triazine ring after demethylation forming the metabolite 635M01 with a maximum amount of 56 % (after 60 d). It is followed by a successive shortening of the amino side chain (via 635M03 with a maximum amount of 15 % after 121 d) until formation of the sulfonamide metabolite 635M02 (maximum amount of 23 % after 118 d). This metabolite is preferably bound to the soil matrix. Metabolite 635M04 (AMTT) could be detected in soil in maximum amounts of 6.3 % after 90 d. Photolytical degradation leads to the same degradation products, however, all metabolites were formed in amounts less than 10 % of applied radioactivity. Under anaerobic conditions, the reduced amount of oxygen in the soil seems to slow down the reactions at the triazine moiety. Therefore, the demethylated tritosulfuron (635M19), which could only be postulated during aerobic degradation and is unstable, did appear in the anaerobic metabolism study in measurable amounts (16 % after 28 d). Here again, the triazine ring opened and 635M01 is by far the most important metabolite with amounts up to 53 % of applied radioactivity on day 120. The basic pathway is the same, but the degradation of tritosulfuron was slow. A mineralisation to CO_2 was not detected during the incubation period of 120 days. The DT_{50} values of tritosulfuron were between 61 - 82 days (1^{st} order kinetics).
Tritosulfuron degraded in soil under laboratory conditions (20 °C and 40 % MWHC) with DT_{50} values (1^{st} order) ranging from 16 to 56 days in microbially active soils (n = 6), in one soil a DT_{50} value of 141 days was determined. Photolysis does not significantly influence the degradation rate. In the laboratory studies the major metabolites 635M01 (DT_{50} 23 - 184 d), 635M02 (28 - 96 d), 635M03 (32 - 347 d) and 635M04 (AMTT) (98 d) are more stable in soil than the active substance.
Field studies were conducted in three regions in Germany, two Spanisch sites and one Swedish site with a duration of one year. Using 1^{st} order kinetics DT_{50} values between 11 and 21 days (DT_{90} 40 - 70 d) were calculated for tritosulfuron. The following DT_{50} values were calculated for the metabolites (if possible): 635M01: 30 - 336 d, 635M02: 36 - 216 d and 635M04 (AMTT): 11 - 133 d. 635M03 could only be found in trace amounts under field conditions.
An additional field study in the U.S.A. at four field sites with a duration of 540 days confirmed the DT_{50} values measured in the European field studies. The DT_{50} values of tritosulfuron calculated with a non-linear approach (Gustafson and Holden) range from 3 to 15 days. For the metabolites following DT_{50} values were calculated (if possible): 635M01: 65 - > 621 d, 635M02: 76 - > 614 d and 635M03: 53 - > 417. Metabolite 635M04 (AMTT) has shorter half lives in soil (5 - 69 d).
All the results presented indicate that tritosulfuron is not stable in an active soil environment and therefore, no risk of persistence exists.
Adsorption studies show that tritosulfuron as well as its metabolites 635M01, 635M02, 635M03 and 635M04 (AMTT) can be classified as potentially mobile in soil. There seemed to be an influence of the pH value of the soils on the adsorption. The lower the pH value of the soil, the more adsorption of tritosulfuron and its metabolites 635M01, 635M02, 635M03 and

635M04 (AMTT) on the soil occurs. The following K_{OC}-values were determined: tritosulfuron: 2 - 11 l/kg, 635M01: 18 - 184 l/kg, 635M02: 16 -79 l/kg, 635M03: 18 - 51 l/kg and 635M04 (AMTT): 8 -57 l/kg. These results were supported for the as by the column leaching studies. Therefore, lysimeter studies were performed. The results clearly showed, that there was no substantial displacement of the active substance into deeper soil layers or ground water. The concentrations of the active substance found in the leachates were clearly below 0.1 µg/l. Three metabolites (635M01, 635M02 and 635M03) exceeded the concentration of 0.1 µg/l in yearly average with maximum annual average concentration of 1.04, 0.11 and 0.57 µg/l, repectively. Metabolite 635M04 (AMTT) was detected in only one out of 26 leachate samples at a concentration of < 0.1 µg/l. These results were confirmed by FOCUS-PELMO (1.1.1) calculations.
In acid soils no leaching of tritosulfuron and 635M04 (AMTT) is expected. However, the leaching behaviour in neutral or alkaline soils needs to be addressed further. The metabolites 635M01, 635M02 and 635M03 show a significant leaching potential. Regardless of the soil type, entries into groundwater > 0.1 µg/l cannot be excluded. While these metabolites are neither biological active nor ecotoxicological relevant, their toxicological relevance still needs to be addressed.

2.5.3 Fate and behaviour in water

Tritosulfuron is hydrolytically almost stable at pH 5 and 7 (DT_{50} > 70 d at 25 °C). Under acidic conditions (pH 4), a slow degradation is observed (DT_{50} 56 d). Cleavage of the sulfonylurea chain results in the formation of 635M02 (maximum 26 % at 35 d) and 635M04 (AMTT, maximum 22 % at 31 d). 635M02 can be further degraded in the water phase of natural water bodies as shown in the water sediment study. Under alkaline conditions (pH 9), a faster degradation is observed (DT_{50} 20 d). The opening of the triazine ring is the preferred reaction which leads to a formation high amounts of 635M01 (maximum 34 % on day 31 at pH 9). Direct photolysis of tritosulfuron could not be observed under continous irradiation with a xenon lamp. Metabolite 635M01 was photo-degraded with a half life of 3.6 d in a sensitzing aquatic environment.
In a water/sediment study mineralisation was low (0.7 and 5.0 % after 100 d) and bound residues increased to a maximum of 9.8 % of the applied radioactivity. Tritosulfuron degraded in the water phases with DT_{50} values between 32 and 67 days and in the total system with DT_{50} values between 36 and 77 days. Minor amounts of the active substance were found in the sediment (12 - 13 % between 14 and 28 d). 635M01, again the most important metabolite with a maximum of 29 % of the applied radioactivity in the water phase and a maximum of 35 % in the sediment phase, constantly increased in the course of incubation. 635M02 with maximum values up to 15 % of the applied radioactivity on day 14 in the water phases degraded with half lives of 67 and 132 days. Metabolite 635M03 showed maximum amounts of 3.9 % after 100 days. All these results show that in case tritosulfuron reaches the water of a natural water body, it disappears from the water phase and is degraded.

2.5.4 Fate and behaviour in air

The vapur pressure of tritosulfuron is $< 1 \cdot 10^{-5}$ Pa and the Henry constant is $< 1 \cdot 10^{-7}$ Pa m^3 mol^{-1}. Investigation about the volatilisation from plant surfaces (3 %, 24 h) and soil surfaces (2 %, 24 h) showed a very low potential for the active substance to be displaced into the atmosphere. Even if small amounts of tritosulfuron reach the troposphere, the half life would be very short. The photochemical half life for reactions with OH-radicals was determined to be less than 5.2 hours.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

Studies were conducted with technical tritosulfuron of different batch numbers. According to the toxicity values (get out from the studies with different batch no. as listed below) the toxicity of tritosulfuron to birds and mammals is very low. Thereby it is to mention that an Annex I inclusion is only supported when impurities of AMTT in technical tritosulfuron is below 0.02 %. Otherwise, long-term risk to mammals is not acceptable.

Taking into account the intended use and impurities of AMTT lower than 0.02 % even under worst case assumptions all toxicity-exposure-ratios are far above the Annex-VI-triggers, i.e. the risk to terrestrial vertebrates is acceptable.

Acute toxicity to mammals:	LD_{50}	4700 mg as/kg bw (rat)
		(batch no. N12, AMTT content: 0.16-0.24 %)
Long-term toxicity to mammals:	NOAEL	600 mg as/kg diet (from rat multi-gen.study)
		(batch no. N34, AMTT content: 0.024 %)

All studies with birds were done with the batch no N24 (AMTT content: 2.45 %):

Acute toxicity to birds:	LD_{50}	> 2000 mg as/kg bw (bobwhite quail)
Acute toxicity to birds:	LD_{50}	> 2000 mg as/kg bw (mallard duck)
Dietary toxicity to birds:	LC_{50}	> 5000 mg as/kg diet (bobwhite quail)
Dietary toxicity to birds:	NOEC	5000 mg as/kg diet (bobwhite quail)
Dietary toxicity to birds:	NOEC	625 mg as/kg diet (mallard duck)
Dietary toxicity to birds:	LC_{50}	> 5000 mg as/kg diet (mallard duck)
Reproductive toxicity to birds:	NOAEL	1000 mg as/kg diet (bobwhite quail)
Reproductive toxicity to birds:	NOAEL	300 mg as/kg diet (mallard duck)

2.6.2 Effects on aquatic species

The toxicity data which have been evaluated so far are not sufficient for conducting a final risk assessment. All metabolites tested are clearly less toxic than the active substance and should currently be regarded as ecotoxicologically not relevant. However, the most important metabolite 635M01 (BH 635-4) was not tested with the most sensitive group of organisms, higher aquatic plants, in the tests with the active substance. Due to the low log P_{ow} and partioning into sediment no further data on bioaccumulation and toxicity to sediment-dwellers must be submitted. The active substance is more toxic than the formulated product for the

most sensitive organism *L. gibba*. Therefore no further testing with the product is needed. However, a Lemna study with the metabolite 635M01 (BH 635-4) should be submitted to conduct a final risk assessment. Therefore, only a preliminary risk assessment has been conducted so far.

The metabolites 635-M01 and 635-M 02 were measured in considerable amounts in the water/sediment study but both were less toxic than the active substance. However, for the most important metabolite 635-M01 the effects on the species showing the highest sensitivity to tritosulfuron, L. gibba needs to be addressed.

Currently, higher aquatic plants (L. gibba EC50 0.026 mg/l) and algae (P. subcapitata EC50 0.23 mg/l) are the most sensitive group of organisms and 0.026 mg/L is relevant for the risk assessment. Fish and Daphnia were clearly less sensitive (acute EC50 > 100 mg/l; long-term/chronic NOEC 21.5 and 56 mg/l). The TER-value of 54 in a distance of 1 m is higher than the relevant trigger of 10 indicating an acceptable risk to non-target aquatic organisms. Therefore, no risk mitigation measures are to be set.

Tritosulfuron must be labelled with N and R 50/53.

2.6.3 Effects on bees and other arthropod species

2.6.3.1 Effects on bees

To determine the possible side effects of tritosulfuron on honeybees 2 laboratory studies were performed, one with the active substance and one with a formulated product. Both studies have been performed under GLP-conditions according to EPPO-guideline No.170. The determined LD_{50} values for oral and contact toxicity indicate that tritosulfuron is not toxic to honeybees. Hazard quotients were calculated according to EPPO/CoE-RiskAssessment Scheme: LD_{50}^{-1} x g as/ha. All quotients are below the trigger of 50. This indicates that honeybees will not be put at risk when tritosulfuron containing products are used according to the applied intended uses.

2.6.3.2 Effects on other arthropod species

Non-target arthropods are likely to be exposed to formulated tritosulfuron by direct spray, contact or fresh or dry residues. Oral uptake of contaminated pollen, nectar and honey dew, prey or via host organisms is considered of minor importance. As a tier one worst-case exposure scenario, the predicted environmental exposure of non-target arthropods is assumed to be equivalent to the maximum nominal field rate. The nominal field rate is 70 g BAS 635 00 H/ha (corresponding to 50 g as tritosulfuron/ha) + 1250 ml BAS 152 00 S/ha.

Two tests with *Typhlodromus pyri* were conducted. In the test on glass plates (ANA 2001-480) an LR_{50} of 40.1 g BAS 635 00 H + 716.1 ml/ha BAS 152 00 S was determined. On natural substrate (ANA 2001-486) in both tested rates of 3.5 g/ha BAS 635 00 H + 62.5 ml/ha BAS 152 00 S and 70 g/ha BAS 635 00 H + 1250 ml/ha BAS 152 00 S no effects on mortality and reproduction were observed. *Aphidius rhopalosiphi* was tested at 210 g/ha BAS 635 00 H + 3750 ml/ha BAS 152 00 S and showed at this rate a mortality of 10 % and a reduction of the parasitisation capacity of 30 %. The tests with the plant dwelling species *Chrysoperla carnea*

and the soil dwelling species *Poecilus cupreus*, *Aleochara bilineata* and *Pardosa spec*. showed no or low effects up to 70 g BAS 635 00 H + 1250 ml/ha BAS 152 00 S.

The available data indicate that *T. pyri* was the most sensitive species. As in the test on natural substrate no effects on mortality and no reduction of fertility were observed, the risk for non-target terrestrial arthropods is considered acceptable.

2.6.4 Effects on earthworms and other soil macro-organisms

The studies on the acute toxicity of tritosulfuron and the formulation BAS 635 00H + BAS 152 00 S indicate that the acute toxicity for earthworms is low. The TER values are above the relevant trigger of 10. Thus the acute risk for earthworms is considered acceptable. No reproduction test has been conducted as DT_{90} values are < 100 days.
The metabolites 635M02 (BH 635-2), 635M03 (BH 635-3), 635M01 (BH635-4) and 635M04 (BH 635-5) were tested in acute tests and the TER values are above the relevant trigger of 10 and demonstrate an acceptable acute risk.

Acute toxicity: LC_{50} > 1000 mg/kg (technical tritosulfuron)
LC_{50} > 1000 mg/kg (formulation BAS 635 H + BAS 152 00 S)
(corresponds to 34.2 mg as tritosulfuron)
LC_{50} > 1000 mg/kg (metabolite 635M02 (BH 635-2))
LC_{50} > 1000 mg/kg (metabolite 635M03 (BH 635-3))
LC_{50} > 1000 mg/kg (metabolite 635M01 (BH 635-4))
LC_{50} = 671 mg/kg (metabolite 635M04 (BH 635-5))

As the metabolites 635M02 (BH 635-2), 635M03 (BH 635-3) and 635M01 (BH 635-4) show a slow degradation pattern in soil with DT_{90}-values > 100 days, the longterm risk of these metabolites for earthworms has to be addressed.

2.6.5 Effects on soil micro-organisms

The influence of the mixture BAS 635 00 H + BAS 152 00 S on nitrogen and carbon conversion is < 25 % compared to the untreated control. The metabolites 635M02 (BH 635-2), 635M03 (BH 635-3), 635M01 (BH 635-4) and 635M04 (BH 635-5) have been tested concerning N-mineralisation in two different loamy sand soils. The effect was < 25 % compared to the control for all metabolites. For the metabolites no carbon conversion was tested.
When applying tritosulfuron containing plant protection products according to the recommended pattern of use, no lasting effects on microbial activities are to be expected.

2.6.6 Effects on other non-target organisms (flora and fauna)

Effects on non-target terrestrial plants

Tritosulfuron is an active substance belonging to the sulfonylureas. It is a systemic herbicide acting via the blockage of the enzyme acetolactate-synthase (ALS). The herbicidal action is mainly via the leaves. The application rate is 70 g product/ha (corresponding to 50 g tritosulfuron/ha) + 1.25 l/ha adjuvant. The product is intended to be used in cereals and maize.

A seedling emergence test (PFL2001-66) was done with 6 plant species with the formulation BAS 635 00 H (71.4 % tritosulfuron) in a mixture with the adjuvant BAS 152 00 S (40 % purity). Assessment of phytotoxicity was done 7, 14 and 21 days after treatment, plant height and fresh weight were evaluated after 21 days. The most sensitive species was *Phacelia tanacetifolia*.

A vegetative vigor test (PFL 2001-67) was done with 6 plant species with the formulation BAS 635 00 H (71.4 % tritosulfuron) in a mixture with the adjuvant BAS 152 00 S (40 % purity). The highest tested dose was 49.5 g BAS 635 00 H + 884 ml BAS 152 00 S/ha for *Brassica napus* and *Linum usitatissimum* and 35 g BAS 635 00 H + BAS 152 00 S for all other species. Assessment of phytotoxicity was done 7, 14 and 21 days after treatment, plant height and fresh weight were evaluated after 21 days. The most sensitive species was *Brassica napus* with an ED_{50} of 4.3 g BAS 635 00 H + 76.4 ml BAS 152 00 S/ha.

Field tests with *Brassica napus* (PFL 2001-68), *Pisum sativum* (PFL 2001-69) and *Linum usitatissimum* (PFL 2001-70) were conducted. The most sensitive species was *Brassica napus* with a field ED_{50} of 8.7 g BAS 635 00 H + 156 ml BAS 152 00 S.

The risk assessment is based on the ED_{50} of *Brassica napus* of 4.3 g BAS 635 00 H + 76.4 ml BAS 152 00 S/ha, which was the most sensitive species in the vegetative vigor test in the laboratory, and on the ED_{50} of 8.7 g BAS 635 00 H + 156 ml BAS 152 00 S/ha in the field. The TER of 4.5 for the field test is considered acceptable.

Risk assessment for BAS 635 00 H + BAS 152 00 S concerning non-target terrestrial plants based on the species *Brassica napus*

Distance from treated area (m)	**Drift (%)**	**Amount of drift (g product/ha)**	**TER laboratory (ED_{50} 4.3 g/ha)**	**TER field (ED_{50} 8.7 g/ha)**
1	2.77	1.94	2.2	4.5
5	0.57	0.399	10.8	21.8

Herbicidal activity

The metabolites 635 M01 (BH 635-4), 635 M02 (BH 635-2), 635 M03 (BH 635-3) and 635 M04 (BH 635-5) were tested in the greenhouse at pre-emergence application. The tests were done with 6 species (5 dicotyledonous and one monocotyledonous species) with 3 replicates in comparison with an untreated control. Four application rates were tested. The metabolites 635 M04 and 635 M02 showed some effects on *Matricaria inodora*, but these were low at the lowest test rate of 0.0625 kg/ha. This rate is much higher than the maximum expected amount of the metabolites in soil taking into account the molecular weight (the theoretical maximum amount of 635 M04 is 21.8 g/ha and for 635 M02 it is 25.3 g/ha).

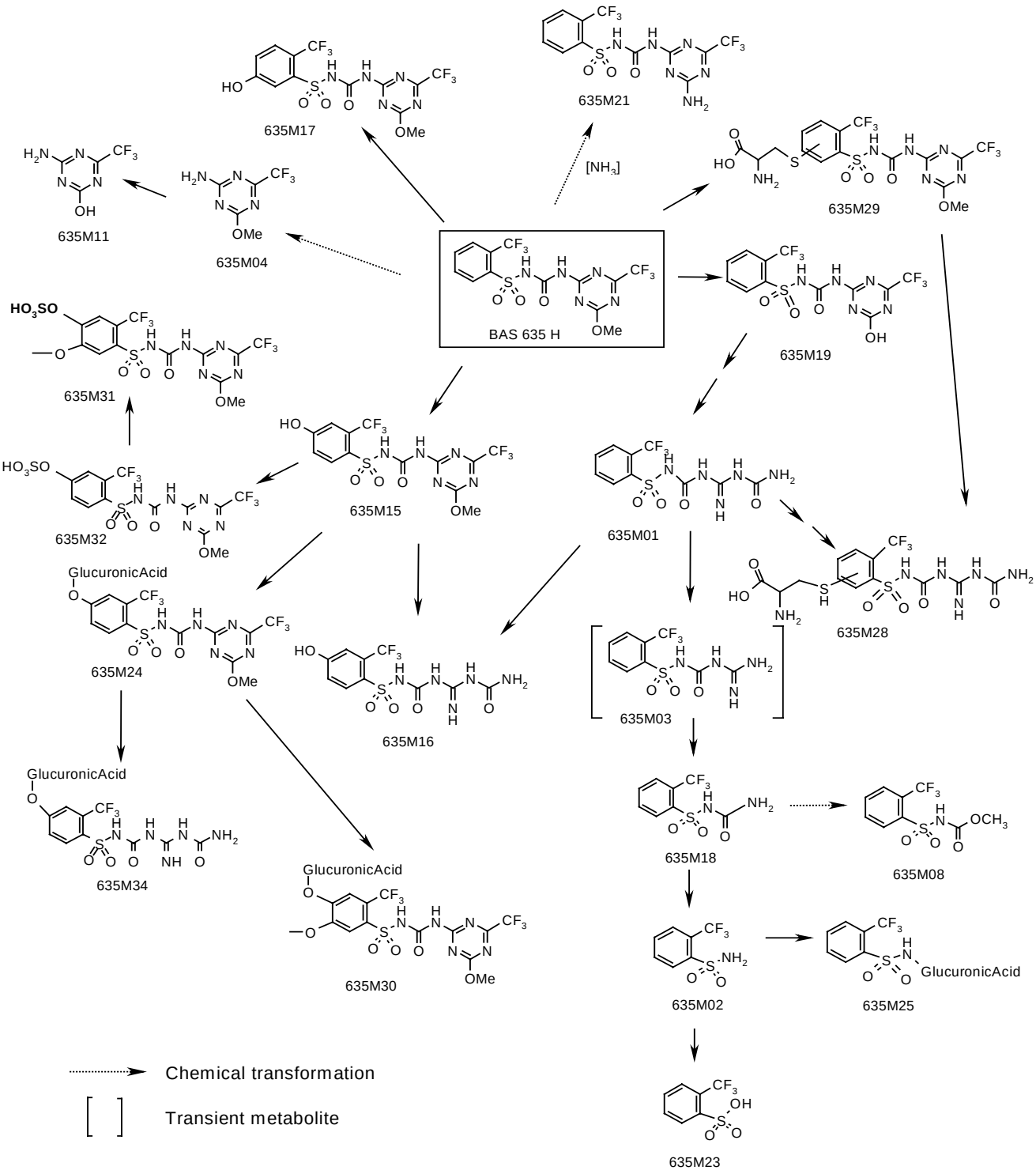
2.6.7 Effects on biological methods of sewage treatment

Data on *Pseudomonas putida* show that no unacceptable effects on biological methods of sewage treatment plants are to be expected.

2.7 Overall conclusion (metabolism schemes)

2.7.1 Toxicology (laboratory animals)

Figure 2.7-1: Metabolic pathway of tritosulfuron in rats



2.7.2 Residues (plant, plant products, livestock animals)

Figure 2.7-2: Metabolic pathway of tritosulfuron in maize

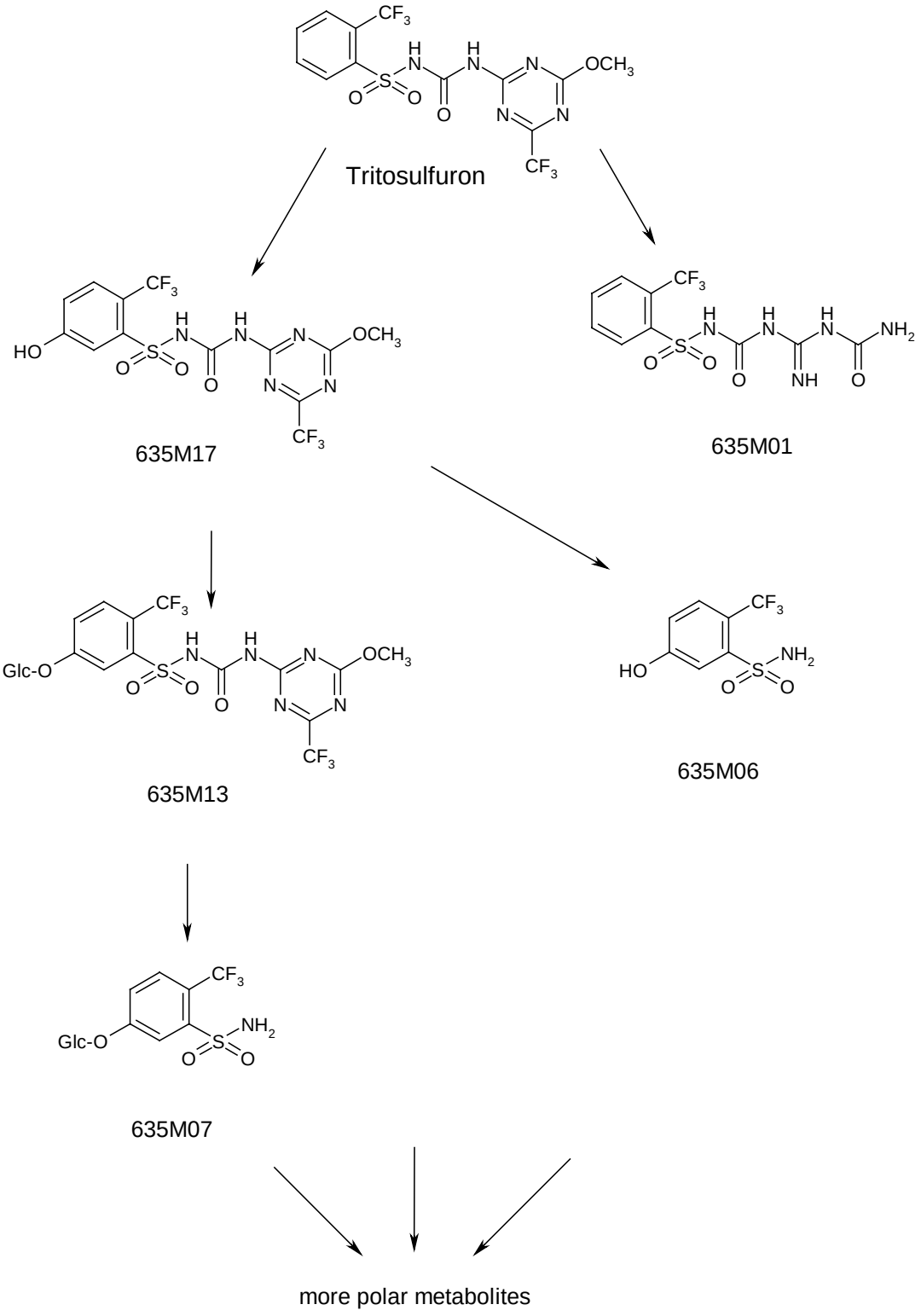


Figure 2.7-3: Metabolic pathway of tritosulfuron in rotational crops

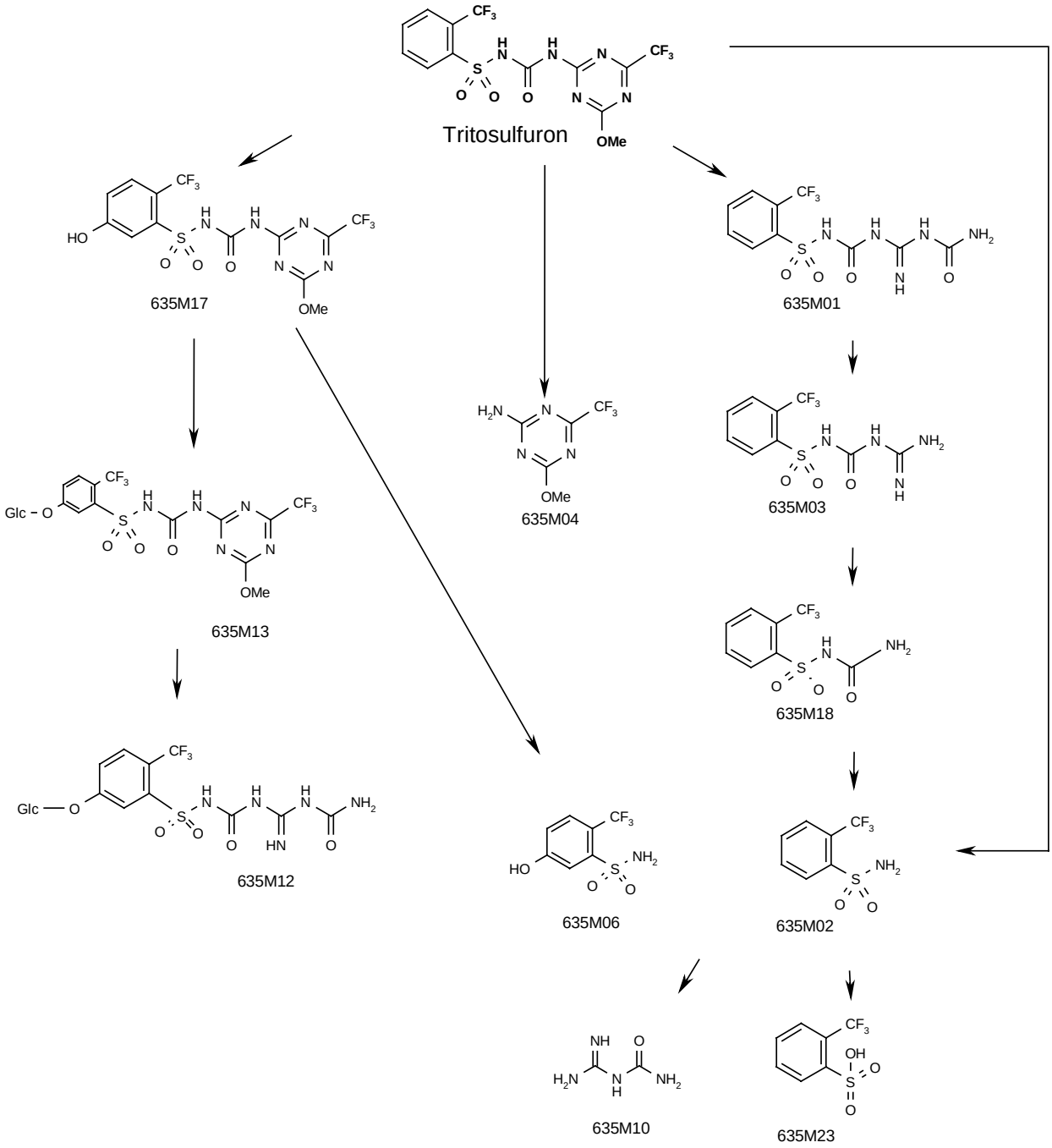
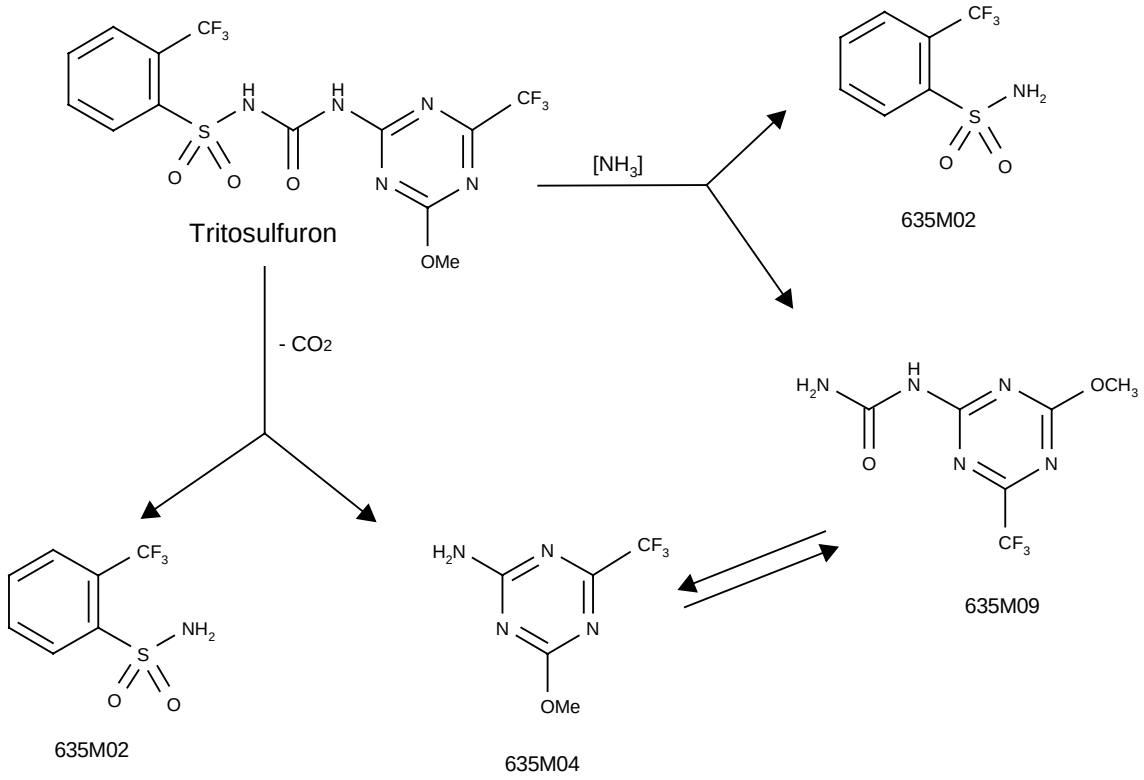


Figure 2.7-4: Metabolic pathway of tritosulfuron in goats and hens



2.7.3 Fate and behaviour in the environment (soil, water, air)

Figure 2.7-5: Proposed metabolism of tritosulfuron in soil under aerobic conditions

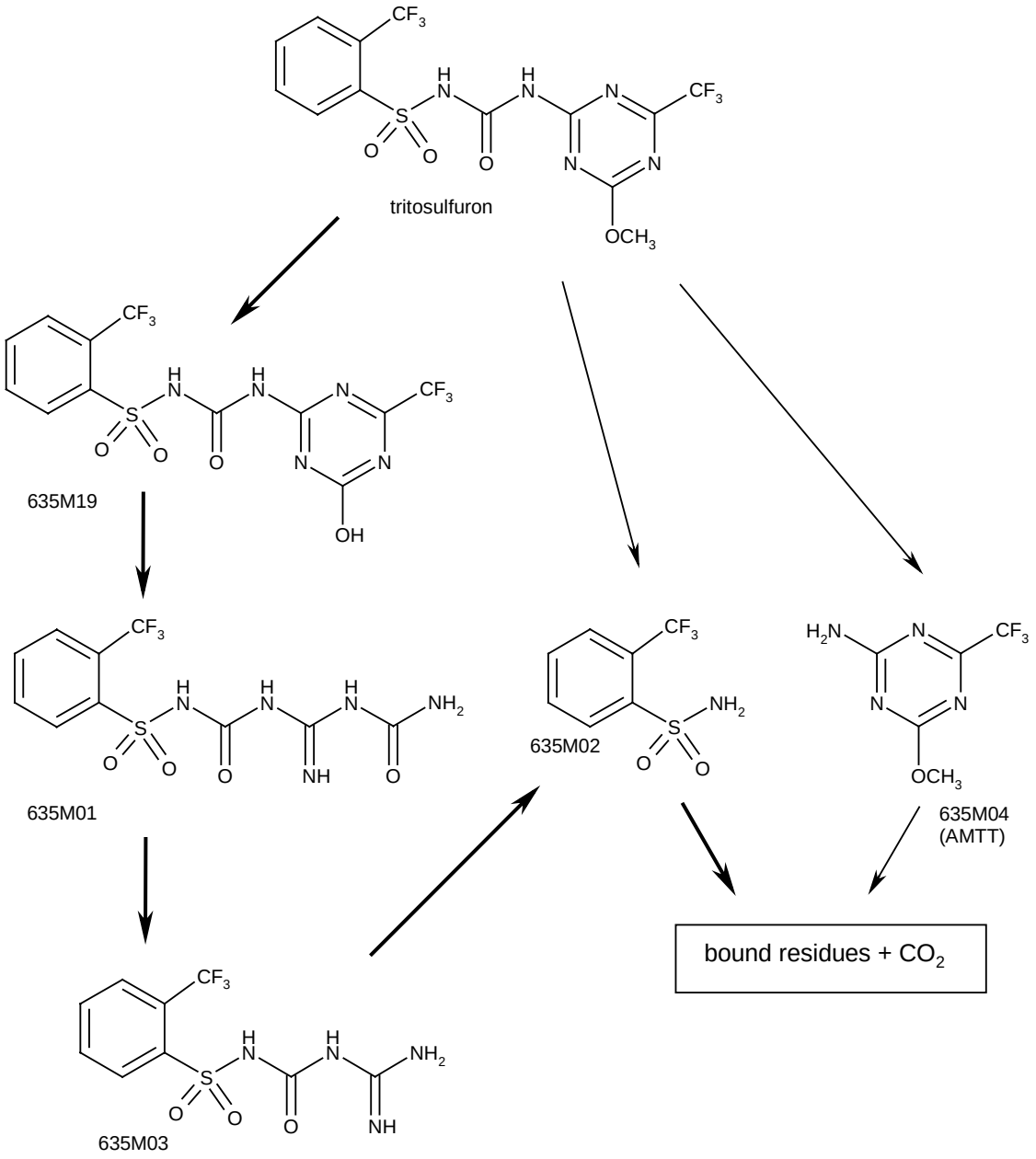


Figure 2.7-6: Proposed hydrolytic pathway of tritosulfuron

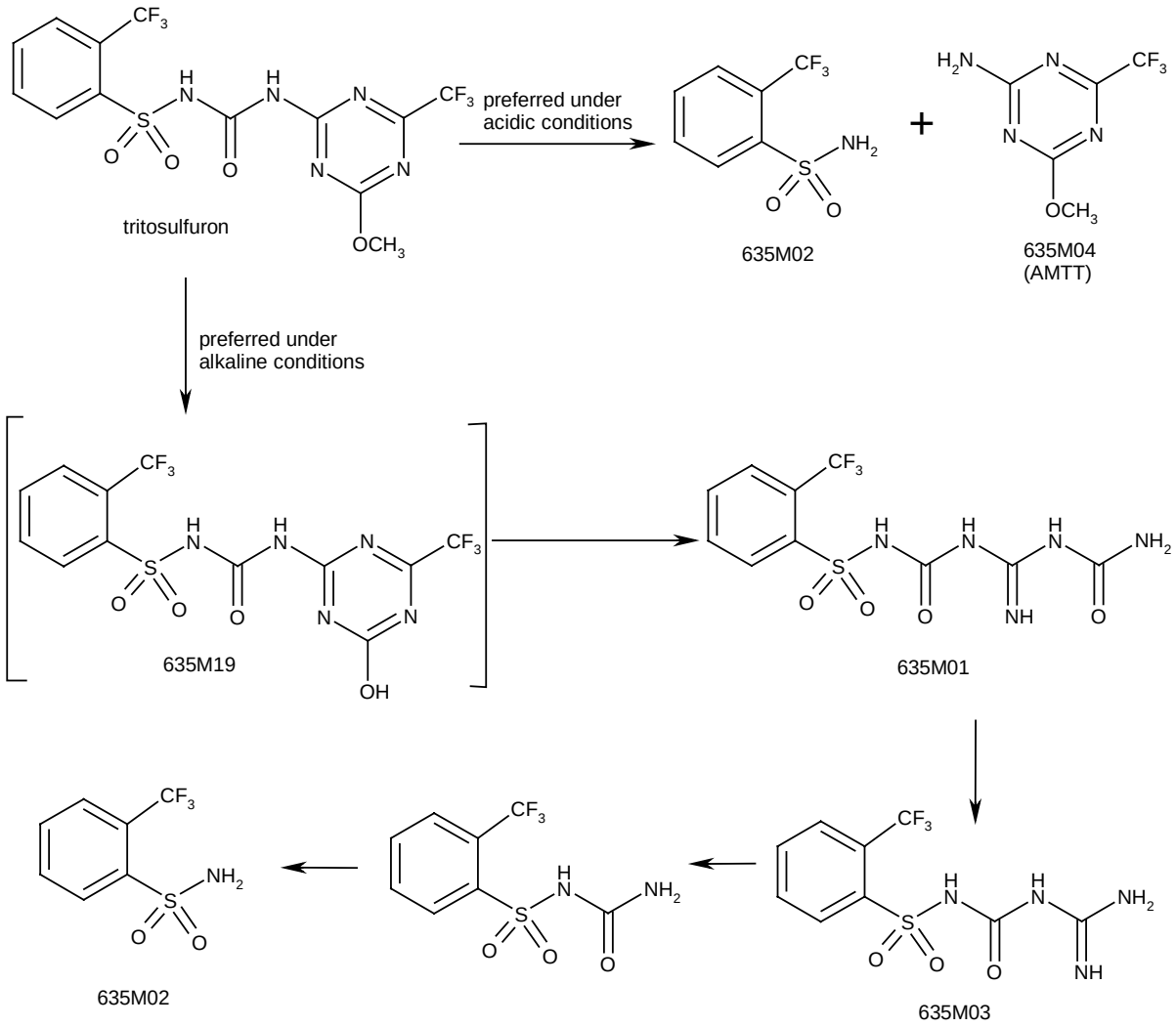
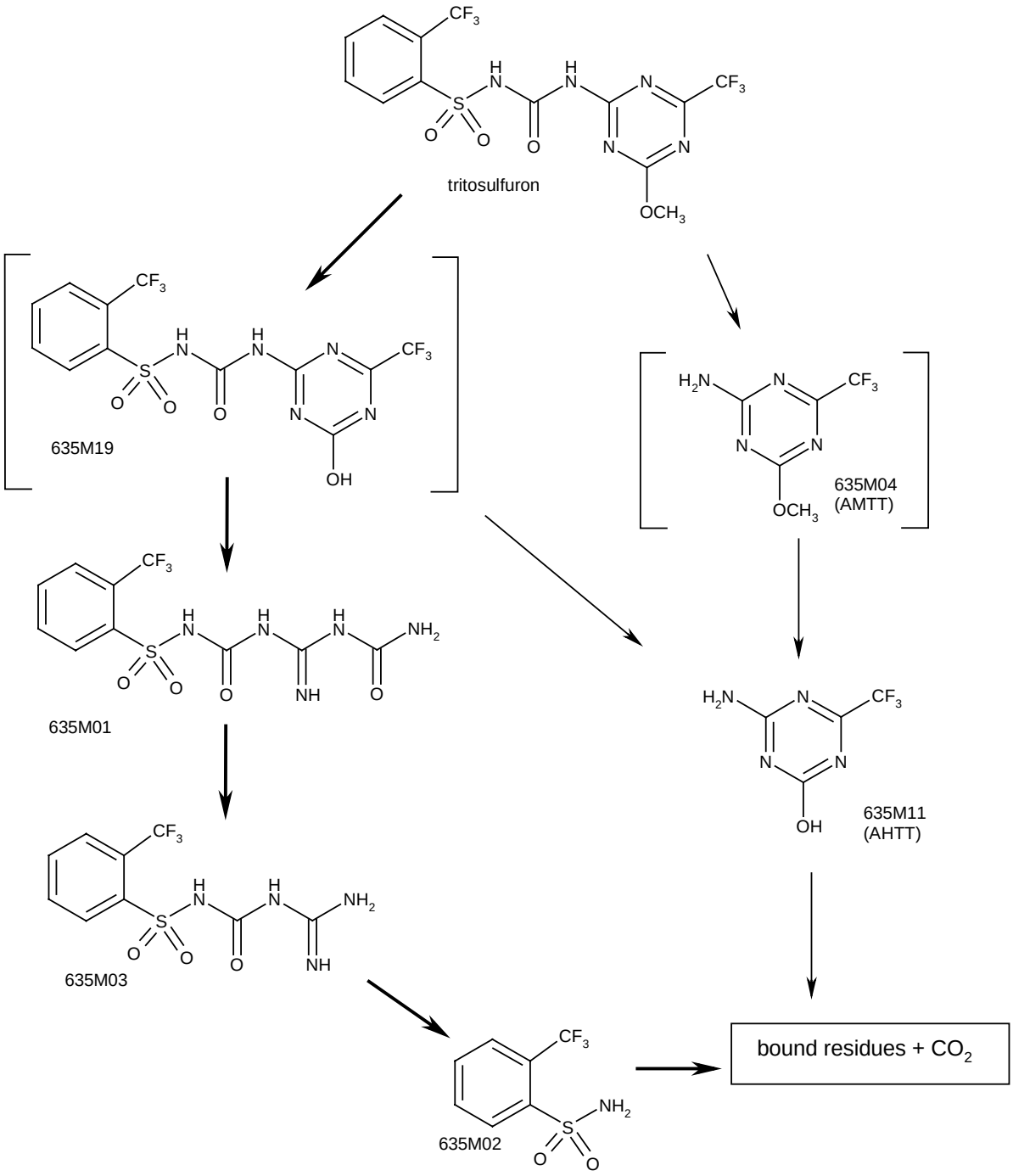


Figure 2.7-7: Proposed route of degradation of tritosulfuron in water-sediment systems



Appendix 1

Tritosulfuron

Standard Terms and Abbreviations

2.8 Appendices

2.8.1 Appendix I: Standard terms and abbreviations

Part 1 Technical Terms

A	ampere
ACH	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50 %
ALT	alanine amitrotransferase (SGPT)
AMD	automatic multiple development
ANOVA	analysis of variance
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)

cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days past inoculation
DRES	dietary risk evaluation system
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionisation detector
FOB	functional observation battery

fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulose virus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hl	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
Hs	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilisation concentration

ICM	integrated crop management
ID	ionisation detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	in vitro fertilisation
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
l	litre
LAN	local area network
LASER	light amplification by stimulated emission
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LCLo	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDLo	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content

MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
ml	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mol
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue limit or level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NAEL	no adverse effect level
nd	not detected
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter content
op	organophosphorus pesticide

Pa	Pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
PIXE	proton induced X-ray emission
pK_a	negative logarithm (to the base 10) of the dissociation constant
PNEC	predicted no effect concentration
po	by mouth (per os)
P_{ow}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
R_f	ratio of fronts
RfD	reference dose
RH	relative humidity
RL_{50}	residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	reversed phase material
rRNA	ribosomal ribonucleic acid
RRT	relative retention time

RSD	relative standard deviation
s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedure
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{1/2}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TCLo	toxic concentration low
TID	thermionic detector, alkali flame detector
TDLo	toxic dose low
TDR	time domain reflectrometry
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake

TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic chlorine
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comité des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information of the European Communities

ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export an Import of Dangerous Chemicals
EHC (number)	Environment Health Criteria (number)
EHCD	Environmental Health Criteria Document
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organisation
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organisation of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GIFAP	Groupement International des Association Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organisation
IMO	International Maritime Organisation
IOBC	International Organisation for Biological Control of noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organisation
ISO	International Organisation for Standardisation

IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticides Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organisation
WTO	World Trade Organisation
WWF	World Wide Fund for Nature

Appendix 2

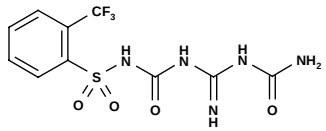
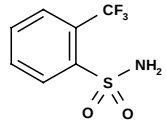
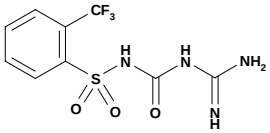
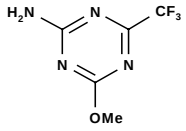
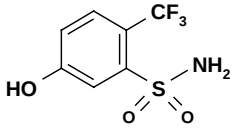
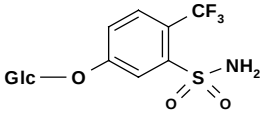
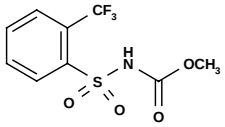
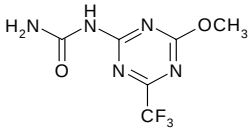
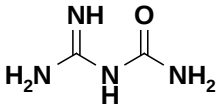
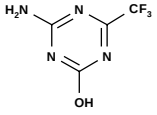
Tritosulfuron

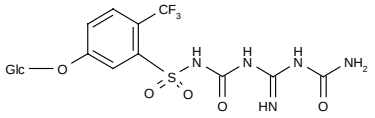
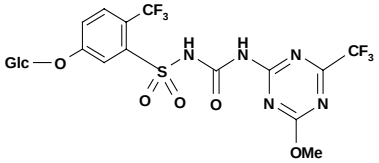
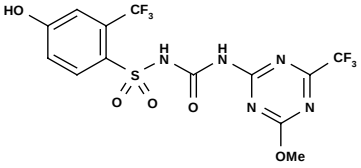
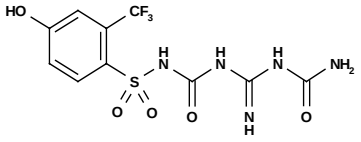
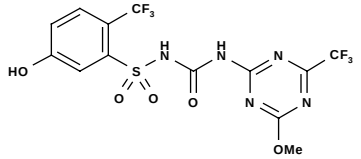
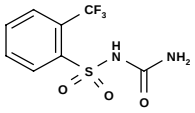
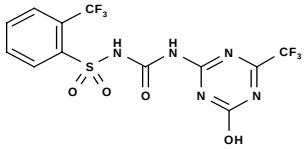
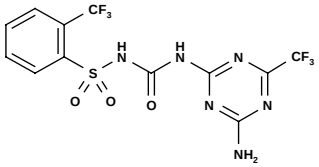
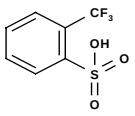
Specific Terms and Abbreviations

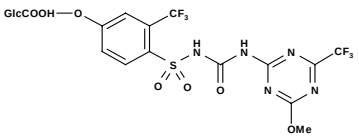
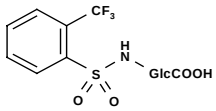
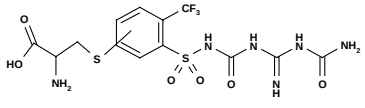
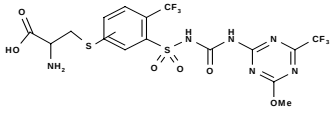
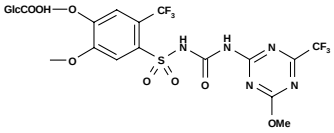
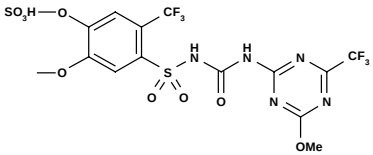
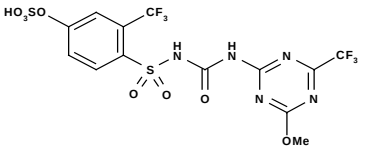
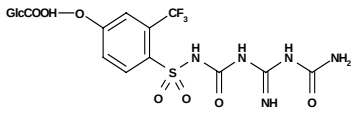
2.8.2 Appendix II: Specific terms and abbreviations

DAP	days after planting
DAT	days after treatment
DMSO	dimethylsulphoxide
ERR	extractable radioactive residue
PAS	pure active substance
RRR	residual radioactive residue
TAS	technical active substance
TRR	total radioactive residue
BrdU	5-Bromodeoxyuridine
CHO	Chinese hamster ovary
HPRT	Hypoxanthine-phosphoribosyl-transferase
PCNA	Proliferating cell nuclear antigen
TUNEL	Terminal deoxyribosyl-transferase mediated dUTP(deoxyuridinetriphosphate) nick end labelling

List of metabolites of tritosulfuron found in different matrices

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M01		1-(carbamoylamidino)-3-(2-trifluoromethyl-benzenesulfonyl) urea	335 184 (BH 635-4)	rat, maize, rotat. crops, soil, water, sediment
635M02		2-trifluoromethyl-benzenesulfonamide	TBSA, 292 564 (BH 635-2)	rat, goat, hen, rotat. crops, soil, water, sediment
635M03		1-amidino-3-(2-trifluoromethyl-benzenesulfonyl) urea	335 182 (BH 635-3)	rotat. crops, soil, water, sediment
635M04		2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine	AMTT, 231 700 (BH 635-5)	rat, goat, hen, rotat. crops, soil, water
635M06		3-Hydoxy-6- trifluoromethyl-benzenesulfonamide	n.a.	maize, rotat. crops
635M07		5-(hexopyranosyloxy)-2-(trifluoromethyl)benzene-sulfonamide	n.a. 347 666	maize
635M08		N-(Methoxycarbonyl)-2-trifluoromethyl-benzenesulfonamide	n.a.	rat
635M09		*N*-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]urea	n.a. 347 667	goat, hen
635M10		Amino{[amino(imino)methyl]amino}oxomethane	n.a. 432 8983	rotat. crops
635M11		2-amino-4-hydroxy-6-trifluoromethyl-1,3,5-triazine	276 164 (BH 635-14)	rat, water

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M12		3-{[({[[(aminocarbonyl)amino]-(imino)methyl]amino}carbonyl)-amino]sulfonyl}-4-(trifluoromethyl)-phenyl hexopyranoside	n.a.	rotat. crops
635M13		3-{[({[4-methoxy-6-(trifluoro-methyl)-1,3,5-triazin-2-yl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl hexopyranoside	n.a.	maize, rotat. crops
635M15		3-{[({[4-methoxy-6-(trifluoro-methyl)-1,3,5-triazin-2-yl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl hexopyranoside	n.a.	rat
635M16		1-{[({[[(aminocarbonyl)amino]-(imino)methyl]amino}carbonyl)-amino]sulfonyl}-4-hydroxy-2-(trifluoromethyl) benzene	n.a.	rat
635M17		1-[(4-methoxy-6-trifluoromethyl)-1,3,5-triazin-2-yl]-3-(5-hydroxy-2-trifluoromethyl-benzenesulfonyl) urea	373 906 (BH 635-16)	rat, maize, rotat. crops, water
635M18		1-{[(aminocarbonyl)amino]-sulfonyl}-2-(trifluoromethyl) benzene	n.a.	rat, rotat. crops
635M19		2-hydroxy-4-(trifluoromethyl)-6-{[({[2(trifluoromethyl)phenyl]-sulfonyl}amino)carbonyl]amino}-1,3,5-triazine	n.a.	rat, soil, water
635M21		1-[(4-amino-6-trifluoromethyl)-1,3,5-triazin-2-yl]-3-(2-trifluoro-methyl-benzenesulfonyl) urea	362 561 (BH 635-15)	rat
635M23		2-(trifluoromethyl)benzene sulfonic acid	324 543 (BH 635-1 as Na-Salt)	rat, rotat. crops

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M24		n.a.	n.a.	rat
635M25		n.a.	n.a.	rat
635M28		e.g. [3-{[({[[(aminocarbonyl) amino](imino)methyl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl] cysteine	n.a.	rat
635M29		[3-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl] cysteine	n.a.	rat
635M30		n.a.	n.a.	rat
635M31		2-methoxy-4-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-5-(trifluoromethyl)phenyl hydrogen sulfate	n.a.	rat
635M32		4-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-3-(trifluoromethyl)phenyl hydrogen sulfate	n.a.	rat
635M34		n.a.	n.a.	rat

Appendix 3

Tritosulfuron

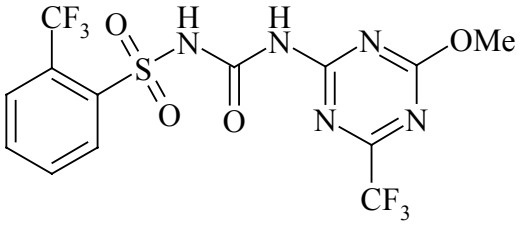
List of End Points

2.8.3 Appendix III: Listing of end points

2.8.3.1 Appendix III.1: Chapter 1 (identity, physical and chemical properties, details of uses, further information, classification and labelling)

Active substance (ISO Common Name)	Tritosulfuron (ISO)
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	Federal Republic of Germany

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	1-(4-methoxy-6-trifluoromethyl-1,3,5-triazin-2-yl)-3-(2-trifluoromethyl-benzenesulfonyl)urea
Chemical name (CA)	N-[[[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino]carbonyl]-2-(trifluoromethyl)benzene-sulfonamide
CIPAC No	735
CAS No	142469-14-5
EEC No (EINECS or ELINCS)	not assigned
FAO Specification (including year of publication)	n. a. (new active substance)
Minimum purity of the active substance as manufactured (g/kg)	950
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	AMTT: 0.2 g/kg (max. content)
Molecular formula	$C_{13}H_9F_6N_5O_4S$
Molecular mass	445.3
Structural formula	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	166.5 – 169.4 °C (99.8 %)
Boiling point (state purity)	–
Temperature of decomposition	approx. 340 °C
Appearance (state purity)	white crystalline solid, odourless (99.8 %)
Relative density (state purity)	d_4^{20} = 1.678 (99.8 %)
Surface tension	64.6 mN/m 1.0 % (w/w) (93.8 %, at 20 °C) 71.3 mN/m 0.5 % (w/w) and 71.0 mN/m 2.0 % (w/w) (99.8 %, both at 20 °C)
Vapour pressure (in Pa, state temperature)	1.0 x 10^{-5} (20 °C), 99.8 %
Henry's law constant (Pa m^3 mol^{-1})	< 1.012 x 10^{-4} (20 °C)
Solubility in water (g/l or mg/l, state temperature)	38.6 mg/l pH 4.7 (deionized water) 78.3 mg/l pH 10.2 0.94 mg/l pH 1.7 all at 20 °C
Solubility in organic solvents (in g/l or mg/l, all at 20 °C).	Toluene < 10 g/l Dichloromethane 25 g/l Methanol 23 g/l Aceton 250-300 g/l Ethyl acetate 83-86 g/l Acetonitrile 90-94 g/l 1-Octanol 13 g/l 2-Propanol < 10 g/l olive oil < 10 g/l
Partition co-efficient (log P_{OW}) (state pH and temperature)	2.93 non ionised form 2.93 pH 2.7, 2.85 pH 4, 0.62 pH 7, -2.38 pH 10 all at 20 °C
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 4: 39-56 d (25 °C), pH 5: > 62 d (25 °C) pH 7: > 62 d (25 °C) pH 9: 17-20 d (25 °C)
Dissociation constant	pK_a 4.69 (20 °C), 99.7 %
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	pH 0.5: 202 nm (ε 24440), 212 nm (ε 21412), 226 nm (ε 25172), 254 nm (ε 7037), 300 nm (ε 212) pH 6.7: 202 nm (ε 18331), 215 nm (ε 18515), 237 nm (ε 21494), 260 nm (ε 13021), 300 nm (ε 144) pH 13.3: 219 nm (ε 18151), 235 nm (ε 15825), 260 nm (ε 11908), 300 nm (ε 1890)
Photostability (DT_{50}) (aqueous, sunlight, state pH)	stable over 15 days at pH 5 and pH 7
Quantum yield of direct phototransformation in water at λ > 290 nm	< 1.05 x 10^{-4} (pH 5) < 2.23 x 10^{-4} (pH 7)
Flammability	not highly flammable
Explosive properties	none

List of uses supported by available data

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests Controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of g as/kg (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Maize	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	12-18	1	-	0.013-0.033	150-400	0.05	F	
Maize	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	12-18	1	-	0.013-0.033	150-400	0.05	F	
Cereals, winter	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	21-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, winter	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	21-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, summer	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	13-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, summer	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	13-39	1	-	0.013-0.033	150-400	0.05	F	

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	none
with regard to toxicological data	R43
with regard to fate and behaviour data	none
with regard to ecotoxicological data	R50, R53

2.8.3.2 Appendix III.2: Chapter 2 (methods of analysis)

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	HPLC-UV
Impurities in technical as (principle of method)	HPLC-UV
Plant protection product (principle of method)	HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	HPLC-UV LC-MS/MS	0.01 mg/kg (wheat, maize) 0.001 mg/kg (wheat, maize)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	HPLC-UV	0.01 mg/kg (milk, muscle, fat, egg, kidney, liver)
Soil (principle of method and LOQ)	LC-MS/MS GC-ECD	0.001 mg/kg 0.001 mg/kg
Water (principle of method and LOQ)	LC-MS/MS GC-MS	0.05 µg/l 0.05 µg/l
Air (principle of method and LOQ)	HPLC-UV	2.8 µg/m³
Body fluids and tissues (principle of method and LOQ)	not relevant	

2.8.3.3 Appendix III.3: Chapter 3 (impact on human and animal health)

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption	Rapid and complete (≥ 90 % based on urinary and bile excretion over 48 h)
Distribution	Widely distributed
Potential for accumulation	Low potential for accumulation
Rate and extent of excretion	Rapid (approx. 80 % via urine and 12 % via feces over 48 h)
Metabolism in animals	Limited (hydroxylation at the 4-position of the phenyl ring followed by conjugation; cleavage of the triazine ring and degradation to sulfonamide and sulfonate)
Toxicologically significant compounds (animals, plants and environment)	Parent compound and metabolites (especially AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine).

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral (N12)		4700 mg/kg bw
Rat LD_{50} oral**		> 200 < 2000 mg/kg bw
Rat LD_{50} dermal	(N12)	> 2000 mg/kg bw
Rat LC_{50} inhalation	(N12)	> 5.4 mg/l air (dust aerosol, 4 h,)
Skin irritation	(N12)	Not irritating
Eye irritation	(N12)	Not irritating
Skin sensitisation (test method used and result) (N12)		Sensitising (M&K test) **R43**

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect		Liver, kidney/centrilobular hypertrophy, nephropathy
Lowest relevant oral NOAEL/NOEL	(N14)	90-day, rat: 1000 ppm (75 mg/kg bw/d)
Lowest relevant oral overall NOAEL/NOEL* (N24)		90-day & 12-month, dog: 500 ppm (15 mg/kg bw/d) AMTT: 0.37 mg/kg bw/d
Lowest relevant dermal NOAEL/NOEL*	(N24)	28-day, rat: 1000 mg/kg bw
Lowest relevant inhalation NOAEL / NOEL		No data-not necessary

Genotoxicity* (Annex IIA, point 5.4)

(N24)	No evidence of genotoxic potential

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target / critical effect		Kidney, liver/interstitial nephritis, pericholangitis
Lowest relevant NOAEL / NOEL	(N34-59)	2-year, rat: 1000 ppm (48 mg/kg bw/d)
Lowest relevant NOAEL / NOEL*	(N24)	2-year, rat: 100 ppm (5 mg/kg bw/d) AMTT: 0.123 mg/kg bw/d
Carcinogenicity	(N34-59)	No evidence of a carcinogenic potential
Carcinogenicity*	(N24)	Mammary gland tumours in rats

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	(N34)	Lower bw gain, increased incidence of dilated renal pelves
Reproduction target / critical effect*	(N24)	Pup mortality in absence of maternal toxicity
Lowest relevant reproductive NOAEL / NOEL (N34)		2-gen. rat: 600 ppm (40 mg/kg bw/d)
Lowest relevant reproductive NOAEL / NOEL* (N24)		2-gen. rat: 25 ppm (2.4 mg/kg bw/d, premating period) AMTT: 0.06 mg/kg bw/d
Developmental target / critical effect (N12/N14)		Slightly increased incidences of hydrourethers in combination with renal pelves dilatation (rat) and of accessory 13t^{h} rib(s) (rabbits). Tritosulfuron is not teratogenic
Lowest relevant developmental NOAEL / NOEL	(N12/14)	120 mg/kg bw/d (rat) 150 mg/kg bw/d (rabbit)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

Acute oral and 90-day neurotoxicity*	(N24)	No signs of neurotoxicity
Developmental neurotoxicity	(N59)	No developmental neurotoxicity
Lowest relevant NOAEL for neurotoxicity*		90-day rat: 3500 ppm (243 mg/kg bw/d)

Other toxicological studies (Annex IIA, point 5.8)

Supplementary studies with metabolites: 635M02: LD50 oral rat: 1000 mg/kg bw (0.5 % Tylose CB 30.000 in aqua bidest); > 2000 mg/kg bw (olive oil); Ames test, CHO-HPRT test, in vitro chromosome aberration test: negative BH 635-3: LD50 oral rat: > 5000 mg/kg bw; subchronic study in rats: no effects; Ames test, CHO-HPRT test, in vitro chromosome aberration test: negative 635M01: LD50 oral rat: > 5000 mg/kg bw; Ames test, CHO-HPRT test, in vitro chromosome aberration test: negative Reg.-No. 373 906: LD50 oral rat: > 2000 mg/kg bw; Ames test, CHO-HPRT test, in vivo mouse micronucleus test: negative Supplementary studies with the impurity AMTT (635M04): Biokinetik and metabolism study in rats: rapid excretion, major metabolite AHTT (635M11); LD50 oral rat: > 200 < 2000 mg/kg bw; subchronic study with estrus cycle determination and hormone analysis in female rats: no changes in estrus cycle and hormone analysis parameters; Ames test, CHO-HPRT test, mouse micronucleus test: negative; pre-/postnatal screening toxicity study in rats: maternal and developmental toxicity at 20 and 50 mg/kg bw/d; Study of a possible bond of AMTT and tritosulfuron to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line: extremely low bonding capacity of tritosulfuron and AMTT to the estrogen receptor in the presence of endogenous estrogens

Medical data (Annex IIA, point 5.9)

Limited data (new compound); no human health problems reported

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI	0.5 mg/kg bw	2-gen. rat & 24-month rat	100
ADI**	0.0006 mg/kg bw	2-gen. rat	100
AOEL systemic	0.75 mg/kg bw/d	90-day rat	100
AOEL systemic**	Not allocated-	Not necessary	
ARfD	Not allocated-	Not necessary	
ARfD**	0.0006 mg/kg bw	2-gen. rat	100

Dermal absorption (Annex IIIA, point 7.3)

1% (in vivo rat, in vitro rat/human)

Acceptable exposure scenarios (including method of calculation)

Operator	Intended uses acceptable (operator exposure < systemic AOEL; German model and UK-POEM without PPE)
Workers	Intended uses acceptable
Bystanders	Intended uses acceptable

* batch no. N24 is containing 2.45 % AMTT
** AMTT

2.8.3.4 Appendix III.4: Chapter 4 (residues)

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	maize
Rotational crops	radish, lettuce, wheat
Plant residue definition for monitoring	tritosulfuron
Plant residue definition for risk assessment	tritosulfuron
Conversion factor (monitoring to risk assessment)	none

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	goat, hen
Animal residue definition for monitoring	tritosulfuron
Animal residue definition for risk assessment	tritosulfuron
Conversion factor (monitoring to risk assessment)	Not applicable
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	no

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

30, 120, 365 days plant back interval after application of 60 g as/ha to soil. The total radioactive residues were low for carrot root (≤ 0.011 mg/kg / parent: ≤ 0.001 mg/kg), green beans (≤ 0.005 mg/kg), lettuce head (≤ 0.022 mg/kg/ parent: ≤ 0.006 mg/kg) and wheat grain (≤ 0.019 mg/kg / parent: < 0.001 mg/kg)) after all 3 plant back intervals. In carrot foliage and bean plants only few samples showed residues of tritosulfuron slightly above 0.01 mg/kg. The metabolite AMTT (635M04) was detected in almost all samples of the triazine label but mostly at low absolute concentrations (< 0.01 mg/kg). Only after plant back intervals of 30 days in early samplings of bean plant and wheat forage and in wheat straw amounts in the range of 0.011 – 0.029 mg/kg were found.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

Food of plant origin (maize grain, maize forage, wheat grain, wheat straw, radish root): tritosulfuron was stable over a period of 3 years.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle Liver Kidney Fat Milk Eggs	No ruminant feeding study conducted	No hen feeding study conducted	No pig feeding study conducted. Metabolism in rat and ruminant similar

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
Summer barley	N	7 x < 0.01 mg/kg	grain	0.01 mg/kg	0
	S	5 x < 0.01 mg/kg			
Winter barley	N	11 x < 0.01 mg/kg	grain	0.01 mg/kg	0
	S	8 x < 0.01 mg/kg			
Summer wheat	N	3 x < 0.01 mg/kg	grain	0.01 mg/kg	0
Winter wheat	N	15 x < 0.01 mg/kg	grain	0.01 mg/kg	0
	S	10 x < 0.01 mg/kg			
Durum wheat	S	6 x < 0.01 mg/kg	grain	0.01 mg/kg	0
Winter rye	N	1 x < 0.01 mg/kg	grain	0.01 mg/kg	0
Maize	N	15 x < 0.01 mg/kg	grain	0.01 mg/kg	0
	S	21 x < 0.01 mg/kg			

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x < 0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.5 mg/kg bw/d for tritosulfuron with max 0.02 % AMTT
TMDI (European Diet) (% ADI)	0.07 % (German diet) / 0.04 % (WHO diet)
NEDI (% ADI)	not calculated
Factors included in NEDI	-
ARfD	Not assigned
Acute exposure (% ARfD)	Not applicable

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studies	Transfer factor	% Transference *
Not conducted			

* Calculated on the basis of distribution in the different portions, parts or products as determined through balance studies

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

barley, oats, maize, rye, triticale, wheat	0.01 mg/kg

2.8.3.5 Appendix III.5: Chapter 5 (fate and behaviour in the environment)

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralisation after 100 days	5 % after 90 d, (21 % after 358 d), triazine label 0 % after 91 d (< 3 % after 358 d), phenyl label 0 % after 122 d, phenyl label
Non-extractable residues after 100 days	17-25 % after 90 d (both labels) 43 % after 358 d (phenyl label 28 % after 358 d (triazine label)
Relevant metabolites - name and/or code, % of applied (range and maximum)	635M01 max. 56 % after 60 d (n = 5) 635M03 max. 15 % after 120 d (n = 5) 635M02 max. 23 % after 118 d (n = 5) 635M04 (AMTT) max 6 % after 90 d (n = 1)

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation	tritosulfuron: 33 % (phenyl) and 24 % (triazine) remained after 120 d, bound residues 6 % major metabolites: 635M01 max. 53 % after 120 d 635M19 max. 16 % after 28 d
Soil photolysis	after 15 d: 78 - 81 % tritosulfuron remained, 3 - 5 % bound residues, < 1 % CO_2, no major metabolites (> 10 %)

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation: ModelMaker 3.0.3/3.0.4 (Cherwell Scientific Publishing Limited); TOPFIT pharmacokinetic analysis; Timme and Frehse, 1st order kinetics, DT_{50} of metabolites calculated from studies with tritosulfuron

Laboratory studies (range or median, with n value, with r^2 value): DT_{50lab} (20 °C, aerobic) in days:

soil	as	635M01	635M02	635M03	635M04
Li35b	31/32	110/184	96	347/737	98
Lufa2.2	16	65	37	203	nc
US-soil	19	59	44	32	nc
Bruch	38	23	28	nc	nc
Canad.	(124)	44	nc	nc	nc
Speyer	20	115	nc	nc	nc
mean	26	86	51	330	-
r^2 (low)	0.970	0.886	0.900	0.893	0.962
r^2 (high)	0.997	0.979	0.951	0.977	-

tritosulfuron: DT_{90lab} (20°C, aerobic): 53 - 125 d (409 d)

tritosulfuron: DT_{50lab} (10°C, aerobic, calc.): 42 - 271 d

tritosulfuron: DT_{50lab} (20°C, anaerobic): 61 - 82 d

degradation in the saturated zone: not relevant

Field studies (state location, range or median with n value)	DT_{50f}: 10 locations (3 Germany, 2 Spain, Sweden, California, South Dakota, Indiana, Texas) method of calculation: EU: 1st order, USA: non-linear tritosulfuron: EU: 11 - 21 d, USA: 3 - 15 d 635M01: EU: 30 - 336 d, USA: 65 - > 621 d 635M02: EU: 36 - 216 d, USA: 76 - > 614 d 635M03: EU: nc, USA: 53 - > 417 d 635M04 (AMTT): EU: 11 - 133 d, USA: 5 - 69 d
	tritosulfuron DT_{90f}: EU: 37 - 77 d
Soil accumulation and plateau concentration	based on degradation studies, no accumulation is expected

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} K_d	soils: 5 German, 2 US

	Koc	(mean)	K_F	1/n
tritosulfuron	4 - 11	(7)	0.04 – 0.16	0.76 - 0.98
635M01	18 – 184	(89)	0.32 – 1.47	0.90 - 0.96
635M02	16 – 79	(40)	0.18 – 0.52	0.92 - 0.98
635M03	18 – 51	(30)	0.11 – 0.42	0.85 - 0.97
635M04	8 – 57	(21)	0.1 – 0.29	0.90 - 0.98

pH dependence (yes / no) (if yes type of dependence)	yes, decreasing sorption with increasing pH

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching	guideline: BBA IV, 4-2 precipitation: 200 mm in 2 days 86 % in leachate (all unchanged tritosulfuron)
Aged residues leaching	guideline: BBA IV, 4-2 precipitation: 200 mm in 2 days, aeging 30 d 40 % in leachate (mostly unchanged tritosulfuron)
Lysimeter/ field leaching studies	5 lysimeters, location: Limburgerhof, RP, Germany application: 50 g (^{14}C-phenyl) as/ha in spring, 1st year (lys 5, 6, 16, 17), 1st + 2nd year (lys 18) annual rainfall incl. add. irrigation (mm): 802 - 836 annual leachate volume (l): 200 - 487 annual average concentrations (highest concentration during the study) [µg/l]:

	lys 5	lys 6	lys 16	lys 17	lys 18
tritosulfuron	0.04	0.02	0.02	0.02	0.04
635M01	0.54	0.39	0.1	0.36	1.04
635M02	0.09	0.09	0.02	0.06	0.11
635M03	0.26	0.20	0.07	0.22	0.57
635M04*	<0.05	<0.05	<0.1	<0.05	<0.05
635M17	0.05	0.02	0.05	0.03	0.08
NIR	0.42	0.32	0.59	0.64	0.68
^{14}C (as-eq.)	1.44	1.22	0.75	1.13	2.50

* analysed by GC/MS, not possible to detect as ^{14}C, because of the labeling position

PEC (soil) (Annex IIIA, point 9.1.3)

Method of calculation	First order kinetics (with the worst case field half-life standardised to 15° C): tritosulfuron: 49 d, 635M01: 133 d, 635M02: 171 d, 635M03: 187 d, 635M04: 34 d Maximum amounts of metabolites formed in field studies (% of as): 635M01: 30 %, 635M02: 27 %, 635M03: 16 %, 635M04: 19 % 5 cm soil layer, bulk density of 1.5 kg/l
Application rate	Single application to maize and cereals tritosulfuron: 0.05 kg as/ha (no interception)

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application twa	Single application Actual	Single application twa	Single application Actual	Single application twa
		tritosulfuron		**635M01**		**635M02**	
Initial		0.067	0.067	0.020	0.020	0.018	0.018
Short term	24 h	0.066	0.066	0.020	0.020	0.018	0.018
	2 d	0.065	0.066	0.020	0.020	0.018	0.018
	4 d	0.063	0.065	0.020	0.020	0.018	0.018
Long term	7 d	0.060	0.063	0.019	0.020	0.017	0.018
	28 d	0.045	0.055	0.017	0.019	0.016	0.017
	50 d	0.033	0.048	0.015	0.018	0.015	0.016
	100 d	0.016	0.036	0.012	0.016	0.012	0.015

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application twa	Single application Actual	Single application twa
		635M03		**635M04 (AMTT)**	
Initial		0.011	0.011	0.013	0.013
Short term	24 h	0.011	0.011	0.012	0.013
	2 d	0.011	0.011	0.012	0.012
	4 d	0.011	0.011	0.012	0.012
Long term	7 d	0.010	0.011	0.011	0.012
	28 d	0.010	0.010	0.007	0.010
	50 d	0.009	0.010	0.005	0.008
	100 d	0.007	0.009	0.002	0.005

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	pH 4 (25 °C): tritosulfuron: 56 d (phenyl), 39 d (triazine) 635M01 (11 % after 35 d) 635M02 (26 % after 35 d) 635M04 (22 % after 31 d)
	pH 7 (25 °C): tritosulfuron : > 62 d 635M04 : no hydrolysis in sterile buffer at pH 6.5 and 7.5 and in natural water pH 8.1
	pH 9 (25 °C): tritosulfuron: 20 d (phenyl), 17 d (triazine) 635M01 (34 % after 31 d) 635M19 (28 % after 23 d)

Photolytic degradation of active substance and relevant metabolites		Suntest apparatus, 15 days continuous irradiation tritosulfuron: stable (15 d, 22 °C, pH 5 and 7) 635M01: sensitized water : DT_{50} = 3.6 d
Readily biodegradable (yes/no)		no
Degradation in water/sediment	- DT_{50} water	32 - 67 d
	- DT_{90} water	107 - n.c.
	- DT_{50} whole system	36 - 77 d
	- DT_{90} whole system	n.c.
Mineralization		≤ 5 % after 100 d
Non-extractable residues		< 5 % - 10 % after 100 d
Distribution in water / sediment systems (active substance)		sediment: max. 14 % after 14 d, max. 13 % after 28 d
Distribution in water / sediment systems (metabolites)	water: 635M01	max. 28.1 % after 100 d
	635M02	max. 15 % after 14 d
	635M03	max. 3.8 % after 100 d
	sediment: 635M01	max. 35 % after 100 d
	635M02	max. 0.9 % after 100 d
	635M03	max. 4.8 % after 100 d

PEC (surface water) (Annex IIIA, point 9.2.3)

Method of calculation	static water body, depth: 30 cm tritosulfuron: 1st order kinetics (67 d), metabolites: no degradation Maximum amounts of metabolites formed (% as): in water-sediment study (drift-entry): 635M01: 28 %, 635M02: 15 %, 635M04: not formed in w/s-study. Mean of maximum amounts of metabolites formed in field soil (runoff entry): 635M01: 14 %, 635M02: 15 %, 635M04: 12 % The PEC_{actual} are based on the worst case of the $PEC_{initial}$ calculated for spray drift and runoff events
Application rate	Single application of 0.050 kg as/ha to maize and cereals
Main routes of entry	**Spray Drift:** 2.77 % of the applied as (90th percentiles for field crops with 1 m buffer) **Runoff:** 0.5 % of the concentration (as) in soil at day 3 after application or 0.5 % of the max. concentrations of metabolites observed reach the water body with a volume of 130000 l. Interception of 25 % of the applic. rate and a dilution factor of 0.5 are considered for calculation.

PEC$_{(sw)}$	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
	tritosulfuron (drift entry)		**635M01 (drift entry)**	
Initial	0.46	0.46	0.103	0.103
Short term 24 h	0.46	0.46	0.103	0.103
2 d	0.45	0.46	0.103	0.103
4 d	0.44	0.45	0.103	0.103
Long term 7 d	0.43	0.45	0.103	0.103
14 d	0.40	0.43	0.103	0.103
21 d	0.37	0.41	0.103	0.103
28 d	0.35	0.40	0.103	0.103
42 d	0.30	0.37	0.103	0.103

PEC$_{(sw)}$	Single application Time weighted average	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
	635M02 (runoff)	**635M02 (drift)**	**635M04 (runoff)**	
Initial	0.055	0.034	0.039	0.039
Short term 24 h	0.055	0.034	0.039	0.039
2 d	0.055	0.034	0.039	0.039
4 d	0.055	0.034	0.039	0.039
Long term 7 d	0.055	0.034	0.039	0.039
14 d	0.055	0.034	0.039	0.039
21 d	0.055	0.034	0.039	0.039
28 d	0.055	0.034	0.039	0.039
42 d	0.055	0.034	0.039	0.039

PEC (sediment)

Method of calculation	sediment: 2 cm layer, 1.3 kg/l bulk density (wet sediment), entry route as for surface water (drift and runoff), pattern of decline reflecting that measured in the water sediment study.
Application rate	Single application of 0.050 kg as/ha to maize and cereals

PEC$_{(sed)}$ [mg/kg]	tritosulfuron drift (1 m buffer)	635M01 drift (1 m buffer)
maximum PEC_{sed}	0.00066 at day 28	0.00042 at day 100

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	lysimeter studies and modelling using FOCUS-PELMO v.1.1.1 (all locations) and MACRO FOCUS v1.2.1 (Chateaudun)
Application rate	0.05 kg as/ ha
PEC$_{(gw)}$	
Maximum concentration	lysimeter: tritosulfuron: 0.07 µg/l 635M01: 1.24 µg/l 635M02: 0.18 µg/l 635M03: 0.91 µg/l 635M04: 0.09 µg/l 635M17 0.17 µg/l modelling: not calculated
Average annual concentration	lysimeter: tritosulfuron: 0.04 µg/l 635M01: 1.04 µg/l 635M02: 0.11 µg/l 635M03: 0.57 µg/l 635M04: < 0.1 µg/l 635M17: 0.08 µg/l modelling: see below

Method of calculation and type of study	Modelling using FOCUS-PELMO v.1.1.1
Application rate	0.05 kg as/ ha to winter cereals in early spring with 50 % interception

Location	Application time	Predicted 80th percentile concentration (µg/l)				
		tritosulfuron	635M01	635M02	635M03	635M04
Châteaudun	01/04	0.008	0.01	0.156	0.097	0.001
Hamburg	01/04	0.066	0.040	0.218	0.166	0.008
Jokionen	01/06	0.082	0.018	0.216	0.129	0.008
Kremsmünster	01/04	0.079	0.059	0.207	0.153	0.014
Okehampton	01/04	0.089	0.067	0.189	0.152	0.014
Piacenza	01/04	0.074	0.071	0.232	0.178	0.009
Porto	10/03	0.006	0.002	0.058	0.032	0.001
Sevilla	10/03	0.000	0.000	0.007	0.002	0.000
Thiva	10/03	0.000	0.001	0.105	0.053	0.000

Method of calculation and type of study	Modelling using FOCUS-PELMO v1.1.1
Application rate	0.05 kg as/ ha to spring cereals 3 weeks after emergence with 25 % interception

Location	Application time	Predicted 80th percentile concentration (µg/l)				
		tritosulfuron	635M01	635M02	635M03	635M04
Châteaudun	31/03	0.004	0.006	0.179	0.097	0.001
Hamburg	22/04	0.063	0.046	0.324	0.237	0.009
Jokionen	01/06	0.143	0.018	0.296	0.166	0.009
Kremsmünster	22/04	0.075	0.065	0.305	0.213	0.011
Okehampton	22/04	0.099	0.064	0.309	0.224	0.017
Porto	31/03	0.002	0.001	0.060	0.025	0.000

Method of calculation and type of study	Modelling using FOCUS-PELMO v1.1.1
Application rate	0.05 kg as/ ha to maize 3 weeks after emergence with 25 % interception

Location	Application time	Predicted 80th percentile concentration (µg/l)				
		tritosulfuron	635M01	635M02	635M03	635M04
Châteaudun*	22/05	0.015	0.012	0.212	0.124	0.002
Hamburg	26/05	0.084	0.048	0.347	0.240	0.013
Kremsmünster	26/05	0.050	0.033	0.273	0.183	0.006
Okehampton	15/06	0.083	0.050	0.298	0.223	0.011
Piacenza*	05/06	0.062	0.091	0.254	0.218	0.010
Porto	22/05	0.001	0.000	0.036	0.010	0.000
Sevilla*	28/03	0.000	0.000	0.000	0.000	0.000
Thiva*	11/05	0.000	0.000	0.060	0.023	0.000

*Scenarios with irrigation

Method of calculation and type of study	Modelling using MACRO FOCUS v1.2.1 Location: Chateaudun
Application rate	0.05 kg as/ ha to winter cereals in early spring (50 % interception), spring cereals 3 weeks after emergence (25 % interception), to maize 3 weeks after emergence (25 % interception)

Crop	Application time (julian days)	Predicted 80th percentile concentration (µg/l)	
		tritosulfuron	635M04 (AMTT)
Winter cereals	91	0.012	0.002
Spring cereals	90	0.017	0.003
Maize	144	0.064	0.009

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air	no data, not required
Quantum yield of direct phototransformation	< 1.05 x 10^{-4} (pH 5) < 2.23 x 10^{-4} (pH 7)
Photochemical oxidative degradation in air	calculation according to Atkinson (AOP, ver 1.51, Syracuse), DT_{50}: 5.2 h (12 h-day)
Volatilization	from plant surfaces: 3 % (24 h)
	from soil: 2 % (24 h)

PEC (air)

Method of calculation	not calculated due to low volatility and rapid photochemical oxidative degradation

$PEC_{(a)}$

Maximum concentration	not calculated

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	tritosulfuron and metabolites 635M01, 635M02 and 635M03 Metabolites 635M01, 635M02 and 635M03 show no biological activity. The ecotoxicological risk assessment 635M01, 635M02 and 635M03 is not yet finished. The toxicological relevance of 635M01 and 635M02 is open.

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	none
Surface water (indicate location and type of study)	none
Ground water (indicate location and type of study)	none
Air (indicate location and type of study)	none

2.8.3.6 Appendix III.6: Chapter 6 (effects on non-target species)

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals	LD_{50} = 4700 mg as/kg bw/d (rat) (batch no. N12)
Reproduction toxicity to mammals	NOAEL 600 mg as/kg diet (two-generation-test, rat) (batch no. N34)
Acute toxicity to birds	LD_{50} > 2000 mg as/kg bw/d (mallard duck, bobwhite quail) (batch no. N24)
Dietary toxicity to birds	LC_{50} > 5000 mg as/kg diet (mallard duck, bobwhite quail) (batch no. N24)
Reproductive toxicity to birds	NOAEL = 300 mg as/kg diet (one-generation-test, mallard duck) (batch no. N24)

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
0.05 kg as/ha	maize/cereals	herbivorous bird	acute	> 1429	10
0.05 kg as/ha	maize/cereals	herbivorous bird	subacute	111	10
0.05 kg as/ha	maize/cereals	herbivorous bird	long-term/ reproduction (one-generation-study)	53	5
0.05 kg as/ha	maize/cereals	insectivorous bird	acute	> 3448	10
0.05 kg as/ha	maize/cereals	insectivorous bird	short-term	431	10
0.05 kg as/ha	maize/cereals	insectivorous bird	long-term / reproduction (one-generation-study)	207	5
0.05 kg as/ha	maize/cereals	herbivorous mammal	acute	3357	10
0.05 kg as/ha	maize/cereals	herbivorous mammal	long-term/ reproduction (two-generation-study, rat)	107	5

Toxicity data for aquatic species (most sensitive species of each group)
(Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Laboratory tests				
C. carpio	active substance	acute	Mortality EC_{50}	> 100
L. macrochirus	"	"	Mortality EC_{50}	> 100
O. mykiss	"	"	Mortality EC_{50}	> 100
"	"	chronic	Mortality NOEC	21.5
"	"	"	Growth NOEC	21.5
"	"	"	Behaviour NOEC	21.5
D. magna	"	acute	Immobilization EC_{50}	> 100
"	"	chronic	Mortality NOEC	100
"	"	"	Growth NOEC	56
"	"	"	Reproduction NOEC	56
A. flos-aquae	"	chronic	Biomass EC_{50}	0.58
"	"	"	Growth EC_{50}	> 1
P. subcapitata	"	"	Biomass EC_{50}	0.23
"	"	"	Growth EC_{50}	1.09
L. gibba	"	"	Biomass EC_{50}	0.0255
"	"	"	Growth EC_{50}	0.0476
P. putida	"	acute	Growth EC_{50}	> 10000
B. rerio	635M04 (BH 635-5, AMTT, Metab.)	"	Mortality EC_{50}	170
O. mykiss	635M02 (BH 635-2, Metab.)	"	Mortality EC_{50}	> 100
D. magna	"	"	Mortality EC_{50}	> 100
P. subcapitata	"	chronic	Biomass EC_{50}	> 100
"	"	"	Growth EC_{50}	> 100
O. mykiss	635M03 (BH 635-3, Metab.)	acute	Mortality EC_{50}	> 100
D. magna	"	"	Mortality EC_{50}	> 100
P. subcapitata	"	chronic	Biomass EC_{50}	> 100
"	"	"	Growth EC_{50}	> 100
O. mykiss	635M01 (BH 635-4, Metab.)	acute	Mortality EC_{50}	> 100
D. magna	"	"	Mortality EC_{50}	> 100
P. subcapitata	"	chronic	Biomass EC_{50}	> 100
"	"	"	Growth EC_{50}	> 100
D. magna	635M04 (BH 635-5, Metab.)	"	Mortality EC_{50}	> 100
P. subcapitata	"	chronic	Biomass EC_{50}	> 100
"	"	"	Growth EC_{50}	> 100

O. mykiss	BAS 635 00 H	acute	Mortality EC_{50}	> 114
D. magna	"	"	Mortality EC_{50}	> 100
P. subcapitata	"	chronic	Biomass EC_{50}	0.42
"	"	"	Growth EC_{50}	2.71
O. mykiss	70 g BAS 635 00 H + 1.5 L BAS 15200 S	acute	Mortality EC_{50}	> 100
D. magna	"	"	Mortality EC_{50}	> 100
L. gibba	"	chronic	Fronds EC_{50}	0.0355
"	"	"	Growth EC_{50}	0.0618
Microcosm or mesocosm tests				

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Application Rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.05	field crop	*L. gibba*	chronic	0	1.5	10
"	"	"	"	1	54	10

Bioconcentration

Bioconcentration factor (BCF)	not relevant; logPow < 3
Annex VI Trigger for the bioconcentration factor	
Clearance time (CT_{50}) (CT_{90})	
Level of residues (%) in organisms after the 14 day depuration phase	

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity	LD_{50} = 200 µg/bee (active substance) LD_{50} = 121.62 µg/bee (formulation: BAS 63500 H + BAS 15200 S)
Acute contact toxicity	LD_{50} = 200 µg/bee (active substance) LD_{50} = > 100 µg/bee (formulation: BAS 63500 H + BAS 15200 S)

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests (active substance)				
0.05	maize, cereals	oral	0.25	50
0.05	maize, cereals	contact	0.25	50
Laboratory tests (formulation: BAS 635 00 H + BAS 15200 S)				
0.05	maize, cereals	oral	0.41	50
0.05	maize, cereals	contact	0.5	50

Field or semi-field tests
Not required

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect (%)	Annex VI Trigger
Laboratory tests						
T. pyri	protonymphs	BAS 635 00 H + BAS 152 00 S	0.002-0.05	mortality fertility	LR_{50}: 28.6 g as/ha	30
T. pyri (natural substrate)	protonymphs	"	0.05	mortality fertility	0 3.6	30
A. rhopalos.	imagines	"	0.150	mortality parasitation capacity	10 30	30
C. carnea	larvae	"	0.05	mortality fertility	0 0 (+ 11)	30
P. cupreus	imagines	"	0.05	mortality food uptake	0 0	30
A. bilineata	imagines	"	0.05	parasitation capacity	14	30
Pardosa sp.	adult	"	0.05	mortality food uptake	0 0 (+ 23)	30

Field or semi-field tests
Not required

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity	LC_{50} > 1000 mg as/kg (technical tritosulfuron) LC_{50} > 1000 mg/kg (metabolite 635M02 (BH 635-2)) LC_{50} > 1000 mg/kg (metabolite 635M03 (BH 635-3)) LC_{50} > 1000 mg/kg (metabolite 635M01 (BH 635-4)) LC_{50} = 671 mg/kg (metabolite 635M04 (BH 635-5)) LC_{50} > 34.2 mg as/kg (formulation BAS 635 00 H + BAS 152 00 S)
Reproductive toxicity	-

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
0.05	maize, cereals	Acute	> 510	10

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralisation	No effects > 25 % up to 0.35 kg BAS 635 00 H + 6.25 L BAS 152 00 S
Carbon mineralisation	No effects > 25 % up to 0.35 kg BAS 635 00 H + 6.25 L BAS 152 00 S

Effects on terrestrial non-target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Greenhouse test	*Brassica napus* (most sensitive species): ED_{50} 4.3 g BAS 635 00 H + 76.4 ml BAS 152 00 S
Field test	*Brassica napus* (most sensitive species): ED_{50} 8.7 g BAS 635 00 H + 126 ml BAS 152 00 S

Toxicity/exposure ratios for terrestrial non-target plants (Annex IIIA, point 10.8)

Distance from treated area (m)	Drift (%)	Amount of drift (g product/ha)	TER lab. (*Brassica napus*, ED_{50} 4.3 g/ha)	TER field (*Brassica napus*, ED_{50} 8.7 g/ha)
1	2.77	1.94	2.2	4.5
5	0.57	0.399	10.8	21.8

Level 3

Tritosulfuron

Proposal for the Decision

3 Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

Tritosulfuron, 1-(4-methoxy-6-trifluoromethyl-1,3,5-triazin-2-yl)-3-(2-trifluoromethyl-benzenesulfonyl)urea (IUPAC), as a sulfonylurea is a herbicidal active substance. It is intended to be used in agriculture. The formulated product is a water dispersible granules (WG) containing 714 g/kg tritosulfuron.

It is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in cereals (winter and spring wheat, winter and spring barley, winter rye, oats, triticale) and maize. Only weeds which have emerged at the time of application will be controlled. Optimum timing is when weeds are still small and have not begun to compete with the crop.

Analytical methodology is available for the determination of the active substance and the impurities in the technical material as manufactured and for the active substance in the formulation. The methods are fully validated.

Residues of the as can be determined by LC-UV or MS/MS in all matrices. For soil and water also GC-MS methods are available.

The metabolism and distribution of tritosulfuron was investigated in maize. In most samples tritosulfuron was the main component. The metabolite AMTT (635M04) was not detected in the maize metabolism study. Therefore, parent only is included in the residue definition.
The metabolism of tritosulfuron was investigated in lactating goats and laying hens. The parent compound was detected at significant proportions in all matrices, even though it occurred at very little absolute residue levels. With focus on the metabolite AMTT (635M04), it can be assumed that this compound would be present in animal matrices at levels below 0.001 mg/kg after feed up-take with realistic residues and therefore, it would not be detected by any residue analytical method. The residue definition for food of animal origin is proposed as parent compound only.
The residue situation for the intended uses of tritosulfuron in cereals and maize is covered by a sufficient number of residue trials. No residues above the LOQ are to be expected in grain of cereals and maize. There appears to be no chronic dietary consumer risk for tritosulfuron with a maximum content of 0.02 % AMTT.

The available data on mammalian toxicology, mutagenicity and animal metabolism are considered to adequately support the risk evaluation of tritosulfuron in humans.
Concerning toxicology and metabolism all studies required by Directive 91/414/EEC are available and were conducted according to Guideline requirements under Good Laboratory Practice regulations.
In the course of toxicity testing for tritosulfuron different batches containing different impurities were used. In the long-term and the 2-generation studies which were conducted with a batch containing high quantities of AMTT severe effects were observed, including mammary gland tumors and a high pup mortality in rats, respectively. The studies were repeated with batches containing lower levels of AMTT. These studies did not show the effects observed before, with regard to mammary gland tumors and pup mortality. Therefore, it might be considered that AMTT was responsible for these effects.

Laboratory and field test indicate that tritosulfuron is not stable in the environment. There is no potential for accumulation of tritosulfuron in soil or water/sediment. Both parent as well as soil metabolites are potentially mobile in soil according to results of column leaching studies. The results of subsequent lysimeter studies clearly showed, that there was no substantial displacement of the active substance into deeper soil layers or ground water. The concentrations of the active substance found in the leachates were clearly below 0.1 µg/l. Three metabolites (635M01, 635M02 and 635M03) exceeded the concentration of 0.1 µg/l in yearly average. Metabolite 635M04 (AMTT) was detected in only one out of 26 leachate sample at a concentration of < 0.1 µg/l. Calculations with simulations models confirmed the results of the lysimeter study. The assessment of the leaching potential of tritosulfuron and metabolites on soils with high pH values is not yet finished. The metabolites 635M01, 635M02 and 635M03 show no biological activity. The toxicological relevance of 635M01 and 635M02 in groundwater and the final ecotoxicological risk assessment of 635M01, 635M02 and 635M03 in soil and of metabolite 635M01 in surface water is still open.

According to the recommended use pattern risk to terrestrial vertebrates (birds and mammals), bees and other non-target arthropods, soil micro-organisms, non-target higher terrestrial plants, and biological methods of sewage treatments is considered to be low.

According to the low P_{ow}-value there is no risk concerning the accumulation of the active substance in food chain.

A first risk assessment was conducted to effects on earthworms and aquatic organisms. Low risk for these organisms have been concluded yet. However, for final risk assessment further studies have to be submitted.

3.2 Proposed decision concerning inclusion in Annex I

Concerning the submitted data a postponement of the inclusion of the active substance tritosulfuron in Annex l of Directive 91/414/EEC is recommended pending submission and evaluation of further information about the leaching behaviour in soils with a high pH value, effects on aquatic and non-target terrestrial organisms and the toxicological relevance of metabolites 635M01 and 635M02 in groundwater.

Concerning ”Toxicology and Metabolism” and ”Ecotoxicology”, the Annex I inclusion is only supported for technical tritosulfuron with a specified AMTT content of ≤ 0.02 % (as impurity).

3.3 Rational for the postponement of the decision to include the active substance in Annex I, or for the conditions and restrictions to be associated with a proposed inclusion in Annex I, as appropriate

Data should be submitted for the evaluation of the leaching potential of tritosulfuron and metabolites in soils with a high value.
Data on the effects of the metabolite 635M01 (BH 635-4) on a higher aquatic plant and the metabolites 635M02 (BH 635-2), 635M03 (BH 635-3), and 635M01 (BH 635-4) on earthworm reproduction should be submitted for risk assessment.
Further data is required for the assessment of the toxicological relevance of metabolites 635M01 and 635M02 in groundwater.

Level 4

Tritosulfuron

Demand for Further Information

4 Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in Annex I

4.1 Data which are necessary for an unrestricted inclusion in Annex I of Council Directive 91/414/EEC

Identity of the active substance
None.

Physical and chemical properties of the active substance
None.

Data on application and further information
Data on application
None.

Further information
None.

Classification and labelling
None.

Methods of analysis
Analytical methods for formulation analysis
None.

Analytical methods for residue analysis
None.

Toxicology and metabolism
With reference to the Draft working document "Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances regulated under council directive 91/414 EEC" (Sanco/221/2000, presently rev. 7, 7th March 2002), for evaluation of the toxicological relevance of the metabolites 635M01 and 635M02 the following studies are required in addition to the already submitted studies:

- Repeat-dose oral toxicity studies in rats of at least 28 days of duration each and at least 10 animals/sex/group (investigation parameters according to a 90-day oral toxicity study in rodents / revised OECD guideline 408). Dose levels selected should be based on the dose levels tested in the most relevant short-term studies with the parent compound.

Residue data
None.

Environmental fate and behaviour
None.

Ecotoxicology
Annex II, point 8.2.8:
Test with the metabolite 635M01 (BH 635-4) on higher aquatic plants.

Justification:
Lemna is the most sensitive organism in the tests with the active substance. Data on higher aquatic plants for the metabolite 635M01 (BH 635-4) were not submitted.

Annex IIA, point 8.4.2:
Tests on effects of the metabolites 635M02 (BH 635-2), 635M03 (BH 635-3) and 635M01 (BH 635-4) on reproduction of earthworms.

Justification:
Slow degradation of metabolites 635M02 (BH 635-2), 635M03 (BH 635-3) and 635M01 (BH 635-4) in soil.

4.2 Data which should be submitted for an assessment on Member State level

Identity of the active substance
Annex IIA, point 1.10:
The IUPAC name of the impurities must be given.

Physical and chemical properties of the active substance
None.

Data on application and further information
Data on application
None.

Further information
None.

Classification and labelling
None.

Methods of analysis
Analytical methods for formulation analysis
None.

Analytical methods for residue analysis
Annex IIA, point 4.2.1:
In the proposed enforcement method for plant material (method 405/1, Sasturain, 2001) is stated for the extraction step, that if the recovery is low, 5 ml of the buffer solution must be added prior extraction. Clarification is needed for the cases where unknown samples will be analysed.

Annex IIA, point 4.2.1:
In the ILV (IF-97-22870-00, Schulz, 1999) is stated that in the clean up procedure in the phase partitioning at acidic conditions ethyl acetate is used instead of *i*-octane for grain samples. A clarification is needed, because the different polarity of these two solvents.

Annex IIA, point 4.2.1:
Figures of the relevant mass spectra are missing in the methods using the LC-MS/MS technology.

Annex IIA, point 4.2.1:
Figures of the relevant mass spectra are missing in the methods using the GC-MS technology.

Annex IIA, point 4.2.1:
Validation data for crops with high water and high acid content are missing.
Justification:
According to the guidance document SANCO/825/00 validation data for all four mentioned crop groups must be submitted, in the case that the use is not restricted to one of them.

Toxicology and metabolism
Specification of batch and purity of the test substances (Reg.-No. 231 700 and Reg.-No. 271 272) used in the study “Vollmer G. 2000; Study of a possible bond of AMTT and tritosulfuron to the estrogen receptor ... "(BASF RegDoc#2000/1019272).

Residue data
Submission of the results of the storage stability study for the metabolite AMTT after finalisation.

Environmental fate and behaviour
None.

Ecotoxicology
None.

Monograph

20 August 2002

Tritosulfuron

Volume 2

Annex A

List of Tests and Studies

Rapporteur Member State: Germany

Contents

A.1 Identity (Annex IIA 1, 3.1 to 3.4; Annex IIIA 1, 3.1 to 3.7, 3.9 and 12.1)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[1]
Fietz, G.	AIIA-1.11	1998	Characterization of BAS 635 H Batch N34 by HPLC-Method CP 217. BASF DocID 1998/1001137 GLP, unpublished CHE2001-562	Y	BAS
Guentner, A.	AIIA-1.11	1998	Determination of the total N-Nitrosamine content and the content of Flouride, Bromide, Sulfate, Phosphate, Nitrite, Nitrat and Chloride in "BAS 635 H". BASF DocID 2001/1003843 GLP, unpublished CHE2001-568	Y	BAS
Hassink, J.	AIIA-1.8	2001	Tritosulfuron TC Description of the Manufacturing Process. BASF DocID 2001/1003807 not GLP, unpublished CHE2001-560	Y	BAS
Hassink, J.	AIIA-1.9	2001	Tritosulfuron TC Composition of the Technical Active Ingredient. BASF DocID 2001/1003808 not GLP, unpublished CHE2001-561	Y	BAS
Hassink, J.	AIIA-1.11	2000	Characterization of BAS 635 H Batch N 59 by HPLC-Method CP 217 (AI) and CP300 (By-products). BASF DocID 2000/1018876 GLP, unpublished CHE2001-567	Y	BAS
Hassink, J.	AIIA-1.11	2000	Determination of technical impurities in BAS 635 H Batch N 53 by HPLG-Method CP300. BASF DocID 2000/1018874 GLP, unpublished CHE2001-565	Y	BAS
Hassink, J.	AIIA-1.11	2000	Reanalysis of BAS 635 H Batch N 53 by HPLC-Method CP217. BASF DocID 2000/1018875 GLP, unpublished CHE2001-566	Y	BAS

[1] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[1]
Hassink, J.	AIIA-1.11	1998	Characterization of BAS 635 H (Reg.No. 271272), Batch N42 by HPLC-Method CP 217, Determination of Technical Impurities (HPLC-Method CP 300) and Water. BASF DocID 1998/1001139 GLP, unpublished CHE2001-564	Y	BAS
Hassink, J.	AIIA-1.11	1998	Determination of Technical impurities in TGAI BAS 635 H (Reg. No. 271272) Batch N34 by HPLC-Method CP 300. BASF DocID 1998/1001138 GLP, unpublished CHE2001-563	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

A.2 Physical and chemical properties (Annex IIA 2; Annex IIIA 2)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
Daum, A.	AIIA-2.6	2001	Determination of the solubility in water of Tritosulfuron (BAS 635 H, Reg.No.271272). 2001/1001015 GLP, unpublished CHE2001-500	Y	BAS
Daum, A.	AIIA-2.5	2000	UV-, NMR-,IR-, MS-Spectra of Tritosulfuron PAI (BAS 635 H, Reg. No.271272. 2000/1018472 GLP, unpublished CHE2001-499	Y	BAS
Kaestel, R.	AIIA-2.1.1; AIIA-2.2; AIIA-2.4; AIIA-2.12; AIIA-2.14	1996	Physical and chemical properties Report for 271 272. 96/10136 GLP, unpublished CHE2001-497	Y	BAS
Kaestel, R.	AIIA-2.2	1994	Physical and chemical properties Report for 271 272. 94/10728 GLP, unpublished CHE2001-498	Y	BAS
Kaestel, R.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-4.1	1998	Shelf Life in Original Container of BAS 635 00 H Physical Properties Report [24 month-storage]. 98/10679 GLP, unpublished PHY2001-611	Y	BAS
Kaestel, R.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-2.8.8	1997	Physical and chemical properties Report for BAS 635 00 H. 97/10398 GLP, unpublished PHY2001-607	Y	BAS

[2] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
Kaestel, R.	AIIIA-2.7	2000	Accelerated Storage Stability of BAS 635 00 H Final Report. 2000/1000089 GLP, unpublished PHY2001-609	Y	BAS
Kaestel R.	AIIA-2.3.1	1994	Physical and chemical properties. 1994/10728 GLP, unpublished LUF2001-191	Y	BAS
Koenig, W.	AIIIA-2.7	1998	Storage Stability in Original Container of BAS 635 00 H 24 month-storage; Analytical Results. 98/10855 GLP, unpublished PHY2001-610	Y	BAS
Kroehl, T.	AIIA-2.14	2001	Determination of the Surface Tension (Ring-/Plate-Method). 2001/1010679 not GLP, unpublished CHE2001-504	Y	BAS
Kröhl, T.	AIIA-2.3.1	2001	Method of determining the vapor pressure, CF-P 006. 2001/1010678 not GLP, unpublished LUF2001-192	Y	BAS
Loeffler, U.	AIIA-2.11.1; AIIA-2.11.2; AIIA-2.13; AIIA-2.15	1996	Safety characteristics of the active ingredient 271 272. 96/10135 GLP, unpublished CHE2001-503	Y	BAS
Loeffler, U.	AIIIA-2.2; AIIIA-2.3	1996	Safety characteristics of the crop protection product BAS 635 00 H. 96/11117 GLP, unpublished PHY2001-608	Y	BAS
Ohnsorge U.	AIIA-2.3.2; AIIA-7.2.2	2000	Physical and chemical properties (Henry's law constant). 2000/1013447 not GLP, unpublished LUF2001-188	Y	BAS
Scharf J.	AIIA-2.9.2; AIIA-2.9.3; AIIA-7.2.1.2	1998	Aqueous photolysis of BAS 635 H at pH 5 and pH 7. 1998/10981 GLP, unpublished LUF2001-186	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
Scharf J.	AIIA-2.10; AIIA-7.2.2	1995	Photochemical oxidative degradation of BAS 635 H. 1995/11094 not GLP, unpublished LUF2001-190	Y	BAS
Scharf J.	AIIA-2.10; AIIA-7.2.2	1998	Laboratory study on the volatilization of BAS 635 H after application of BAS 635 00 H on soil and plant surfaces. 1998/10982 GLP, unpublished LUF2001-189	Y	BAS
Schneider, K.-H.	AIIIA-2.9	1999	Physical and Chemical Compatibility in Aqueous Tank Mixtures of BAS 635 00 H + BAS 152 00 S. 1999/1005345 not GLP, unpublished PHY2002-73	Y	BAS
Schneider, K.-H.	AIIIA-2.9	2001	Physical and Chemical Compatibility in Aqueous Tank Mixtures of BAS 635 00 H + BAS 152 00 S with other products. 2001/1001033 not GLP, unpublished PHY2001-612	Y	BAS
Singh M.	AIIA-2.9.1; AIIA-7.2.1.1	1997	Hydrolysis of 14C-BAS 635 H (triazine label) in aqueous media. 1996/5091 GLP, unpublished WAS2001-211	Y	BAS
Singh M.	AIIA-2.9.1; AIIA-7.2.1.1	1997	Hydrolysis of 14C-BAS 635 H (phenyl label) in aqueous media. 1996/5057 GLP, unpublished WAS2001-210	Y	BAS
Tuerk, W.	AIIA-2.7	1994	Determination of the solubility of Reg.-No. 271272 technical active ingredient (TAI) in organic solvents at 20°C. 94/11101 GLP, unpublished CHE2001-501	Y	BAS
Tuerk, W.	AIIA-2.8	1994	Determination of the Octanol/Water-partition Coefficient of Reg.No. 271272 by HPLC. 94/10658 GLP, unpublished CHE2001-502	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
Tuerk, W.	AIIA-2.1.1; AIIA-2.1.3; AIIA-2.4	1994	Determination of the appearance, the melting point and thermal conversions of Reg.-No. 271272 (PAI). 94/11228 GLP, unpublished CHE2001-496	Y	BAS
Tuerk W.	AIIA-2.9.4	1994	Determination of the pKa of Reg.No. 271272 in water at 20°C. 1994/10525 GLP, unpublished WAS2001-216	Y	BAS

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A.3 Further information (Annex IIA 3; Annex IIIA 3, 4 and 6)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[3]
Anonymous	AIIA-3.6	1999	Detecting herbicide resistance Guidelines for conducting diagnostic tests and interpreting results. HRAC. www.plantprotection.org/HRAC/detecting.html (2001-09-14), 1999 not GLP, published BIO2001-311	N	-
Anonymous	AIIA-3.6	2001	Herbicide Resistance Action Committee. Partnership in the management of resistance. HRAC. www.plantprotection.org/HRAC/Partnership.html(2001-09-14) not GLP, published BIO2001-310	N	-
Anonymous	AIIA-3.6	2001	Guideline to the management of herbicide resistance, HRAC guidelines. www.plantprotection.org/HRAC/Guideline.html(2001-09-14) not GLP, published BIO2001-309	N	-
Claude, J.-P., Cornes, D.	AIIA-3.6	1999	Status of ALS-Resistance in Europe (Poster). 11. EWRS Symposium, Basel, 1999, 1999 not GLP, published BIO2001-304	N	-
Devine, M. D., Preston, C.	AIIA-3.6	2000	The molecular basis of herbicide resistance. Sheffield Academic Press, England, Cobb, A. H., Kirkwood, R. C., Herbicides and their mechanism of action, 2000, 73-104 not GLP, published BIO2001-303	N	-
Gerlach, H.	AIIA-3.7	2001	Safety data sheet - BAS 635 H. 2001/1004138 not GLP, unpublished CHE2001-505	Y	BAS
Heap, I.	AIIA-3.6	2001	Herbicide resistant weed summary table (2001-01-08). www. weedre-search.com/Case/reference.asp(2001-09-14), 2001 not GLP, published BIO2001-306	N	-

[3] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[3]
Heap, I.	AIIA-3.6	2001	Herbicide resistant weed summary table (2001-01-08). www. weedre-search.com/summary/MOAsummary.asp(2001-09-14), 2001 not GLP, published BIO2001-305	N	-
Kaestel, R.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-4.1	1998	Shelf Life in Original Container of BAS 635 00 H Physical Properties Report [24 month-storage]. 98/10679 GLP, unpublished PHY2001-611	Y	BAS
Kudsk, P. et al.	AIIA-3.6	1995	Sulfunylurea resistance in Stellaria media L. Weed research, 35, 1995, 19-24 not GLP, published BIO2001-307	N	-
Powles, S. B., Preston, C.	AIIA-3.6	1995	Herbicide cross-resistance and multiple re-sistance in plants, Monograph 2, HRAC publi-cations. www.plantprotection.org/HRAC/mono2.html(2001-09-14), 1995 not GLP, published BIO2001-308	N	-
Schenk, W.	AIIA-3.9	2000	Possible Procedures of the Decontamination of Water from BAS 635 H. 2000/1013207 not GLP, unpublished CHE2001-506	Y	BAS
Stadler, R.	AIIIA-4.2	2001	"BAS 635 00 H" (Tritosulfuron); Effectiveness of Procedures for Cleaning Application E-quipment and Protective Clothing. 2001/1001640 not GLP, unpublished PHY2001-613	Y	BAS

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A.4 Classification, packaging and labelling (Annex IIA 10; Annex IIIA 12.3 and 12.4)

No references submitted.

A.5 Methods of analysis (Annex IIA 4; Annex IIIA 5)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
Benz, A. and Mackenroth, C.	AIIIA-5.2	2001	Validation of BASF Method No. 472/0: Determination of BAS 615 H and BH 615-3 in Cereal Forage, Grain and Straw Study Code 96355. 2001/1000994 GLP, unpublished MET2001-383	Y	BAS
Binski, C. and Perez, R.	AIIA-4.2.1	2000	Independent Method Validation of BASF Technical Procedure 405/1 (April 1998 Draft) for BAS 635 H Residues in Corn and Wheat Study No. 98052. 2000/5219 GLP, unpublished MET2001-374	Y	BAS
Dötzer, R.	AIIA-4.1	1994	Validation of HPLC method CP 217 for determination of BAS 635 H (Reg.No. 271 272) in BAS 635 H technical Laboratory Study Code: PCP03052. 1994/10405 GLP, unpublished CHE2002-12	Y	BAS
Dötzer, R.	AIIA-4.1	1994	Analytical method CP-No. 217: Determination of Reg.No. 271 271 (BAS 635 H) in technical Reg.No. 271 272 by HPLC. 1994/1000351 not GLP, unpublished CHE2002-11	Y	BAS
Grosshans, F.	AIIA-4.2.1	1998	The Validation of BASF Method 413/0: Determination of BAS 635 H (Reg. No. 271272) in Animal Matrices Study Code 19468. 98/10979 GLP, unpublished MET2001-375	Y	BAS
Hassink, J.	AIIA-4.1	2000	Additional analyses for statistical verification of analytical method CP 217. 2000/1018732 GLP, unpublished CHE2002-15	Y	BAS

[4] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
Hassink J.	AIIA-4.1	2001	Validation of analytical method CP 300: Determination of technical by-products in BASF technical grade BAS 635 H (Reg.No. 271 272). 2001/1001004 GLP, unpublished CHE2002-9	Y	BAS
Hassink J.	AIIA-4.1	2001	Analytical Method CP 300 Determination of by-products in technical BAS 635 H using HPLC. 2001/1001008 not GLP, unpublished CHE2002-7	Y	BAS
Jordan, J. and Malinsky, S.	AIIA-4.2.1	2001	Method Validation of BASF Analytical Method D0002 entitled "Method for the Determination of BH 635-5 (AMTT) 2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5 triazine Residues in Plant and Animal Matrices by GC/MS" Study No. 59280. 2001/5000983 GLP, unpublished MET2001-371	Y	BAS
Keller, W.	AIIA-4.2.2	1998	Validation of Analytical Method No. 390 Total Method for Determination of BAS 635 H Residues in Soil Study No. 24395. 98/10097 GLP, unpublished MET2001-377	Y	BAS
Malinsky, S.	AIIA-4.2.1	2000	Independent Method Validation of BASF Analytical Method No. 413/0: "Determination of BAS 635 H in Animal Matrices" at BASF Study No. 98127. 1999/5054 GLP, unpublished MET2001-376	Y	BAS
Richter, T.	AIIA-4.2.2	2001	Validation of Analytical Method 406/0 for the Determination of BAS 635 H and the following Metabolites in Soil: BH 635-2 (Reg.no. 292564), BH 635-3 (Reg.no. 335182), BH 635-4 (Reg.no. 335184) Study code 39262. 2000/1013299 GLP, unpublished MET2001-378	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
Richter, T.	AIIA-4.2.3	2001	Method 433/0; Validatiion of Analytical Method 433/0 for the determination of BAS 635 H (Reg.no. 271272), BH 635-2 (Reg.no. 292564), BH 635-3 (Reg.no. 335182), BH 635-4 (Reg.no. 335184) and BH 635-5 (reg.no.231700) in tap and surface water Study Code 37274. 2000/1013298 GLP, unpublished MET2001-381	Y	BAS
Sasturain, J.	AIIA-4.2.1; AIIIA-5.2	1999	Validation of BASF Method No. 438/0: Determination of Bentazon and its Metabolites 6-OH-Bentazon and 8-OH-Bentazon in Maize Matrices Study Code 59041. 99/11014 not GLP, unpublished MET2000-68	Y	BAS
Sasturain, J.	AIIIA-5.2	1999	Validation of BASF Method No. 444/0: Determination of Dicamba and its Metabolite 5-OH Dicamba in Maize Matrices Study Code 59649. 99/11013 not GLP, unpublished MET2001-384	Y	BAS
Sasturain, J.; Bross, M. and Mackenroth, C.	AIIA-4.2.1	2001	Validation of BASF Method No. 405/1: Method for the Determination of BAS 635 H (LAB 271 272) in Plant Matrices (Wheat, Maize) Study Code 19438. 2001/1000996 GLP, unpublished MET2001-369	Y	BAS
Schulz, H.	AIIA-4.2.1	1999	Determination of BAS 635 H in Wheat - Validation of the BASF Method No. 405/1 Study No. IF-97/22870-00. 99/11493 GLP, unpublished MET2001-373	Y	BAS
Smith, K. and Clouser-Roche, A.	AIIA-4.2.2	2001	Determination of BAS 635 H and Metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in Soil by LC/MS/MS Method No. D9907. 1999/5128 GLP, unpublished MET2001-379	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
Stewart, J.	AIIA-4.2.1	2001	Validation of BASF Method D0003/1: Analytical Method for Determination of Residues of BAS 635 H in Plant Matrices using LC/MS/MS Study No. 64186. 2001/5001043 GLP, unpublished MET2001-370	Y	BAS
Weeren, R. D. and Pelz, S.	AIIA-4.2.1	1998	Examination of the Applicability of DFG Method S19 for the Determination of BAS 635 H Final report BAS-9804V, Az. 67460/98. 98/11322 GLP, unpublished MET2001-372	Y	BAS
Zangmeister, W.	AIIA-4.2.4	1998	Validation of BASF Analytical Method 394 - Determination of BAS 635 H in Air by HPLC Study No. 24402. 98/10659 GLP, unpublished MET2001-382	Y	BAS
Ziegler, G.	AIIA-4.2.3	1998	Validation of Analytical Method No. 401 Total Method for the Determination of BAS 635 H (271 272) Residues and its Metabolites 292 564, 335 182 and 335 184 in Water Study Code 24398. 98/10663 GLP, unpublished MET2001-380	Y	BAS
Ziegler, H.	AIIIA-5.1	1999	Analytical Method CF-A 588: Quantitative determination of the substance Reg.No. 231700 in BAS 635 00 H by HPLC. 1999/1004107 not GLP, unpublished CHE2002-18	Y	BAS
Ziegler, H.	AIIIA-5.1	2000	Development and validation of the analytical method CF-A 588: Determination of Reg.No. 231 700 in water dispersible granules (BAS 635 00 H). 2000/1000323 GLP, unpublished CHE2002-19	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
Ziegler, H.	AIIIA-5.1	1998	Validation of the analytical method CF-A 506/1: Determination of Reg.No. 271 272 in water dispersible granules (BAS 635 00 H). 1998/10813 GLP, unpublished CHE2002-17	Y	BAS
Ziegler, H.	AIIIA-5.1	1997	Analytical Method CF-A 506/1: Quantitative determination of active ingredient Reg.No. 271 272 in BAS 635 00 by HPLC. 1997/1000591 not GLP, unpublished CHE2002-16	Y	BAS

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A.6 Toxicology and metabolism (Annex IIA 5; Annex IIIA 7)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Anonym	AIIIA-7.2.3.1	1998	Policy # 003 - Science advisory council for exposure - Regarding: Agricultural default transfer coefficients. United States Environmental Protection Agency, 1998 #BASF 98/11675 not GLP, published TOX2001-891	N	-
Cotton, H.	AIIA-5.1	2001	(14C)-BAS 635 H: Rates of penetration through rat and human skin using an in vitro system. 729/206 ! 2001/1006076 GLP, unpublished TOX2001-896	Y	BAS
Czich, A.	AIIA-5.8.1	1999	In vitro chromosome aberration assay in Chinese hamster V79 cells with reg. no. 335 182 (BH 635-3). 633600 ! 32M0576/969428 ! #BASF 99/11504 GLP, unpublished TOX2001-944	Y	BAS
Engelhardt, G.	AIIA-5.8.1	2001	Amendment no. 3 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 2001/1007726 GLP, unpublished TOX2001-942	Y	BAS
Engelhardt, G.	AIIA-5.8.1	2000	Amendment no. 1 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 2000/1019291 GLP, unpublished TOX2001-941	Y	BAS
Engelhardt, G.	AIIA-5.8.1	1999	Amendment no. 1 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 1999/11629 GLP, unpublished TOX2001-940	Y	BAS

[5] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Engelhardt, G.	AIIA-5.8.2	1997	Amendment no. 1 to the report on the study of AMTT, techn. cas-nr. [5311-05-7] (ZHT test substance no.: 96/38) in the salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test). 40M0038/964034 ! 1997/1000920 GLP, unpublished TOX2001-961	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.1	1998	In vitro chromosome aberration assay with BAS 635 H in V79 cells. 32M0167/954100 ! 98/11437 GLP, unpublished TOX2001-912	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.1	1998	In vitro gene mutation test with BAS 635 H in CHO cells (HPRT locus assay). 50M0167/954099 ! 98/11436 GLP, unpublished TOX2001-911	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.1	2000	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with BAS 635 H. 40M0290/944382 ! 2000/1018507 GLP, unpublished TOX2001-910	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.1	1998	In vitro unscheduled DNA synthesis (UDS) assay with BAS 635 H in primary rat hepatocytes. 81M0167/954145 ! #BASF 98/10811 GLP, unpublished TOX2001-913	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.1	1998	Report on the study of BAS 635 H (ZHT test substance no.: 95/167-1) in the Ames Test (salmonella/mammalian-microsome mutagenicity test - Standard plate test and preincubation test). 40M0167/954105 ! 1998/11634 GLP, unpublished TOX2001-909	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.4.2	1998	Cytogenetic study in vivo with BAS 635 H in the mouse micronucleus test single intraperitoneal administration. 26M0167/954101 ! #BASF 98/10581 GLP, unpublished TOX2001-914	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	1998	Salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! #BASF 98/10810 GLP, unpublished TOX2001-939	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	1999	In vitro chromosome aberration assay with reg.-no. 292 564; BH 635-2 in V79 cells. 32M0599/964427 ! 1999/11684 GLP, unpublished TOX2001-935	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	2000	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg.-no. 373 906. 40M0298/004076 ! 2001/1006087 GLP, unpublished TOX2001-952	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	2000	Cytogenetic study in vivo with reg. no. 373 906 in the mouse micronucleus test after two intraperitoneal administrations. 26M0298/004077 ! 2000/1018736 GLP, unpublished TOX2001-954	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	2000	In vitro gene mutation test with reg.-no. 373 906 in CHO cells (HPRT locus assay). 50M0298/004079 ! 2001/1006073 GLP, unpublished TOX2001-953	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	1999	In vitro chromosome aberration assay with reg.-no. 335 184 (BH 635-4) in V79 cells. 32M0577/964426 ! 1999/11685 GLP, unpublished TOX2001-950	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	1998	Salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg. no. 335 184 (BH 635-4). 40M0577/964422 ! 1998/11635 GLP, unpublished TOX2001-948	Y	BAS
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.1	1999	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg.-no. 292 564; BH 635-2. 40M0599/964425 ! 1999/11412 GLP, unpublished TOX2001-933	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Engelhardt, G. and Hoffmann, H.D.	AIIA-5.8.2	1996	Report on the study of AMTT, techn. cas-nr. [5311-05-7] (ZHT test substance no.: 96/38) in the Ames salmonella/mammalian.microsome mutagenicity test and escherichia coli / mammalian-microsome reverse mutation assay (standard plate test and preincubation test). 40M0038/964034 ! 1996/1000679 GLP, unpublished TOX2001-960	Y	BAS
Gamer, A.O. and Hoffmann, H.D.	AIIA-5.2.3	1995	Study on the acute inhalation toxicity LC50 of reg. no. 271 272 as a dust aerosol in rats 4-hour exposure. 13I0290/947009 ! #BASF 95/10410 GLP, unpublished TOX2001-899	Y	BAS
Gamer, A.O. and Hoffmann, H.D.	AIIA-5.8.1	2000	Reg. no. 373906 - Acute oral toxicity study in Wistar rats. 10A0298/001071 ! 2001/1006074 GLP, unpublished TOX2001-955	Y	BAS
Gamer, A.O. and Hoffmann, H.D.	AIIIA-7.1.3	1997	BAS 635 00 H - Acute inhalation toxicity study in Wistar rats 4-hour dust exposure. 13I0278/967008 ! #BASF 97/10289 GLP, unpublished TOX2001-887	Y	BAS
Hafemann, C.	AIIA-5.1	2000	The metabolism of 14C-BAS 635 H (reg. no. 271272) in rats. 19461 ! 2000/1013501 GLP, unpublished TOX2001-893	Y	BAS
Hellwig, J. and Hildebrand, B.	AIIA-5.6.2	1998	BAS 635 H - Prenatal toxicity in Himalayan rabbits after oral administration (gavage). 40R0385/94040 ! #BASF 98/10227 GLP, unpublished TOX2001-928	Y	BAS
Hellwig, J. and Hildebrand, B.	AIIA-5.6.2	1996	Reg. no. 271 272 - Prenatal toxicity in Wistar rats after oral administration (gavage). 30R0290/94017 ! #BASF 96/10210 GLP, unpublished TOX2001-927	Y	BAS
Kirsch, P. and Hildebrand, B.	AIIA-5.2.1	1995	Study on the acute oral toxicity of reg. no. 271 272 in rats. 10A0290/941062 ! #BASF 95/10634 GLP, unpublished TOX2001-897	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Kirsch, P. and Hildebrand, B.	AIIA-5.2.2	1995	Study on the acute dermal toxicity of reg. no. 271 272 in rats. 11A0290/941063 ! #BASF 95/10635 GLP, unpublished TOX2001-898	Y	BAS
Kirsch, P. and Hildebrand, B.	AIIA-5.8.1	1995	Study on the acute oral toxicity of TBSA in rats. 10A0148/941038 ! #BASF 95/11408 GLP, unpublished TOX2001-936	Y	BAS
Kuehlem, C. and Hellwig, J.	AIIIA-7.1.1	1997	Study on the acute oral toxicity of BAS 635 00 H in rats. 10A0278/961084 ! #BASF 97/10617 GLP, unpublished TOX2001-885	Y	BAS
Kuehlem, C. and Hellwig, J.	AIIIA-7.1.2	1997	Study on the acute dermal toxicity of BAS 635 00 H in rats. 11A0278/961085 ! #BASF 97/10523 GLP, unpublished TOX2001-886	Y	BAS
Kuehlem, C. and Hellwig, J.	AIIIA-7.1.4	1997	Study on the acute dermal irritation/corrosion of BAS 635 00 H in rabbit. 14H0278/962156 ! #BASF 97/10490 GLP, unpublished TOX2001-888	Y	BAS
Kuehlem, C. and Hellwig, J.	AIIIA-7.1.5	1997	Study on the acute eye irritation of BAS 635 00 H in rabbit. 13H0278/9621567 ! #BASF 97/10491 GLP, unpublished TOX2001-889	Y	BAS
Leibold, E. and Hoffmann, H.D.	AIIA-5.1	2001	Investigation of the formation of AMTT after oral administration of 14C-BAS 635 H in rats. 02B0380/996010 ! 2000/1013503 GLP, unpublished TOX2001-894	Y	BAS
Leibold, E., Hafemann, C. and Hoffmann, H.D.	AIIA-5.8.2	2001	14C-eg. no. 231 700 - Study of the biokinetics and metabolism in rats. 02B0491/986012 ! 2000/1018485 GLP, unpublished TOX2001-956	Y	BAS
Leibold, E., Hoffmann, H.D. and Hildebrand, B.	AIIA-5.1	1998	14C-BAS 635 H - Study of the dermal absorption in rats. 01B0020/956022 ! #BASF 98/10802 GLP, unpublished TOX2001-895	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Leibold, E., Hoffmann, H.D. and Hildebrand, B.	AIIA-5.1	1998	14C-BAS 635 H - Study of the biokinetics in rats. 02B0300/946013 ! #BASF 98/10506 GLP, unpublished TOX2001-892	Y	BAS
Mellert, W.	AIIA-5.7	2001	BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats administration in the diet for 3 months. 50S0167/95102 ! 2001/1006068 GLP, unpublished TOX2001-931	Y	BAS
Mellert, W., Deckardt, K., Gembardt, Ch. and Van Ravenzwaay, B.	AIIA-5.8.1	2001	Reg.-no. 335182 (BH 635-3) - Subchronic toxicity study in Wistar rats administration in the diet for 3 months. 50C0576/96195 ! 2001/1006072 GLP, unpublished TOX2001-947	Y	BAS
Mellert, W., Deckardt, K., Gembardt, Chr. and Hildebrand, B.	AIIA-5.3.1	1998	BAS 635 H - Repeated dose dermal toxicity study in Wistar rats administration for 4 weeks. 33S0167/95101 ! #BASF 98/10479 GLP, unpublished TOX2001-905	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.3.1	1996	Reg. no. 271 272 - Repeated dose oral toxicity study in B6C3F1 CrlBr mice administration in the diet for 4 weeks. 40S0385/94030 ! #BASF 96/10430 GLP, unpublished TOX2001-904	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.3.1	1997	Reg. no. 271 272 - Repeated dose oral toxicity study in Wistar rats administration in the diet for 4 weeks. 30S0385/94029 ! #BASF 97/10819 GLP, unpublished TOX2001-903	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.3.2	1997	BAS 635 H - Subchronic oral toxicity study in B6C3F1 Crl BR mice administration in the diet for 3 months. 60S0385/94034 ! #BASF 97/11511 GLP, unpublished TOX2001-907	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.3.2	2000	BAS 635 H - Subchronic oral toxicity study in Wistar rats administration in the diet for 3 months. 50S0385/94036 ! 2000/1003966 GLP, unpublished TOX2001-906	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Supplementary carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0167/95080 ! 2001/1006065 GLP, unpublished TOX2001-922	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0167/95022 ! 2001/1006064 GLP, unpublished TOX2001-921	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Supplementary chronic toxicity study in Wistar rats administration in the diet for 24 months. 82S0167/95081 ! 2001/1006061 GLP, unpublished TOX2001-918	Y	BAS
Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	AIIA-5.8.2	2001	AMTT - Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats administration in the diet up to 32 weeks. 99S0100/98131 ! 2001/1006078 GLP, unpublished TOX2001-959	Y	BAS
Mellert, W., Deckardt, K., Küttler, K. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Carcinogenicity study in B6C3F1/CrlBR mice administration in the diet for 18 months. 76S0167/95021 ! 2001/1006084 GLP, unpublished TOX2001-923	Y	BAS
Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Chronic toxicity study in Wistar rats administration in the diet for 24 months. 82S0167/95023 ! 2001/1006060 GLP, unpublished TOX2001-917	Y	BAS
Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0042/98025 ! 2001/1006062 GLP, unpublished TOX2001-919	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Supplementary carcinogenicity study in Wistar rats administration in the diet for 24 months. 82C0042/98049 ! 2001/1006063 GLP, unpublished TOX2001-920	Y	BAS
Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	AIIA-5.5	2001	BAS 635 H - Chronic toxicity study in Wistar rats administration in the diet for 12 months. 70C0042/98065 ! 2001/1006059 GLP, unpublished TOX2001-916	Y	BAS
Mellert, W., Kaufmann, W. and Hildebrand, B.	AIIA-5.7	1998	BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats administration in the diet for 3 months. 50S0167/95102 ! #BASF 98/10678 GLP, unpublished TOX2001-930	Y	BAS
Mellert, W., Kaufmann, W. and Hildebrand, B.	AIIA-5.7	1998	BAS 635 H - Acute oral neurotoxicity study in Wistar rats. 20S0167/95103 ! 98/11438 GLP, unpublished TOX2001-929	Y	BAS
Menges, S., Schilling, K., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.3.2	2000	BAS 635 H - Subchronic oral toxicity study in Beagle dogs administration in the diet for 3 months. 31D0167/95044 ! 2000/1012355 GLP, unpublished TOX2001-908	Y	BAS
Menges, S., Schilling, K., Deckardt, K., Kaufmann, W. and Hildebrand, B.	AIIA-5.5	2000	BAS 635 H - Chronic oral toxicity study in Beagle dogs administration in the diet for 12 months. 33D0167/95074 ! 2000/1012356 GLP, unpublished TOX2001-915	Y	BAS
Nemec, M.D.	AIIA-5.7	2001	Dietary developmental neurotoxicity study of BAS 635 H in rats. WIL-403001 ! 2001/1006071 GLP, unpublished TOX2001-932	Y	BAS
Poelloth, C.	AIIA-5.8.2	1997	Amendment no. 1 to the report study on the acute oral toxicity of AMTT, techn. in rats. 10A0038/961019 ! 1997/1000919 GLP, unpublished TOX2001-958	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Poelloth, C. and Hellwig , J.	AIIA-5.8.2	1996	Study on the acute oral toxicity of AMTT, techn. cas-nr. [5311-05-7] in rats. 10A0038/961019 ! 1996/1000678 GLP, unpublished TOX2001-957	Y	BAS
Rossbacher, R. and Hellwig, J.	AIIA-5.2.4	1995	Study on the acute dermal irritation/corrosion of reg. no. 271 272 in rabbits. 14H0290/942094 ! #BASF 95/10533 GLP, unpublished TOX2001-900	Y	BAS
Rossbacher, R. and Hellwig, J.	AIIA-5.2.5	1995	Study on the acute eye irritation of reg. no. 271 272 in rabbits. 13H0290/942095 ! #BASF 95/10532 GLP, unpublished TOX2001-901	Y	BAS
Rossbacher, R. and Hellwig, J.	AIIA-5.2.6	1995	Report on the maximization test for the sensitizing potential of reg. no. 271 272 in guinea pigs. 30H0290/942096 ! #BASF 95/10523 GLP, unpublished TOX2001-902	Y	BAS
Schilling, K., Deckardt, K., Gembardt, Chr. and Van Ravenzwaay, B.	AIIA-5.6.1	2001	BAS 635 H - Two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0167/95088 ! 2001/1006077 GLP, unpublished TOX2001-925	Y	BAS
Schilling, K., Gembardt, C. and Van Ravenzwaay, B.	AIIA-5.6.1	2001	BAS 635 H - Supplementary two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0167/95110 ! 2001/1006067 GLP, unpublished TOX2001-926	Y	BAS
Schilling, K., Gembardt, Chr. and Van Ravenzwaay, B.	AIIA-5.6.1	2001	BAS 635 H - Two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0042/98010 ! 2001/1006066 GLP, unpublished TOX2001-924	Y	BAS
Schilling, K., Gembardt, Chr. and Van Ravenzwaay, B.	AIIA-5.8.2	2001	AMTT and BisSH - Pre-/postnatal screening toxicity study in Wistar rats oral administration (gavage). 19R0100/98014 ! 2001/1003834 not GLP, unpublished TOX2001-964	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Völkner, W.	AIIA-5.8.2	1998	Micronucleus assay in bone marrow cells of the mouse after a single intraperitoneal administration of AMTT. 614800 ! 26M0100/989050 ! #BASF 98/11043 GLP, unpublished TOX2001-963	Y	BAS
Vollmer, G.	AIIA-5.8.2	1999	Study of a possible bond of reg. no. 231700 and reg. no. 271272 to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line. 99P0100/989150 and 99P0042/989151 not GLP, unpublished TOX2001-965	Y	BAS
Wiemann, C.	AIIA-5.8.1	1998	Amendment no. 1 - Reg.-no. 335 182 (BH 635-3): Acute oral toxicity in rats. 10A0576/961216 ! 1999/11221 GLP, unpublished TOX2001-946	Y	BAS
Wiemann, C.	AIIA-5.8.1	1999	Amendment no. 1 - Reg.-no. 292564; BH 635-2: Acute oral toxicity in rats. 10A0599/961217 ! 1999/10381 GLP, unpublished TOX2001-938	Y	BAS
Wiemann, C. and Hellwig, J.	AIIA-5.8.1	1999	Reg. no. 335 184 (BH 635-4): Acute oral toxicity in rats. 10A0577/961218 ! #BASF 99/10213 GLP, unpublished TOX2001-951	Y	BAS
Wiemann, C. and Hellwig, J.	AIIA-5.8.1	1998	Reg.-no. 335 182 (BH 635-3): Acute oral toxicity in rats. 10A0576/961216 ! #BASF 98/10843 GLP, unpublished TOX2001-945	Y	BAS
Wiemann, C. and Hellwig, J.	AIIA-5.8.1	1999	Reg.-no. 292564; BH 635-2: Acute oral toxicity in rats. 10A0599/961217 ! #BASF 99/10099 GLP, unpublished TOX2001-937	Y	BAS
Wiemann, C. and Hellwig, J.	AIIIA-7.1.6	2000	BAS 635 00 H - Modified Buehler test (9 inductions) in guinea pigs. 33H0167/992193 ! 2000/1013137 GLP, unpublished TOX2001-890	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
Wollny, H.-E.	AIIA-5.8.1	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 335 184; BH 635-4. 640403 ! 50M0577/969431 ! 1999/12016 GLP, unpublished TOX2001-949	Y	BAS
Wollny, H.-E.	AIIA-5.8.1	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 335 182; BH 635-3. 640402 ! 50M0576/969430 ! 1999/12026 GLP, unpublished TOX2001-943	Y	BAS
Wollny, H.-E.	AIIA-5.8.1	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 292 564; BH 635-2. 640401 ! 50M0599/969429 ! 1999/11691 GLP, unpublished TOX2001-934	Y	BAS
Wollny, H.-E.	AIIA-5.8.2	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with AMTT. 631700 ! 50M0100/989153 ! 1999/10870 GLP, unpublished TOX2001-962	Y	BAS

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A.7 Residue data (Annex IIA 6; Annex IIIA 8 and 12.2)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Beck J., Bross, M., Mackenroth, C,	AIIA-6.3	2000	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 641 00 H under field conditions in Belgium, France, Germany, Great Britain , Spain, Sweden and the Netherlands, 1998. 2000/1012391 GLP, unpublished RIP2001-602	Y	BAS
Beck J., Bross, M., Mackenroth, C.	AIIA-6.3	2000	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 641 00 H under field conditions in France, Germany, Great Britain, Spain and Sweden, 1997. 2000/1014843 GLP, unpublished RIP2001-600	Y	BAS
Goetz A.J.	AIIA-6.5.1	1996	Hydrolysis of 14C-BAS 635 H at 100 °C and pH5. 96/5200 GLP, unpublished RIP2001-612	Y	BAS
Hofmann M.	AIIA-6.1	1997	Plant uptake study with BAS 635 H (triazin-2,4-14C) and maize use rate: 180 g a.i./ha. 97/10843 GLP, unpublished RIP2001-588	Y	BAS
Hofmann M.	AIIA-6.1	1997	Plant uptake study with BAS 635 H (triazin-2,4-14C) and maize use rate: 120 g a.i./ha. 97/10838 GLP, unpublished RIP2001-587	Y	BAS
Hofmann M.	AIIA-6.1	1997	Plant uptake study with 14C-BAS 635 H (Phenyl-U-14C) and maize use rate: 180 g a.i./ha. 97/10844 GLP, unpublished RIP2001-586	Y	BAS

[6] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Hofmann M.	AIIA-6.1	1997	Plant uptake with 14C-BAS 635 H (phenyl-U-14C) and maize use rate: 120 g a.i./ha. 97/10837 GLP, unpublished RIP2001-585	Y	BAS
Hofmann M.	AIIA-6.1	1998	Plant uptake study with 14C-BAS 635H and maize use rate: 180 g a.i./ha [phenyl-U-14C and triazine-2,4-14C]. 98/10630 GLP, unpublished RIP2001-584	Y	BAS
Hofmann M.	AIIA-6.6	1998	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 365 Tage. 98/10633 GLP, unpublished RIP2001-617	Y	BAS
Hofmann M.	AIIA-6.6	1998	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 120 Tage. 98/10634 GLP, unpublished RIP2001-619	Y	BAS
Hofmann M.	AIIA-6.6	1998	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 120 days. 2000/1014897 GLP, unpublished RIP2001-620	Y	BAS
Hofmann M.	AIIA-6.6	1998	Nachbaustudie mit 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 365 Tage. 98/10631 GLP, unpublished RIP2001-621	Y	BAS
Hofmann M.	AIIA-6.6	1998	Crop rotation study with 14C-271272 (phenyl-U-14C) BAS 635 H - Aging: 365 days. 2000/1014900 GLP, unpublished RIP2001-622	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Hofmann M.	AIIA-6.6	1998	Nachbaustudie mir 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 120 Tage. 98/10632 GLP, unpublished RIP2001-623	Y	BAS
Hofmann M.	AIIA-6.6	1998	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 365 days. 2000/1014898 GLP, unpublished RIP2001-624	Y	BAS
Hofmann M.	AIIA-6.6	1998	Crop rotation study with 14C-271272 (phenyl-U-14C) BAS 635 H - Aging: 120 days. 2000/1014899 GLP, unpublished RIP2001-618	Y	BAS
Hofmann M.	AIIA-6.6	1996	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 30 days. 2000/1014896 GLP, unpublished RIP2001-616	Y	BAS
Hofmann M.	AIIA-6.6	1996	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 30 Tage. 96/10170 GLP, unpublished RIP2001-615	Y	BAS
Hofmann M.	AIIA-6.6	1996	Crop rotation study with 14C-271272 (Phenyl-U-14C) BAS 635 H - Aging: 30 days. 2000/1014894 GLP, unpublished RIP2001-614	Y	BAS
Hofmann M.	AIIA-6.6	1996	Nachbaustudie mit 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 30 Tage. 96/10165 GLP, unpublished RIP2001-613	Y	BAS
Jordan J.	AIIA-6.0	2001	Storage stability of AMTT (BH 635-5) in wheat matrices and radish root. 2001/5001046 GLP, unpublished RIP2001-611	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Kohl W.	AIIA-6.2	1999	The metabolism of 14C-BAS 635 H (14C-Reg. No. 271272) in laying hens. 99/10272 GLP, unpublished RIP2001-594	Y	BAS
Kohl W.	AIIA-6.2	2000	The metabolism of 14C-BAS 635 H (14C-Reg. No. 271272) in lactating goats. 2000/1013502 GLP, unpublished RIP2001-591	Y	BAS
Leibold E.	AIIA-6.2	1997	Amendment No. 1 to the report: 14C-BAS 635 H- Study of the absorption, distribution and excretion after repeated oral administration in laying hens. 97/11241 GLP, unpublished RIP2001-593	Y	BAS
Leibold E., Hoffmann, H. D., Hildebrand, B.	AIIA-6.2	1997	14C-BAS 635 H- Study of the absorption, distribution and excretion after repeated oral administration in lactating goats. 97/11172 GLP, unpublished RIP2001-590	Y	BAS
Leibold E., Hoffmann H. D., Hildebrand, B.	AIIA-6.2	1997	14C-BAS 635 H - Study of the absorption, distribution and excretion after repeated oral abministration in laying hens. 97/11170 GLP, unpublished RIP2001-592	Y	BAS
Meumann H., Bross, M., Mackenroth, C.	AIIA-6.3	2000	Study on the residue behaviour of BAS 639 00 H and BAS 635 01 H in maize under field conditions in Belgium, France, Germany, Great Britain and Spain, 1997. 2000/1012389 GLP, unpublished RIP2001-607	Y	BAS
Meumann H., Bross, M., Mackenroth, C.	AIIA-6.3	2000	Study on the residue behaviour of BAS 635 H after application of BAS 635 01 H and BAS 635 GJH in maize under field conditions in Germany, France and Sweden, 1998. 2000/1012399 GLP, unpublished RIP2001-609	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Meumann H., Bross, M., Mackenroth, C.	AIIA-6.3	2000	Study on the residue behaviour of BAS 639 00 H in maize under field conditions in Germany, the Netherlands and Spain, 1996. 2000/1012388 GLP, unpublished RIP2001-606	Y	BAS
Raunft E., Benz, A., Mackenroth, C.	AIIA-6.3	2001	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 635 00 H and BAS 641 01 H under field conditions in Denmark, Spain and Great Britain, 2000. 2000/1014857 GLP, unpublished RIP2001-598	Y	BAS
Reinhard K.	AIIA-6.1	1998	Metabolism of 14C-BAS 635 H in corn. 98/11379 GLP, unpublished RIP2001-589	Y	BAS
Sasturain J., Mackenroth, C.	AIIA-6.3	2001	Determination of the residues of BAS 635 H after application of BAS 641 01 H (BAS 635 H, BAS 615 H) in spring barley and spring wheat in 1998. 2000/1012397 not GLP, unpublished RIP2001-601	Y	BAS
Schulz H.	AIIA-6.3	2001	Determination of the residues of BAS 641 H and BAS 635 H in wheat and barley following treatment with BAS 641 01 H, BAS 635 00 H and BAS 152 00 S under field conditions in Italy and France 2000. 2000/1014884 GLP, unpublished RIP2001-597	Y	BAS
Schulz H.	AIIA-6.3	2001	Determination of the residues of BAS 655 H in wheat and barley following treatment with BAS 655 00 H and BAS 152 00 S under field conditions in Italy and France 2000. 2000/1014888 GLP, unpublished RIP2001-599	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Schulz H.	AIIA-6.3	2001	Determination of the residues of Reg. No. 271 272 and Bentazone in maize following treatment with BAS 635 00 H, BAS 351 40 H and BAS 152 00 S under field conditions in France 1999. 2001/1000919 GLP, unpublished RIP2001-604	Y	BAS
Schulz H.	AIIA-6.3	2000	Determination of the residues of BAS 635 H in maize following treatment of BAS 639 00 H and BAS 635 01 H under field conditions in Italy 1997. 2000/1012398 GLP, unpublished RIP2001-608	Y	BAS
Schulz H.	AIIA-6.3	2001	Determination of the residues of BAS 655 H in wheat and barley following treatment with BAS 655 00 H and BAS 152 00 S under field conditions in Italy and France 1999. 2001/1000922 GLP, unpublished RIP2001-596	Y	BAS
Schulz H.	AIIA-6.3	2001	Determination of the residues of BAS 641 H in wheat and barley following treatment with BAS 641 01 H and BAS 152 00 S under field conditions in Germany and France 1999. 2001/1000920 GLP, unpublished RIP2001-595	Y	BAS
Stewart J.M.	AIIA-6.0	2001	Storage stability of BAS 635 H in plant matrices. 2001/5001045 GLP, unpublished RIP2001-610	Y	BAS
Treiber S.	AIIA-6.3	2001	Determination of the residues of BAS 635 H in maize following treatment with BAS 635 00 H under field conditions in Germany, Denmark, France, Great Britain, the Netherlands and Spain, 2000. 2000/1014858 GLP, unpublished RIP2001-605	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
Treiber S.	AIIA-6.3	2000	Study on the residue behaviour of BAS 635 H in maize after treatment with BAS 635 00 H under field conditions in Germany and Spain, 1999. 2000/1012406 GLP, unpublished RIP2001-603	Y	BAS
Veit P.	AIIA-6.6	2001	Quantification and identification of radioactive residues in rotantional crop after treatment with 14C-BAS 635 H (14C-271272). 2001/1000995 GLP, unpublished RIP2001-625	Y	BAS

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A.8 Environmental fate and behaviour (Annex IIA 7; Annex IIIA 9)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Becker-Arnold R.	AIIA-7.1.3.3	1998	Outdoor lysimeter study with 14C-BAS 635 H. 1998/11268 GLP, unpublished BOD2001-515	Y	BAS
Beigel C.	AIIIA-9.2.1	2001	Calculation of predicted environmental concentrations (PECgw) for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in groundwater using FOCUS. 2000/1018546 not GLP, unpublished BOD2002-32	Y	BAS
Dressel J.	AIIA-7.1.1.2.2	2001	Estimation of standardized transformation rates of BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 from field dissipation studies. 2000/1018554 not GLP, unpublished BOD2001-502	Y	BAS
Goetz N. von	AIIA-7.2.1.2	1999	Aqueous photolysis of BH 635-4 under sensitising conditions. 1999/10089 GLP, unpublished LUF2001-187	Y	BAS
Gottesbueren B.	AIIA-7.1.1.2.1	1998	Estimation of the transformation coefficients of BAS 635 H during aerobic metabolism in soil. 1998/10617 not GLP, unpublished BOD2001-494	Y	BAS
Gottesbüren, B.	AIIIA-9.1; AIIIA-9.2	2001	Calculation of predicted environmental concentrations (PECsed) for BAS 635 H and metabolite BH 635-4 in sediment. 2000/1018552 not GLP, unpublished BOD2001-520	Y	BAS
Gottesbüren B.	AIIA-7.1.1.2.1	2001	Calculation of the DT50-values of BAS 635 H at 10°C derived from DT50-values at 20°C. 2001/1008965 not GLP, unpublished BOD2001-499	Y	BAS

[7] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Hauck T.	AIIIA-9.1.3	2001	Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in soil. 2000/1017054 not GLP, unpublished BOD2001-519	Y	BAS
Jackson, S., Smith, K. and McDonell, J.	AIIA-7.1.1.2.2	2001	Field dissipation of BAS 635..H in terrestrial use patterns. BASF 2000/5285 GLP, unpublished BOD2001-731	Y	BAS
Keller, W.	AIIA-7.1.1.2.2	1998	Storage stability of BAS 635 H (271272) residues in soil. BASF 98/10899 GLP, unpublished BOD2001-516	Y	BAS
Keller W.	AIIA-7.1.3.1; AIIA-7.1.3.2	1994	Leaching behaviour of 14C-271272 without soil ageing and after aerobic ageing for 30 days. 1994/10924 GLP, unpublished BOD2001-514	Y	BAS
Kellner O.	AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	1997	The aerobic soil metabolism of bas 635 H (14C-Triazine). 1997/11242 GLP, unpublished BOD2001-486	Y	BAS
Kellner O.	AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	1998	The aerobic soil metabolism of BAS 635 H (14C-phenyl). 1998/10619 GLP, unpublished BOD2001-484	Y	BAS
Kellner O.	AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	1998	The anaerobic soil metabolism of BAS 635 H (14C-triazine). 1998/10893 GLP, unpublished BOD2001-491	Y	BAS
Kellner O.	AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	1998	The anaerobic soil metabolism of BAS 635 H (14C-phenyl). 1998/10891 GLP, unpublished BOD2001-490	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Kellner O.	AIIA-7.1.1.2.1	2001	Amendment 1 Soil degradation rates of 14C-BAS 635 H (incl. metabolites BH 635-2,-3,-4) under laboratory conditions. 2001/1008970 GLP, unpublished BOD2001-498	Y	BAS
Kellner O.	AIIA-7.1.1.2.1	2001	Amendment 1 The anaerobic soil metabolism of BAS 635 H (14C-triazine). 2001/1008968 GLP, unpublished BOD2001-497	Y	BAS
Kellner O.	AIIA-7.1.1.2.1	2001	Amendment 1 The anaerobic soil metabolism of BAS 635 H (14C-phenyl). 2001/1008969 GLP, unpublished BOD2001-496	Y	BAS
Kellner O.	AIIA-7.1.1.2.1	1998	Estimation of the transformation coefficients of BAS 635 H, BH 635-2, BH-3, BH-4 and BH-5 during aerobic soil metabolism of 14C-BAS 635 H (Phenyl and Triazine label). 1998/10662 not GLP, unpublished BOD2001-495	Y	BAS
Kellner O.	AIIA-7.1.1.2.2	2001	Field soil dissipation of BAS 635 H (271 272) in formulation BAS 639 00 H. 2000/1013301 GLP, unpublished BOD2001-501	Y	BAS
Kellner O.	AIIA-7.1.1.2.2	1998	Examination of soil dissipation of BAS 635 H (271272) under field conditions after treatment with formulation BAS 639 00 H. 1998/11244 GLP, unpublished BOD2001-500	Y	BAS
Ohnsorge U.	AIIA-2.3.2; AIIA-7.2.2	2000	Physical and chemical properties (Henry's law constant). 2000/1013447 not GLP, unpublished LUF2001-188	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Platz K.	AIIIA-9.2.3	2001	Calculation of predicted environmental concentrations (PECsw) for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in static surface waters. 2000/1018549 not GLP, unpublished WAS2001-218	Y	BAS
Richter T.	AIIA-7.1.3.3	2001	Determination of residues of BH 635-5 in several lysimeter leachates. 2000/1013300 GLP, unpublished BOD2001-504	Y	BAS
Richter, Th.	AIIA-7.1.1.2.2	2001	Evaluation of residue stability of BAS 635 H (271272) and the following metabolites 335184, 335182, 292564 in soil samples under usual storage conditions. BASF 2000/1013302 GLP, unpublished BOD2001-517	Y	BAS
Scharf J.	AIIA-2.9.2; AIIA-2.9.3; AIIA-7.2.1.2	1998	Aqueous photolysis of BAS 635 H at pH 5 and pH 7. 1998/10981 GLP, unpublished LUF2001-186	Y	BAS
Scharf J.	AIIA-7.2.1.2	1996	Absorption coefficient of BAS 635 H at pH 4, pH7 and pH 9. 1996/10021 GLP, unpublished LUF2001-185	Y	BAS
Scharf J.	AIIA-2.10; AIIA-7.2.2	1995	Photochemical oxidative degradation of BAS 635 H. 1995/11094 not GLP, unpublished LUF2001-190	Y	BAS
Scharf J.	AIIA-2.10; AIIA-7.2.2	1998	Laboratory study on the volatilization of BAS 635 H after application of BAS 635 00 H on soil and plant surfaces. 1998/10982 GLP, unpublished LUF2001-189	Y	BAS
Schwarz K.	AIIA-7.2.1.3.1	1995	Determination of the biodegradability of REG.NO. 271 272 in the CO2-evolution test. 1995/10805 GLP, unpublished WAS2001-213	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Seher A.	AIIA-7.1.2	1998	Soil adsorption/desorption study of 292564 (BH 635-2). 1998/10713 GLP, unpublished BOD2001-509	Y	BAS
Seher A.	AIIA-7.1.2	1998	Soil adsorption/desorption study of 335184 (BH 635-4). 1998/10612 GLP, unpublished BOD2001-511	Y	BAS
Seher A.	AIIA-7.1.2	1998	Soil adsorption/desorption study of 231700 (BH 635-5). 1998/11370 GLP, unpublished BOD2001-512	Y	BAS
Seher A.	AIIA-7.1.2	1999	Addendum 1 Soil adsorption/desorption study of 231700 (BH 635-5). 1998/11413 GLP, unpublished BOD2001-513	Y	BAS
Seher A.	AIIA-7.1.2	1998	Soil adsorption/desorption study of 335182 (BH 635-3). 1998/10714 GLP, unpublished BOD2001-510	Y	BAS
Seher A.	AIIA-7.1.2	1999	Adsorption/desorption - Study of 271272 (BAS 635 H), 292564 (BH 635-2), 335182 (BH 635-3), 335184 (BH 635-4) and 231700 (BH 635-5) on a lysimeter soil. 1999/10085 GLP, unpublished BOD2001-508	Y	BAS
Seher A.	AIIA-7.1.2	1997	Addendum 2 Soil adsorption/desorption study of 271272 (BAS 635 H). 1997/11062 GLP, unpublished BOD2001-507	Y	BAS
Seher A.	AIIA-7.1.2	1996	Addendum 1 Soil adsorption/desorption study of 271272 (BAS 635 H). 1996/10748 GLP, unpublished BOD2001-506	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Seher A.	AIIA-7.1.2	1996	Soil adsorption/desorption study of 271272 (BAS 635 H). 1996/10455 GLP, unpublished BOD2001-505	Y	BAS
Singh M.	AIIA-2.9.1; AIIA-7.2.1.1	1997	Hydrolysis of 14C-BAS 635 H (triazine label) in aqueous media. 1996/5091 GLP, unpublished WAS2001-211	Y	BAS
Singh M.	AIIA-2.9.1; AIIA-7.2.1.1	1997	Hydrolysis of 14C-BAS 635 H (phenyl label) in aqueous media. 1996/5057 GLP, unpublished WAS2001-210	Y	BAS
South, N.L. and Smith, K.	AIIA-7.1.1.2.2	2001	Freezer storage stability study with BAS 635 H, BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in sediment. BASF 2000/5279 GLP, unpublished BOD2001-518	Y	BAS
Staudenmaier H.	AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	1999	Degradation behaviour of BAS 635 H in lysimeter soil. 1999/11823 GLP, unpublished BOD2001-485	Y	BAS
Staudenmaier H.	AIIA-7.1.3.3	2001	Outdoor lysimeter study with 14C-BAS 635 H. 2000/1013297 GLP, unpublished BOD2001-503	Y	BAS
Staudenmaier H.	AIIA-7.2.1.3.2	2001	Amendment 1 Degradation of BAS 635 H in aerobic aquatic environment. 2001/1008967 GLP, unpublished WAS2001-215	Y	BAS
Staudenmaier H.	AIIA-7.2.1.3.2	1998	Degradation of BAS 635 H in aerobic aquatic environment. 1998/10950 GLP, unpublished WAS2001-214	Y	BAS
Tong T.R.	AIIA-7.2.1.1	2001	Hydrolysis of 14C-BH 635-5 (AMTT) in aqueous solution. 2000/5260 GLP, unpublished WAS2001-212	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
Venkatesh K.	AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	1996	Photolysis of 14C-BAS 635 H (triazin label) on soil. 1996/5226 GLP, unpublished BOD2001-489	Y	BAS
Venkatesh K.	AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	1996	Photolysis of 14C-BAS 635 H (phenyl label) on soil. 1996/5209 GLP, unpublished BOD2001-488	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

A.9 Ecotoxicology (Annex IIA 8; Annex IIIA 10)

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Bühler, A.	AIIA-8.3.2; AIIIA-10.5.1	2001	Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite Typhlodromus pyri (Acari:Phytoseiidae) in an extended laboratory trial. 63871 ! BASF2000/1012464 GLP, unpublished ANA2001-486	Y	BAS
Bühler, A.	AIIA-8.3.2; AIIIA-10.5.1	2000	Effects of BAS 635 00 H + BAS 152 00 S on the ground dwelling predator Poecilus cupreus (Coleoptera, Carabidae) in a laboratory trial. 57045 ! BASF2000/1012452 GLP, unpublished ANA2001-482	Y	BAS
Dohmen, G.P.	AIIA-8.2.4	2001	Effect of BAS 635 -2 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012469 GLP, unpublished WAT2001-444	Y	BAS
Dohmen, G.P.	AIIA-8.2.4	2001	Effect of BAS 635 -3 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012471 GLP, unpublished WAT2001-445	Y	BAS
Dohmen, G.P.	AIIA-8.2.4	2001	Effect of BAS 635 -5 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012473 GLP, unpublished WAT2001-447	Y	BAS
Dohmen, G.P.	AIIA-8.2.4	2001	Effect of BAS 635 -4 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012472 GLP, unpublished WAT2001-446	Y	BAS
Dohmen, G.P.	AIIA-8.2.4	1998	Effect of BAS 635 H on Daphnia magna STRAUS in a Static Acute Toxicity Test. 97/11190 GLP, unpublished WAT2001-443	Y	BAS

[8] Only notifier listed

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Dohmen, G.P.	AIIA-8.2.5	2000	Effect of BAS 635 on Mortality and Reproduction of Daphnia magna. 2000/1012433 GLP, unpublished WAT2001-448	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635-2 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 99/10320 GLP, unpublished WAT2001-451	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635-3 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10321 GLP, unpublished WAT2001-452	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635 H on the Growth of the Blue-Green Alga Anabaena flos-aquae. 1999/11022 GLP, unpublished WAT2001-450	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635-4 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10322 GLP, unpublished WAT2001-453	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635-5 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10323 GLP, unpublished WAT2001-454	Y	BAS
Dohmen, G.P.	AIIA-8.2.6	1999	Effect of BAS 635 H on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/11021 GLP, unpublished WAT2001-449	Y	BAS
Dohmen, G.P.	AIIA-8.2.8	1999	Effect of BAS 635 H on the Growth of Lemna gibba G3. 1999/11144 GLP, unpublished WAT2001-455	Y	BAS
Dohmen, G.P.	AIIA-8.4.1	1998	Effect of BAS 635 H on mortality and biomass of the earthworm Eisenia foetida. 19534 ! BASF97/11325 GLP, unpublished ARW2001-93	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Dohmen, G.P.	AIIIA-10.2.1	1999	Effect of BAS 635 00 H on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/11147 GLP, unpublished WAT2001-462	Y	BAS
Dohmen, G.P.	AIIIA-10.2.1	2001	Effect of BAS 635 00 H + BAS 152 00 S in the Growth of Lemna gibba in a Seven Day Static Toxicity Test. 2001/1001865 GLP, unpublished WAT2001-463	Y	BAS
Dohmen, G.P.	AIIIA-10.2.1	2001	Effect of BAS 635 00 H on the Immobility of Daphnia magna STRAUS. 2000/1012484 GLP, unpublished WAT2001-460	Y	BAS
Drexler, A.	AIIA-8.3.2; AIIIA-10.5.1	2000	Effects of BAS 635 00 H + BAS 152 00 S on the lacewing Chrysoperla carnea Steph. (Neuroptera, Chrysopidae)) in the laboratory. 7572046 ! BASF2000/1012454 GLP, unpublished ANA2001-485	Y	BAS
Drexler, A..	AIIA-8.3.2; AIIIA-10.5.1	2001	Effects of BAS 635 00 H + BAS 152 00 S on the reproduction of rove beetles Aleochara bilineata Gyll. (Coleoptera, Staphylinidae)) in the laboratory. 7573070 ! BASF2000/1012455 GLP, unpublished ANA2001-483	Y	BAS
Frank, P.	AIIA-8.6; AIIIA-10.8	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects of the test item on seedling emergence of terrestrial plants. 71 171 / BASF2000/1012474 GLP, unpublished PFL2001-66	Y	BAS
Goßmann, A.	AIIA-8.3.2; AIIIA-10.5.1	2000	Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite Typhlodromus pyri Scheuten (Acari, Phytoseiidae) -Dose response design-. 7571063 ! BASF2000/1012453 GLP, unpublished ANA2001-480	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Jatzek	AIIIA-10.2.1	2001	BAS 635 00 H + BAS 152 00 S - Determination of the acute effect on the swimming ability of the water flea Daphnia magns STRAUS. 2001/1001852 GLP, unpublished WAT2001-461	Y	BAS
Kling A.	AIIIA-10.4	2001	Assessment of the Side Effects of BAS 635 00 H + BAS 152 00 S to the Honey Bee, Apis mellifera L. in the Laboratory. BASF98/10117 GLP, unpublished BIE2001-39	Y	BAS
Krieg, W.	AIIA-8.5	1999	Effects of BH 635-3 on the nitrogen turnover in soil. 48362 ! BASF99/10041 GLP, unpublished BMF2001-74	Y	BAS
Krieg, W.	AIIA-8.5	1999	Effects of BH 635-5 on the nitrogen turnover in soil. 483634! BASF99/10043 GLP, unpublished BMF2001-76	Y	BAS
Krieg, W.	AIIA-8.5	1999	Effects of BH 635-4 on the nitrogen turnover in soil. 48363 ! BASF99/10042 GLP, unpublished BMF2001-75	Y	BAS
Krieg, W.	AIIA-8.5	1998	Effects of BH 635-2 on the nitrogen turnover in soil. 48361 ! BASF98/11161 GLP, unpublished BMF2001-73	Y	BAS
Kubitza, J.	AIIA-8.2.6	2002	Effect of BAS 635 H on the Growth of the Blue-green alga Anabaena flos-aquae. 2002/1004393 GLP, unpublished WAT2002-89	N	BAS
Lührs, U.	AIIA-8.4.1	1998	Acute toxicity (14 days) of BH 635-3 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4540021 ! BASF98/11367 GLP, unpublished ARW2001-95	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Lührs, U.	AIIA-8.4.1	1998	Acute toxicity (14 days) of BH 635-4 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4550021 ! BASF98/11397 GLP, unpublished ARW2001-96	Y	BAS
Lührs, U.	AIIA-8.4.1	1998	Acute toxicity (14 days) of BH 635-5 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4560021 ! BASF98/11396 GLP, unpublished ARW2001-97	Y	BAS
Lührs, U.	AIIA-8.4.1	1998	Acute toxicity (14 days) of BH 635-2 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4530021 ! BASF98/11265 GLP, unpublished ARW2001-94	Y	BAS
Lührs, U.	AIIIA-10.6.1.1	2000	Acute toxicity (14 days) of BH 635 00 H + BAS152 00 S to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 7575021 ! BASF2000/1012457 GLP, unpublished ARW2001-98	Y	BAS
Maisch	AIIA-8.7	1998	Determination of the inhibitory effect of BAS 635 H on the cell multiplication of the bacterium Pseudomonas putida. 98/10080 GLP, unpublished WAT2001-457	Y	BAS
Munk, R.	AIIA-8.1.1	1997	Report Reg.No.271 272 - Avian single-dose oral LD50 on the mallard duck (Anas platyrhynchos). 13W0167/95037 /BAS 97/10947 GLP, unpublished AVS2001-141	N	BAS
Munk, R.	AIIA-8.1.2	1997	Report Reg.No.271 272 - Avian dietary LC50 test in chicks of the bobwhite quail (Colinus virginanus). 31W0167/95038 GLP, unpublished AVS2001-143	N	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Munk, R.	AIIA-8.1.2	1997	Report Reg.No.271 272 - Avian dietary LC50 test in chicks of the mallard duck (Anas platyrhynchos L.) + Amendment No. 1. 32W0167/95039 GLP, unpublished AVS2001-142	N	BAS
Munk, R.	AIIA-8.1.3	1998	BAS 635 H - 1-generation reproduction study on the bobwhite quail (Colinus virginanus) by administration in the diet. 71W0167/95040 GLP, unpublished AVS2001-144	N	BAS
Munk, R.	AIIA-8.2.1	1996	Reg.No. 271272 - Acute toxicity study on the common carp (Cyprinus carpio L.) in a static system (96 hours). 96/10981 GLP, unpublished WAT2001-437	Y	BAS
Munk, R.	AIIA-8.2.1	1997	AMTT, techn. CAS - Nr. (5311-05-7) Acute toxicity study on the zebra fish (Brachydanio rerio HAM. and BUCH.) in a static system (96 hours). 97/11694 GLP, unpublished WAT2001-441	Y	BAS
Munk, R.	AIIA-8.2.1	1997	Sublethal toxic effects on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a flow-through system (28 days). 1998/11527 GLP, unpublished WAT2001-442	Y	BAS
Munk, R.	AIIA-8.2.1	1998	Reg. No. 335 184 (BH 635-4) Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 98/10934 GLP, unpublished WAT2001-440	Y	BAS
Munk, R.	AIIA-8.2.1	1996	Reg.No. 271272 - Acute toxicity study on the blue gill sunfish (Lepomis macrochirus) in a static system (96 hours). 96/10980 GLP, unpublished WAT2001-436	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Munk, R.	AIIA-8.2.1	1996	Reg.No. 271272 - Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 96/10979 GLP, unpublished WAT2001-435	Y	BAS
Munk, R.	AIIIA-10.2.1	1997	Report BAS 635 00 H Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 97/10820 GLP, unpublished WAT2001-458	Y	BAS
Munk, R. and Küttler, K.	AIIA-8.1.1	1997	Report Reg.No.271 272 - Avian single-dose oral LD50 on the bobwhite quail (Colinus virginianus). 11W0167/95036 /BAS 97/10377 GLP, unpublished AVS2001-140	N	BAS
Oberwalder, Chr.	AIIA-8.6; AIIIA-10.8	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of Pea (Pisum sativum) under field conditions. 71 175-2 ! BASF2000/1012465 GLP, unpublished PFL2001-69	Y	BAS
Oberwalder, Chr.	AIIA-8.6; AIIIA-10.8	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of Flax (Linum usitatissimum) under field conditions. 71 175-3 ! BASF2000/1012466 GLP, unpublished PFL2001-70	Y	BAS
Oberwalder, Chr.	AIIA-8.6; AIIIA-10.8	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of oilseed rape (Brassica napus L.) under field conditions. 71 175-1! BASF2000/1012461 GLP, unpublished PFL2001-68	Y	BAS
Reuter, St.	AIIA-8.6; AIIIA-10.8	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects of the test item on vegetative vigour of terrestrial plants. 71 173 ! BASF2000/1012470 GLP, unpublished PFL2001-67	Y	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Sack, D.	AIIIA-10.4	1998	Effect of Reg. No. 271 272 on the Honeybee (Apis mellifera L.) in Laboratory Trials. BASF98/10117 GLP, unpublished BIE2001-38	Y	BAS
Schmitzer, St.	AIIA-8.3.2; AIIIA-10.5.1	2001	Effects of BAS 635 00 H + BAS 152 00 S on the wolf spider Pardosa spec. (Araneae, Lycosidae)) in the laboratory. 7574065 ! BASF2000/1012456 GLP, unpublished ANA2001-484	Y	BAS
Schwarz	AIIA-8.7	1995	Determination of the Biodegradability of REG.NO.271 272 in the CO2-Evolution Test. 95/10805 GLP, unpublished WAT2001-456	Y	BAS
Ufer, A..	AIIA-8.3.2; AIIIA-10.5.1	2001	Effects of BAS 635 00 H + BAS 152 00 S on the parasitoid Aphidius rhopalosiphi (Hymenoptera: braconidae) in a laboratory trial. 57048 ! BASF2000/1012463 GLP, unpublished ANA2001-481	Y	BAS
Wachter, S.	AIIA-8.5; AIIIA-10.7.1	2001	Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, short-term respiration. 20001124/02-ABMF ! BASF 2000/1012476 GLP, unpublished BMF2001-78	Y	BAS
Wachter, S.	AIIA-8.5; AIIIA-10.7.1	2001	Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, nitrogen turnover. 20001124/01-ABMF ! BASF 2000/1012475 GLP, unpublished BMF2001-77	Y	BAS
Westphalen, K.-O.	AIIA-8.6; AIIIA-10.8	1997	Herbicide tests of metabolites of SCR 271 272 H (=a.i. of BAS 635 H) on plants in the greenhouse at pre emergence application. Reg.Doc.#BASF98/10434 not GLP, unpublished PFL2002-68	Y	BAS
Zok, S.	AIIA-8.1.3	1999	BAS 635 H - 1-generation reproduction study on the mallard duck (Anas platyrhynchos) by administration in the diet. 72W0167/95041 GLP, unpublished AVS2001-145	N	BAS

Author(s)	Annex point/ reference number	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
Zok, S.	AIIA-8.2.1	1999	Reg No. 335 182 (BH 635-3) Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 1999/11413 GLP, unpublished WAT2001-439	Y	BAS
Zok, S.	AIIA-8.2.1	1999	Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 1999/10578 GLP, unpublished WAT2001-438	Y	BAS
Zok, S.	AIIIA-10.2.1	2000	Report Twinpack BAS 635 00 H incl. BAS 152 00 S Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 2000/1018727 GLP, unpublished WAT2001-459	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Monograph

20 August 2002

Tritosulfuron

Volume 3

Annex B

Summary, Scientific Evaluation and Assessment

Rapporteur Member State: Germany

Contents

Annex B

Tritosulfuron

B-1: Identity

B.1 Identity

B.1.1 Identity of the active substance (Annex IIA 1 and 3.1)

B.1.1.1 Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)

Applicant:

BASF Aktiengesellschaft
Agricultural Center
Product Registration Management
P.O. Box 120
D-67114 Limburgerhof

Contact:

Dr. Karl-Otto Westphalen
Telephone: +49 (0) 621 60-27560
Telefax: +49 (0) 621 60-27559

Alternative person:
Dr. Eberhard Keller
Telephone: +49 (0) 621 60-27343
Telefax: +49 (0) 621 60-27559

Dr. Astrid Gall
Telephone: +49 (0) 621 60-27300
Telefax: +49 (0) 621 60-28135

B.1.1.2 Common name and synonyms (Annex IIA 1.3)

Tritosulfuron (ISO, accepted)

B.1.1.3 Chemical name (Annex IIA 1.4)

IUPAC: 1-(4-methoxy-6-trifluoromethyl-1,3,5-triazin-2-yl)-3-(2-trifluoromethylbenzenesulfonyl)urea

CAS: N-[[[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino]carbonyl]-2-(trifluoromethyl)benzenesulfonamide

B.1.1.4 Manufacturer's development code number (Annex IIA 1.5)

BAS 635 H, LAB 271272, Reg.-No. 271272, PS 271272

B.1.1.5 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

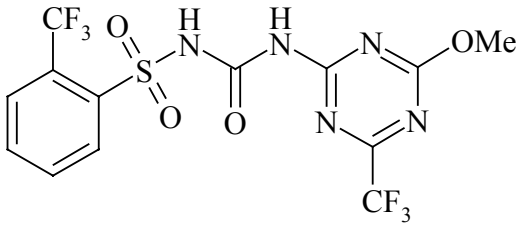
CAS: 142469-14-5
CIPAC: 735
EEC: not assigned
EINECS: not assigned

B.1.1.6 Molecular and structural formulae, molecular mass (Annex IIA 1.7)

Molecular formular: $C_{13}H_9F_6N_5O_4S$

Molecular mass: 445.3 g/mol

Structural formula:



B.1.1.7 Manufacturer or manufacturers of the active substance (Annex IIA 1.2)

Manufacturer:
BASF Aktiengesellschaft
Crop Protection Division
P.O. Box 120
D-67114 Limburgerhof

Person to contact: Dr. Wolfgang Türk (see B.1.1.1)
Production Crop Protection
Telephone: +49 (0) 621 60-79145
Telefax: +49 (0) 621 60-79519

Manufacturing site:
Pilot plant at BASF AG, Ludwigshafen

B.1.1.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C.

B.1.1.9 Specification of purity of the active substance (Annex IIA 1. 9)

950 g/kg (minimum purity)
0.2 g/kg AMTT (maximum content)

B.1.1.10 Identity of isomers, impurities and additives (Annex IIA 1.10)

Confidential information, see Annex C.

B.1.1.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C.

B.1.2 Identity of the plant protection product (Annex IIIA 1)

B.1.2.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name: BAS 635 00 H, preliminary designator
(country specific alternatives are under consideration)

Code number:		
	Plant protection product:	BAS 635 00 H
	Adjuvant:	BAS 152 00 S
		(Citowett 2000, Citowett New)
	Active Substance:	BAS 635 H (Tritosulfuron)
	BASF internal No.:	Reg.-No. 271272

B.1.2.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

BASF Aktiengesellschaft
Crop Protection Division
P.O. Box 1 20
67114 Limburgerhof
Germany

Contact person: Dr. Karl Zoller
Production Crop Protection
Tel. No.: (0)6 21/ 60-7 91 46
Fax No.: (0)6 21/ 60-7 95 19

B.1.2.3 Type of the preparation and code (Annex IIIA 1.5)

Combi-pack solid (WG) / liquid (SL): KK

B.1.2.4 Function (Annex IIA 3.1; Annex IIIA 1.6)

Herbicide

B.1.2.5 Composition of the preparation (Annex IIIA 1.4)

Confidential information, see Annex C.

B.1.3 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[1]
AIIA-1.8	Hassink, J.	2001	Tritosulfuron TC Description of the Manufacturing Process. BASF DocID 2001/1003807 not GLP, unpublished CHE2001-560	Y	BAS
AIIA-1.9	Hassink, J.	2001	Tritosulfuron TC Composition of the Technical Active Ingredient. BASF DocID 2001/1003808 not GLP, unpublished CHE2001-561	Y	BAS
AIIA-1.11	Fietz, G.	1998	Characterization of BAS 635 H Batch N34 by HPLC-Method CP 217. BASF DocID 1998/1001137 GLP, unpublished CHE2001-562	Y	BAS
AIIA-1.11	Guentner, A.	1998	Determination of the total N-Nitrosamine content and the content of Flouride, Bromide, Sulfate, Phosphate, Nitrite, Nitrat and Chloride in "BAS 635 H". BASF DocID 2001/1003843 GLP, unpublished CHE2001-568	Y	BAS
AIIA-1.11	Hassink, J.	2000	Characterization of BAS 635 H Batch N59 by HPLC-Method CP 217 (AI) and CP300 (By-products). BASF DocID 2000/1018876 GLP, unpublished CHE2001-567	Y	BAS
AIIA-1.11	Hassink, J.	2000	Determination of technical impurities in BAS 635 H Batch N53 by HPLG-Method CP300. BASF DocID 2000/1018874 GLP, unpublished CHE2001-565	Y	BAS
AIIA-1.11	Hassink, J.	2000	Reanalysis of BAS 635 H Batch N53 by HPLC-Method CP217. BASF DocID 2000/1018875 GLP, unpublished CHE2001-566	Y	BAS

[1] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[1]
AIIA-1.11	Hassink, J.	1998	Characterization of BAS 635 H (Reg.-No. 271272), Batch N42 by HPLC-Method CP 217, Determination of Technical Impurities (HPLC-Method CP 300) and Water. BASF DocID 1998/1001139 GLP, unpublished CHE2001-564	Y	BAS
AIIA-1.11	Hassink, J.	1998	Determination of Technical impurities in TGAI BAS 635 H (Reg.-No. 271272) Batch N34 by HPLC-Method CP 300. BASF DocID 1998/1001138 GLP, unpublished CHE2001-563	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-2: Physical and chemical properties

B.2 Physical and chemical properties

B.2.1 Physical and chemical properties of the active substance (Annex IIA 2)

Table B.2.1-1: Summary of the physical and chemical properties of the active substance tritosulfuron

PAS: Pure active substance (min purity: 99.8 %)
TAS: Technical active substance (purity: 93.8 %)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.1.1 (IIA 2.1)	Melting point, freezing point or solidification point of purified active substance	PAS *TAS*	EEC A 1	Y	166.5-169.4 °C (capillary method) *165 °C (capillary method, photocell detection)*	Acceptable not required additional info	Türk, 1994 (CHE2001-496) *Kästel, 1996 (CHE2001-497)*
B.2.1.1.2 (IIA 2.1)	Boiling point of purified active substance	PAS	EEC A 2 (DSC method)	Y	see B.2.1.1.2	Acceptable	Türk, 1994 (CHE2001-496)
B.2.1.1.3 (IIA 2.1)	Temperature of decomposition or sublimation	PAS	EEC A 2 (DSC method)	Y	The curve shows an endothermic peak at about 170 °C which in line with the results of the capillary method. At 340-360 °C a strong exothermic effect was observed which can be interpreted as decomposition. No further endothermic effect was observed. Therefore, sublimation or boiling of the as can be excluded.	Acceptable	Türk, 1994 (CHE2001-496)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.2 (IIA 2.2)	Relative density of purified active substance	PAS *TAS*	EEC A 3 (air comparison pycnometer) *EEC A 3 (air comparison pycnometer)*	Y *Y*	d_4^{20} = 1.687 *d_4^{20} = 1.681*	Acceptable not required additional info	Kästel, 1994 (CHE2001-498) *Kästel, 1996 (CHE2001-497)*
B.2.1.3.1 (IIA 2.3)	Vapour pressure of purified active substance	PAS	CF/P 006 = A 4.1.6.4 (v. p. balance)	Y N	< 1 · 10^{-5} Pa (20 °C)	Acceptable	Kästel, 1994 (LUF2001-191) Kröhl, 2001 (LUF2001-192)
B.2.1.3.2 (IIA 2.3)	Volatility, Henry's law constant of purified active substance	PAS	Calculation from vapour pressure and solubility in water	N	< 1.012 · 10^{-4} Pa · m^3 · mol^{-1} (20 °C)	Acceptable	Ohnsorge, 2000 (LUF2001-188)
B.2.1.4.1 (IIA 2.4)	Appearance: physical state	PAS TAS	Visual assessment	Y	PAS: crystalline solid TAS: powder, solid	Acceptable	Türk, 1994 (CHE2001-496) Kästel, 1996 (CHE2001-497)
B.2.1.4.2 (IIA 2.4)	Appearance: colour	PAS TAS	Visual assessment	Y	PAS: white TAS: white	Acceptable	Türk, 1994 (CHE2001-496) Kästel, 1996 (CHE2001-497)
B.2.1.4.3 (IIA 2.4)	Appearance: odour	PAS TAS	Organoleptic assessment	Y	PAS: odourless TAS: faint aromatic odour	Acceptable	Türk, 1994 (CHE2001-496) Kästel, 1996 (CHE2001-497)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.5.1 (IIA 2.5)	Spectra of purified active substance	PAS	UV/VIS OECD 101	Y	**λ_{max} [nm]** **ε** **(pH 6.7)** 202 18331 215 18515 237 21494 260 13021 300 144 **λ_{max} [nm]** **ε** **(pH 0.5)** 202 24440 212 21412 226 25172 254 7037 300 212 **λ_{max} [nm]** **ε** **(pH 13.3)** 219 18151 235 15825 260 11908 300 1890	Acceptable	Daum, 2000 (CHE2001-499)
			IR NMR MS	Y	Spectra are consistent with given structure of tritosulfuron.	Acceptable	

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.5.2 (IIA 2.5)	Spectra for impurities of toxicological, ecotoxicological or environmental concern		UV/VIS IR NMR MS		The structural identity of AMTT is confirmed by ^{1}H-, ^{13}C-NMR, IR- MS- and UV-spectra	Acceptable	Daum, 2000 (CHE2001-499)
B.2.1.6 (IIA 2.6)	Solubility in water of purified active substance	PAS	EEC A 6 (column elution method)	Y	38.6 mg/l pH 4.7 (deionized water) 78.3 mg/l pH 10.2 0.94 mg/l pH 1.7 all at 20 °C	Acceptable	Daum, 2001 (CHE2001-500)
B.2.1.7 (IIA 2.7)	Solubility in organic solvents of the active substance as manufactured	TAS (95.6 %)	US-EPA Subdivision D Reference No. 63-8	Y	**Solvent — Solubility (20 °C)** *n*-Heptane — insoluble Toluene — < 10 g/l Dichloromethane — 25 g/l Methanol — 23 g/l Acetone — 250-300 g/l Ethyl acetate — 83-86 g/l Acetonitrile — 90-94 g/l 1-Octanol — 13 g/l 2-Propanol — < 10 g/l olive oil — < 10 g/l	Acceptable	Türk, 1994 (CHE2001-501)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.8 (IIA 2.8)	Partition coefficient of purified active substance	PAS (99.7 %)	OECD 117 (HPLC-method)	Y	log $P_{o/w}$ = 2.93 pH 2.7 calculated: log $P_{o/w}$ = 2.93 non-ionised form log $P_{o/w}$ = 2.85 pH 4 log $P_{o/w}$ = 0.62 pH 7 log $P_{o/w}$ = -2.38 pH 10 all at room temperature	Acceptable	Türk, 1994 (CHE2001-502)
B.2.1.9.1 (IIA 2.9)	Hydrolysis rate of purified active substance	PAS (98.2 %)	US EPA Subdivision N Ref.-No. 161-1	Y	Phenyl-Label: pH 4 (25 °C): 56 d; pH 9 (25 °C): 20 d; pH 5 and pH 7 (25 °C): > 70 d Triazin-Label: pH 4 (25 °C): 39 d; pH 9 (25 °C): 17 d; pH 5 and pH 7 (25 °C): > 62 d		Singh and Thornton, 1997 (WAS2001-210) Singh and Thornton, 1997 (WAS2001-211)
B.2.1.9.2 (IIA 2.9)	Direct phototrans-formation in purified water of purified active substance	PAS TAS	EPA Subdivision N Ref.-No. 161-2	Y	stable (pH 5 and pH 7)		Scharf, 1998 (LUF2001-186)
B.2.1.9.3 (IIA 2.9)	Quantum yield of direct photodegradation	PAS TAS	EPA Subdivision N Ref.-No. 161-2	Y	$\Phi = 1.05E^{-4}$ (pH 5); $2.23E^{-4}$ (pH 7)		Scharf, 1998 (LUF2001-186)
B.2.1.9.4 (IIA 2.9)	Dissociation constant (pK_a) of purified active substance	PAS (99.7 %)	OECD 112	Y	pk_a = 4.69		Türk, 1994 (WAS2001-216)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.10 (IIA 2.10)	Stability in air, indirect photo-transformation	PAS	Calculation according to the method of Atkinson	**N**	DT_{50} = 0.44 d (24 h day) k = 24.606 · 10^{-12} cm^3 $molecules^{-1}s^{-1}$		Scharf, 1995 (LUF2001-190)
B.2.1.11.1 (IIA 2.11)	Flammability of active substance as manufactured	TAS	EEC A10	Y	The as did not burn under test conditions. Therefore, the as is not considered highly flammable.	Acceptable	Löffler, 1995 (CHE2001-503)
B.2.1.11.2 (IIA 2.11)	Auto-flammability of active substance as manufactured	TAS	EEC A 16	Y	No autoflammability was observed up to 400 °C.	Acceptable	Löffler, 1995 (CHE2001-503)
B.2.1.12 (IIA 2.12)	Flash point of the active substance as manufactured	TAS	EEC A 9		The test was not conducted, because the melting point of the as is higher than 40 °C.	Acceptable	Kästel, 1996 (CHE2001-497)
B.2.1.13 (IIA 2.13)	Explosive properties of active substance as manufactured	TAS	EEC A 14	Y	The test was not conducted, because the chemical structure of the as gives no evidence of explosive properties.	Acceptable	Löffler, 1995 (CHE2001-503)
B.2.1.14 (IIA 2.14)	Surface tension	TAS PAS	EEC A 5 (OECD ring method)	Y	64.6 mN/m 1.0 % (w/w) at 20 °C 71.3 mN/m 0.5 % (w/w) and 71.0 mN/m 2.0 % (w/w) both at 20 °C	Acceptable not required additional info	Kästel, 1996 (CHE2001-497) Kästel, 1994 (CHE2001-498)
B.2.1.15 (IIA 2.15)	Oxidising properties of active substance as manufactured	TAS	EEC A17	Y	The test substance is not considered an oxidising substance.	Acceptable	Löffler, 1995 (CHE2001-503)

B.2.1.16: Summary of data presented under points B.2.1.1 to B.2.1.15

Tritosulfuron (pure and technical active substance) is a white solid. A melting point of approx. 168 °C was determined for PAS. Decomposition of the as was observed at 340 °C. The vapour pressure (< $1 \cdot 10^{-7}$ hPa) and volatility (< $1.012 \cdot 10^{-4}$ Pa · m^3 · mol^{-1}, 20 °C) of tritosulfuron are very low. Tritosulfuron is hydrolytical and photolytical stable under environmental conditions. The water solubility and the log $P_{o/w}$ depends on the pH value (approx. 1 to 78 g/l, 20 °C and approx. 2.9 to – 2.4, respectively). The test substance is soluble in acetone (> 250 g/l), dichloromethane (25 g/l), ethyl acetate (83 g/l), methanol (23 g/l). Lowest solubility are observed in toluene (< 10 g/l). The substances is insoluble in *n*-heptane. The substance is not highly flammable or autoflammable, not explosive and without oxidising properties.

B.2.2 Physical, chemical and technical properties of the plant protection products (Annex IIIA 2)

Product name: BAS 635 00 H (containing 714 g/kg tritosulfuron, WG)

Table B.2.2-1: Summary of the physical, chemical and technical properties of the plant protection product

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.1.1 (IIIA 2.1)	Appearance: colour	Visual assessment	Brown	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.1.2 (IIIA 2.1)	Appearance: odour	Olfactory assessment	Faint aromatic	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.1.3 (IIIA 2.1)	Appearance: physical state	Visual assessment	Solid	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.2.1 (IIIA 2.2)	Explosive properties	Assessment	The test has not been carried out because of the chemical structure of the as and the formulants.	Acceptable	Loeffler, U. (1996) PHY2001-608
B.2.2.2.2 (IIIA 2.2)	Oxidising properties	EEC A 17	Neither as nor formulants have oxidising properties.	Acceptable	Loeffler, U. (1996) PHY2001-608
B.2.2.3.1 (IIIA 2.3)	Flash point		No liquid preparation.	Acceptable	
B.2.2.3.2 (IIIA 2.3)	Flammability	EEC A 10	Not highly flammable.	Acceptable	Loeffler, U. (1996) PHY2001-608
B.2.2.3.3 (IIIA 2.3)	Auto-flammability	EEC A 16	BAS 635 00 H is not considered to be a self-heating substance.	Acceptable	Loeffler, U. (1996) PHY2001-608
B.2.2.4.1 (IIIA 2.4)	Acidity/alkalinity		Not necessary.	Acceptable	
B.2.2.4.2 (IIIA 2.4)	pH	CIPAC MT 75.2	5.2 at 1 % concentration in CIPAC water D	Acceptable	Kaestel, R. (1997) PHY2001-607

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.5.1 (IIIA 2.5)	Kinematic viscosity		Not applicable.	Acceptable	
B.2.2.5.2 (IIIA 2.5)	Dynamic viscosity		Not applicable.	Acceptable	
B.2.2.5.3 (IIIA 2.5)	Surface tension		Not necessary.	Acceptable	
B.2.2.6.1 (IIIA 2.6)	Relative density		Not applicable.	Acceptable	
B.2.2.6.2 (IIIA 2.6)	Bulk (tap) density	CIPAC MT 169	Pour: 645 g/l Tap: 727 g/l	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.7.1 (IIIA 2.7)	Storage stability	CIPAC MT 46	Physically and chemically stable after storage for 2 weeks at 54 °C. There is less than 5 % decrease in the active substance content.	Acceptable	Kaestel, R. (1997) PHY2001-607 Kaestel, R. (2000) PHY2001-609
B.2.2.7.2 (IIIA 2.7)	Low temperature stability		No liquid preparation.	Acceptable	
B.2.2.7.3 (IIIA 2.7)	Shelf-life	GIFAP Monograph 17	Physical and chemical stable after storage for 2 years. There is less than 5 % decrease in the active substance content. The alteration of the observed physical properties (pH-range, wettability, persistant foaming, suspensibility, dispersibility, wet sieving, dust content) are negligible.	Acceptable	Koenig, W. (1998) PHY2001-610 Kaestel, R. (1998) PHY2001-611
B.2.2.8.1 (IIIA 2.8.1)	Wettability	CIPAC MT 53.3	63 sec (without swirling in CIPAC water D)	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.2 (IIIA 2.8.2)	Persistant foaming	CIPAC MT 47.2	Foam after 1 min: 0 ml (at 0.04 % concentration in CIPAC water D)	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.3.1	Suspensibility	CIPAC MT 168	105 %	Acceptable	Kaestel, R. (1997)

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
(IIIA 2.8.3)			(at 0.04 % concentration in CIPAC water D)		PHY2001-607
B.2.2.8.3.2 (IIIA 2.8.3)	Spontaneity of dispersion	CIPAC MT 174	99 % After accelerated storage for 2 weeks at 54 °C: 97 %	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.4 (IIIA 2.8.4)	Dilution stability		Not applicable.	Acceptable	
B.2.2.8.5 (IIIA 2.8.5)	Wet sieve test	CIPAC MT 167	Residue on 75 µm sieve: 0 %	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.6.1 (IIIA 2.8.6)	Particle size distribution	CIPAC MT 170 (Air Jet Sieving)	≤ 10 % 250 µm ≥ 90 % 1000 µm (≤ 50 µm 0.6 %)	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.6.2 (IIIA 2.8.6)	Dust content	CIPAC 171	1.3 mg	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.6.3 (IIIA 2.8.6)	Attrition		No internationally agreed method available	Acceptable	
B.2.2.8.7.1 (IIIA 2.8.7)	Emulsifiability, emulsion stability and re-emulsifiability		Not applicable.	Acceptable	
B.2.2.8.7.2 (IIIA 2.8.7)	Stability of dilute emulsion		Not applicable.	Acceptable	
B.2.2.8.8.1 (IIIA 2.8.8)	Flowability	CIPAC MT 172	100 % (through a 5 mm sieve spontaneous)	Acceptable	Kaestel, R. (1997) PHY2001-607
B.2.2.8.8.2 (IIIA 2.8.8)	Pourability (rinsability)		Not applicable.	Acceptable	
B.2.2.8.8.3 (IIIA 2.8.8)	Dustability		Not applicable.	Acceptable	

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.9.1 (IIIA 2.9)	Physical compatibility with other products	ASTM method E 1518-93	45 different mixtures of BAS 635 00 H and BAS 152 00 S (Citowett 2000, SL) with other plant protection products were tested. All of them were determined to be compatible in aqueous tank mixtures. Test substances: BAS 635 00 H + BAS 152 00 S (Citowett 2000, SL) and BAS 044 26 H (Duplosan DP) or BAS 037 32 H (Duplosan KV) or BAS 140 01 H (U 46 D Fluid) or BAS 141 07 H (U 46 M Fluid) or BAS 358 05 H (Basagran DP) or BAS 451 00 H (Arelon) or BAS 455 13 H (Stomp 400 SC) or BAS 615 00 H (Lotus) or BAS 9106 2 H (Compete 80 EW) or BAS 9109 0 H (Starane 180) or BAS 9228 0 H (Ralon Super) or BAS 9177 3 H (Topik 80 Plus) or BAS 9181 0 H (Gratil) or BAS 9164 1 F (Amistar) or BAS 481 07 F (Opus Top) or BAS 493 04 F (Juwel Top) or BAS 421 12 F (Corbel) or BAS 9072 0 F (Zenit M) or BAS 9151 0 F (Alto) or BAS 9181 0 F (Unix) or BAS 9183 0 F (Fortress Top) or BAS 008 00 D (Schwefelsaures Ammoniak) or BAS 012 00 D (Ensol) or BAS 124 11 I (Perfekthion) or BAS 9095 3 I (Karate WG) or BAS 9095 1 I (Karate EC) or BAS 062 10 W (Cycocel 720) or BAS 9053 0 W (Moddus) or BAS 183 06 H	Acceptable	Schneider, K.-H. (2001) PHY2001-612

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
			(Banvel) or BAS 517 22 H (Focus Ultra) or BAS 238 03 H (Certrol B) or BAS 600 01 H (Artett) or BAS 656 07 H (Frontier X2) or BAS 670 00 H or BAS 9144 0 H (Motivell) or BAS 9174 0 H (Cato) or FHS or BAS 9184 0 H (Mikado) or BAS 9018 1 H (Lentagran WP) or BAS 9018 2 H (Lentagran EC) or BAS 9113 0 H (Stentan) or BAS 9196 0 H (Tacco) or BAS 9310 0 H (Terano) or BAS 9224 0 H (Lido SC)		
B.2.2.9.2 (IIIA 2.9)	Chemical compatibility with other products	ASTM method E 1518-93	There were no indications of chemical reactions between the mixed products. Mixtures with: BAS 635 00 H + BAS 152 00 S (Citowett 2000, SL) and BAS 044 26 H (Duplosan DP) or BAS 037 32 H (Duplosan KV) or BAS 358 05 H (Basagran DP) or BAS 451 00 H (Arelon) or BAS 455 13 H (Stomp 400 SC) or BAS 615 00 H (Lotus) or BAS 9106 2 H (Compete 80 EW) or BAS 9109 0 H (Starane 180) or BAS 9228 0 H (Ralon Super) or BAS 9177 3 H (Topik 80 Plus) or BAS 9181 0 H (Gratil) or BAS 9164 1 F (Amistar) or BAS 481 07 F (Opus Top) or BAS 493 04 F (Juwel Top) or BAS 421 12 F (Corbel) or BAS 9072 0 F (Zenit M) or BAS 9151 0 F (Alto) or BAS 9181 0 F (Unix) or BAS 9183 0 F (Fortress Top) or BAS 008 00 D	Acceptable	Schneider, K.-H. (2001) PHY2001-612

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
			(Schwefelsaures Ammoniak) or BAS 012 00 D (Ensol) or BAS 124 11 I (Perfekthion) or BAS 9095 3 I (Karate WG) or BAS 9095 1 I (Karate EC) or BAS 9053 0 W (Moddus) or BAS 183 06 H (Banvel) or BAS 517 22 H (Focus Ultra) or BAS 238 03 H (Certrol B) or BAS 656 07 H (Frontier X2) or BAS 9144 0 H (Motivell) or FHS or BAS 9184 0 H (Mikado) or BAS 9018 1 H (Lentagran WP) or BAS 9018 2 H (Lentagran EC) or BAS 9310 0 H (Terano) tends to foaming. In such mixtures a foam protection agent should be added.		
B.2.2.10 (IIIA 2.10)	Adherence and distribution to seeds		No seed dressing formulation.	Acceptable	

B.2.2.11: Summary and evaluation of data presented under points B.2.2.1 to B.2.2.10 (IIIA 2.11)

BAS 635 00 H is a brown, free flowing water dispersible granule with a faint aromatic odour. It has neither explosive nor oxidising properties and it is not highly flammable. Its pH-value of 5.25 ± 0.05 lies within the naturally occuring in the acidic range. The results of the accelerated storage test and the shelf life test confirm its stability at least for two years under practical and commercial conditions. Its technical properties indicate no particular problems when used as recommended.
For the purpose of better efficacy BAS 635 00 H is applied together with Citowett 2000 (BAS 152 00 S). The compatibility study according to ASTM method E 1518-93 shows that the tank mixture is applicable without any problems as recommended.

B.2.3 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
AIIA-2.1.1; AIIA-2.2; AIIA-2.4; AIIA-2.12; AIIA-2.14	Kaestel, R.	1996	Physical and chemical properties Report for 271 272. 96/10136 GLP, unpublished CHE2001-497	Y	BAS
AIIA-2.1.1; AIIA-2.1.3; AIIA-2.4	Tuerk, W.	1994	Determination of the appearance, the melting point and thermal conversions of Reg.-No. 271272 (PAI). 94/11228 GLP, unpublished CHE2001-496	Y	BAS
AIIA-2.2	Kaestel, R.	1994	Physical and chemical properties Report for 271 272. 94/10728 GLP, unpublished CHE2001-498	Y	BAS
AIIA-2.3.1	Kaestel R.	1994	Physical and chemical properties. 1994/10728 GLP, unpublished LUF2001-191	Y	BAS
AIIA-2.3.1	Kröhl, T.	2001	Method of determining the vapor pressure, CF-P 006. 2001/1010678 not GLP, unpublished LUF2001-192	Y	BAS

[2] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
AIIA-2.3.2; AIIA-7.2.2	Ohnsorge U.	2000	Physical and chemical properties (Henry's law constant). 2000/1013447 not GLP, unpublished LUF2001-188	Y	BAS
AIIA-2.5	Daum, A.	2000	UV-, NMR-,IR-, MS-Spectra of Tritosulfuron PAI (BAS 635 H, Reg.-No. 271272. 2000/1018472 GLP, unpublished CHE2001-499	Y	BAS
AIIA-2.6	Daum, A.	2001	Determination of the solubility in water of Tritosulfuron (BAS 635 H, Reg.-No. 271272). 2001/1001015 GLP, unpublished CHE2001-500	Y	BAS
AIIA-2.7	Tuerk, W.	1994	Determination of the solubility of Reg.-No. 271272 technical active ingredient (TAI) in organic solvents at 20 °C. 94/11101 GLP, unpublished CHE2001-501	Y	BAS
AIIA-2.8	Tuerk, W.	1994	Determination of the Octanol/Water-partition Coefficient of Reg.-No. 271272 by HPLC. 94/10658 GLP, unpublished CHE2001-502	Y	BAS
AIIA-2.9.1; AIIA-7.2.1.1	Singh M.	1997	Hydrolysis of 14C-BAS 635 H (triazine label) in aqueous media. 1996/5091 GLP, unpublished WAS2001-211	Y	BAS
AIIA-2.9.1; AIIA-7.2.1.1	Singh M.	1997	Hydrolysis of 14C-BAS 635 H (phenyl label) in aqueous media. 1996/5057 GLP, unpublished WAS2001-210	Y	BAS
AIIA-2.9.2; AIIA-2.9.3; AIIA-7.2.1.2	Scharf J.	1998	Aqueous photolysis of BAS 635 H at pH 5 and pH 7. 1998/10981 GLP, unpublished LUF2001-186	Y	BAS
AIIA-2.9.4	Tuerk W.	1994	Determination of the pKa of Reg.-No. 271272 in water at 20 °C. 1994/10525 GLP, unpublished WAS2001-216	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
AIIA-2.10; AIIA-7.2.2	Scharf J.	1995	Photochemical oxidative degradation of BAS 635 H. 1995/11094 not GLP, unpublished LUF2001-190	Y	BAS
AIIA-2.10; AIIA-7.2.2	Scharf J.	1998	Laboratory study on the volatilization of BAS 635 H after application of BAS 635 00 H on soil and plant surfaces. 1998/10982 GLP, unpublished LUF2001-189	Y	BAS
AIIA-2.11.1; AIIA-2.11.2; AIIA-2.13; AIIA-2.15	Loeffler, U.	1996	Safety characteristics of the active ingredient 271 272. 96/10135 GLP, unpublished CHE2001-503	Y	BAS
AIIA-2.14	Kroehl, T.	2001	Determination of the Surface Tension (Ring-/Plate-Method). 2001/1010679 not GLP, unpublished CHE2001-504	Y	BAS
AIIIA-2.1; AIIIA-2.4; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-4.1	Kaestel, R.	1998	Shelf Life in Original Container of BAS 635 00 H Physical Properties Report [24 month-storage]. 98/10679 GLP, unpublished PHY2001-611	Y	BAS
AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-2.8.8	Kaestel, R.	1997	Physical and chemical properties Report for BAS 635 00 H. 97/10398 GLP, unpublished PHY2001-607	Y	BAS
AIIIA-2.2; AIIIA-2.3	Loeffler, U.	1996	Safety characteristics of the crop protection product BAS 635 00 H. 96/11117 GLP, unpublished PHY2001-608	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[2]
AIIIA-2.7	Kaestel, R.	2000	Accelerated Storage Stability of BAS 635 00 H Final Report. 2000/1000089 GLP, unpublished PHY2001-609	Y	BAS
AIIIA-2.7	Koenig, W.	1998	Storage Stability in Original Container of BAS 635 00 H 24 month-storage; Analytical Results. 98/10855 GLP, unpublished PHY2001-610	Y	BAS
AIIIA-2.9	Schneider, K.-H.	1999	Physical and Chemical Compatibility in Aqueous Tank Mixtures of BAS 635 00 H + BAS 152 00 S. 1999/1005345 not GLP, unpublished PHY2002-73	Y	BAS
AIIIA-2.9	Schneider, K.-H.	2001	Physical and Chemical Compatibility in Aqueous Tank Mixtures of BAS 635 00 H + BAS 152 00 S with other products. 2001/1001033 not GLP, unpublished PHY2001-612	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-3: Data on application
and further information

B.3 Data on application and further information

B.3.1 Data on application relevant to the active substance (Annex IIA 3.1 to 3.6)

B.3.1.1 Function

Tritosulfuron (BAS 635 H) as a sulfonylurea is a new active substance developed by BASF Aktiengesellschaft. It is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in winter- and spring-sown cereals and maize.

B.3.1.2 Effects on harmful organisms and translocation in plants

Only weeds which have emerged at the time of application will be controlled. Optimum timing is when weeds are still small and have not begun to compete with the crop. The herbicidal action is mainly over the leaves. Upon uptake by the leaves, tritosulfuron, is to a limited extent, systemically translocated in the plant (i.e. acropetally and basipetally). The application of tritosulfuron results in the blockage of the enzyme acetolactate-synthase (ALS) also referred to as acetohydroxy acid synthase. The inhibition of ALS activity leads to amino acid starvation and to the accumulation of toxic precursors. The primary effect of the herbicide is the restraint of new growth and cell development of susceptible weeds. Tritosulfuron at the recommended application rates is well tolerated in all tested cereals and maize varieties.

B.3.1.3 Field of use

The product is intended to be used in agriculture. It is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in cereals (winter and spring wheat, winter and spring barley, winter rye, oats, triticale) and maize in the Northern and Southern European countries.

B.3.1.4 Harmful organisms

The range of weeds susceptible to tritosulfuron is represented by
Amaranthus spp.
Anthemis spp.
Atriplex spp.
Chenopodium spp.
Cirsium arvense
cruciferous weeds
Galinsoga spp.
Galium aparine
Lamium spp.
Matricaria spp.
Polygonum spp.
Solanum nigrum
Stellaria media

B.3.1.5 Mode of action and details of active metabolites or degradation products

The application of the sulfonylurea tritosulfuron results in the blockage of the enzyme acetolactate-synthase (ALS) also referred to as acetohydroxy acid synthase. ALS is the first enzyme in the pathway for the biosynthesis of the essential branched-chain amino acids valine, leucine and isoleucine. The inhibition of ALS activity leads to amino acid starvation and to the accumulation of toxic precursors. The primary effect of the herbicide is the restraint of new growth and cell development of susceptible weeds.
ALS is inhibited by a number of structurally different classes of chemical herbicides, including the sulfonylureas, imidazolinons, triazolpyrimidins and pyrimidyl-oxy-benzoates. Inhibitors of ALS are so called slow-binding inhibitors, meaning that the inhibition develops with a time lag and an enzyme-inhibitor complex is formed in the presence of all cofactors and pyruvate. This complex dissociates extremely slowly though the inhibitor is not bound covalently. The inhibitors are attached at or close to the quinone-binding site, which is seemingly nonfunctional in ALS. There may be differences in binding among compounds of different chemistry which still has to be clarified.

B.3.1.6 Information on the occurrence or possible occurrence of the development of resistance or cross-resistance and appropriate management strategies

In accordance with the "Guideline for the efficacy evaluation of plant protection products" (Guidelines for efficacy evaluation of plant protection products. Resistance risk analysis. Bulletin OEPP/EPPO, Bulletin 29, PP 1/213 (1), 325 – 347, 1999) the notifier executed the following resistance risk analysis:

Mechanism of resistance
Since ALS-inhibiting herbicides have been used world wide over more than 15 years, there is a huge amount of information about the dissemination of weeds resistant to ALS-inhibitors. The first species, to have evolved resistance to ALS-inhibiting herbicides, were reported already in 1987 (Claude and Cornes 1999). Since then, the number of sites with resistant populations has continuously increased. An overview was given by I. HEAP and updated on January 2001. According to this, ALS-resistant biotypes of 65 plant species have been found world wide up to now (Claude and Cornes 1999). Principally, resistance to herbicides can be caused by target site modification or by increased herbicide metabolism (Devine and Preston 2000). However in the case of ALS-resistant weeds, the majority of the detected ALS-resistant biotypes are based on target site modifications. For example, ALS-resistant biotypes of 11 weed species have been identified in Europe. However, only biotypes of the 2 grass weeds, *Alopecurus myosuroides* and *Lolium multiflorum*, have shown a metabolic resistance. The others, including all broadleaf weeds, were target resistant (Claude and Cornes 1999).

Evidence of resistance

Up to now in the numerous field trials performed by BASF in Europe and the baseline sensitivity trials, no resistant weeds to tritosulfuron have been found. However, in specific greenhouse trials, it could be shown that there are resistant weed species to tritosulfuron (BAS 635 H) in Europe.
In these trials, 3 ALS-resistant biotypes of *Stellaria media,* 1 of them from Denmark, 2 from USA, were treated with tritosulfuron revealing the resistance. It had been published that the

biotype from Denmark is target resistant (Kudsk et al. 1995) and, most likely, the other ones are too.
It can be assumed that, besides of the already mentioned biotype from Denmark, some other ALS-resistant weed biotypes in Europe are resistant to tritosulfuron. From these, only the broad-leaved biotypes are of interest since tritosulfuron is effective against broad-leaved weeds only. In Europe, there are 5 dicotyledonous species from which ALS-resistant biotypes have been described: *Chrysanthemum segetum, Conyca albida, Kochia scoparia, Papaver rhoeas* and *Stellaria media* (Claude and Cornes 1999). These resistant biotypes are existing on only a few sites in Europe, and were selected at these sites by continuous use of ALS-inhibitors over many years. In the following, the 3 species with the largest infested areas are given as examples.

Kochia scoparia:
A large number of sites with ALS-resistant summer-cypress were reported from the Czech Republic where it only grows along railways and roadsides and where it was selected by repeated use of ALS-inhibitors (Heap 2001).

Papaver rhoeas:
ALS-resistant biotypes of *Papaver rhoeas* were found in cereal monocultures in Spain (> 50 sites), Greece (1 site) and Italy (2 - 5 sites) after several years of ALS-inhibitor treatment. In addition, an ALS-resistant biotype with a weak cross-resistance to 2,4-D was described. This biotype grew in a cereal field near Biosca, Spain, which was treated 7 years in succession with tribenuron-methyl. This biotype in laboratory tests revealed a weak cross-resistance (3-fold) to 2,4-D. In the field, it could be effectively controlled by tribenuron-methyl + metribuzine (Heap 2001).

Stellaria media:
ALS-resistant *Stellaria media* was found in Denmark (1991) and in Sweden (1995) on one site each. Spring barley had been grown continuously in the Danish field since 1984 and treated with sulfonylurea herbicides every year (Kudsk et al. 1995). In Sweden monoculture of cereals was continuously treated with sulfonylurea herbicides (Heap 2001).
For further information about the occurrence of ALS-resistant weed biotypes in Europe see (Claude and Cornes 1999).

Cross-Resistance

The technical term ”cross resistance” has different definitions in the scientific literature (Powles and Preston 1995). According to the definition of the EPPO-guideline, this term is used, when weeds resistant to a new compound like tritosulfuron have additional resistance to other compounds of the same or other chemical classes (independent of their mode of action).
The cross-resistance of different ALS-resistant weed species to tritosulfuron as well as to other herbicides was tested in greenhouse trials.

Tested biotypes:	3 resistant biotypes of *Stellaria media*
ALS-inhibitors:	tritosulfuron nicosulfuron metsulfuron

Non-ALS-inhibitors: 2,4-D
CMPP-P
Artett (bentazon + terbuthylazin)

a) Cross-resistance to ALS-inhibiting herbicides
The cross-resistance pattern of the 3 resistant biotypes revealed a weak variation. Biotype BT 444 from Denmark was highly resistant to metsulfuron and nicosulfuron only. In contrast, BT 522 from Canada revealed a higher resistance to metsulfuron and tritosulfuron than to nicosulfuron. Biotype 521 from Canada had the same level of resistance to all of the 3 herbicides. This variation of the resistance pattern of ALS-resistant biotypes to ALS-inhibitors has already been found before (Devine and Preston 2000) and is caused by the occurrence of more than one mutation sites in the ALS gene. On the one hand, these varying mutations lead to the mentioned differences of the resistance patterns of sulfonylurea-herbicides. On the other hand, they also lead to different specific resistance regarding the four chemical classes that inhibit the ALS-enzyme: imidazolinones sulfonylureas, triazolpyrimidine sulfonanilides, and pyrimidinylthiobenzoates (Devine and Preston 2000). Therefore, biotypes resistant to specific ALS-inhibitors can sometimes be controlled in the field by other ALS-inhibitors.

b) Cross-resistance to non-ALS-inhibiting herbicides
The 3 weed biotypes resistant to tritosulfuron were well controlled by 2,4-D, CMPP-P, and Artett. This is not surprising since all of the ALS-resistant weed biotypes have probably a target-site resistance and these three herbicides do not effect the ALS (acetolactate synthase).
2,4-D and CMPP-P are two of the numerous auxin-type herbicides. Although the mechanism of action of these herbicides is not fully understood, it is generally accepted they interfere with several auxin-mediated processes. In contrast, Artett contains terbutylazine and bentazone, and both as are inhibitors of photosystem II.

Baseline Sensitivity

According to the EPPO-Guideline (Kudsk 1995), a baseline sensitivity test with 10 seed samples from Germany, Spain, Italy, France and UK was performed (*Amaranthus retroflexus, Chenepodium album, Stellaria media*). The plant species used are important dicotyledonous weeds in corn and small grain cereals and main targets for tritosulfuron. The measured natural variation of the sensitivity to tritosulfuron between these randomly collected weed biotypes was very small.
Indications for the occurrence of resistant biotypes could not be found by this method since ALS-resistant weed biotypes are confined to very limited areas in Europe with monoculture cropping systems (Claude and Cornes 1999, Heap 2001) and it is difficult to find ALS-resistant weeds randomly.

Test Methods

The cross-resistance and baseline trials were performed in a greenhouse according to the EPPO-Guidelines on Phytotoxicity Assessment (no. 135), on Design and Analysis of Efficacy Evaluation Trials (no. 152), and for the Efficacy Evaluation of Plant Protection Products (no. 181). The plants were cultivated in humous sand to 2 – 8 leaf stage depending on the plant species. The test substances were applied using a laboratory spraying cabin. Following the application, all plants were assessed for symptoms of phytotoxicity (visual assessment) about 7 and 21 days after application. The greenhouse trials were conducted in compliance with

Good Experimental Practice. The testing facility is officially recognised as an organisation for efficacy testing of plant protection products according to the Directive 93/71/EC.

Use Pattern (unrestricted)

The use pattern in the absence of resistance is one application per year of 50 g as/ha tritosulfuron, applied in tank mixture with a surfactant.

Resistance Risk Assessment of Unrestricted Use Pattern and
Acceptability of Resistance Risk

There is a measurable likelihood that all natural weed populations regardless of the application of any herbicide, contain individual plants (biotypes) which are resistant to herbicidal as. Based on the current evidence of ALS-resistance in Europe in general, the resistance risk for tritosulfuron can be stated to be low. However, the risk that, following application, a resistant plant survives and spreads in the field, depends on the cropping system used.

Case A) Herbicide rotation or mixtures

In cropping systems with crop rotation and the use of mixtures or sequences of herbicides with differing modes of action or monocultures and the use of mixtures or sequences of herbicides with differing modes of action, the occurrence or spreading of weeds populations resistant to tritosulfuron or other ALS-inhibiting herbicides is very unlikely. Randomly occurring tritosulfuron-resistant individual plants in the fields are killed at the latest with the succeeding crop by cultivation practice or non-ALS-inhibiting herbicides. This conclusion is in agreement with theoretical investigations of herbicide resistance as well as practical experience on the use of ALS-inhibiting herbicides over many years. For example, metsulfuron-methyl (Ally) and tribenuron-methyl (Granstar) has been routinely used in cereals since 1984 and 1986, respectively, without resistance problems in cropping systems with crop rotation.

Acceptability of the risk (case A):
The resistance risk is acceptable in cropping systems mentioned above.

Case B) Continuous application of tritosulfuron or other ALS-inhibiting herbicides

The frequent use of only one mode of action (i. e. no alternation or combined application with other modes of action) is the most important factor in the development of herbicide resistance. Resistance often becomes a problem because of high selection pressure exerted on a weed population over several years. Therefore, the risk is high when tritosulfuron is used continuously over several years or tritosulfuron is used over several seasons in a sequence with other ALS-inhibiting herbicides. This conclusion can be drawn from the finding that ALS-resistant weed biotypes can be found in Europe only in monocultures with repeated application of ALS-inhibiting herbicides (see ”Evidence of resistance“). Cropping systems mentioned under c) and d) are on the one hand monocultures of monocotyledonous crops like cereals and corn, and on the other hand successions of crop including exclusively monocotyledonous crops such as cereals and corn.

Acceptability of the risk (case B):
The resistance risk is not acceptable in cropping systems as described under B.

Management strategy for unacceptable risk

BASF is a founder member of the HRAC Working Group and has participated in forming the guidelines for management strategy (Anonymous 1999)
The basic principles of resistance management are similar both in the prevention of resistance in a given population as well as in the limitation of resistance after its first occurrence. Once problems have been detected, management strategies have to be adapted to the particular situation. As a rule, the following methods can be recommended:

- mixtures or sequences of herbicides with differing modes of action
- crop rotation
- cultivation practices (Anonymous 1999)

For tritosulfuron, a special resistance risk management strategy is only necessary with regard to case B above. The management strategy is to prevent a continuous straight use of tritosulfuron over several years or the use of straight tritosulfuron over several seasons in a sequence with other ALS-inhibiting herbicides only.

Implementation of Management Strategy

To avoid the occurrence of weed biotypes resistant to tritosulfuron, the following measures will be performed:

a) The instructions for use of the products contain recommendation like the following (as an example):

" important note: With herbicides with the same mode of action as product X the risk of occurring resistant weeds generally exists. Therefore a modification in the effectiveness of the herbicide cannot be excluded under particularly unfavorable conditions. The application rate recommended by the BASF is to be kept absolutely. In repeated measures for the fight against dicotyledonous weeds within the same cultivation period or in successive cultivation periods is is to be paid attention to the use of products with different effect mechanisms.

b) Implementation of the resistance management strategy will be done by the already established methods of informing through product brochures and training seminars.

Monitoring, Reporting and Reaction to changes in Performance

In the case, that BASF obtains information about the occurrence of tritosulfuron-resistant biotypes after application of tritosulfuron-containing products, BASF will inform HRAC, the named competent authority and will take action that the respective farmer applies the resistance management strategies as developed and recommended by tritosulfuron. Once resistant biotypes have been detected, management strategies must be customized to the particular situation under consideration of points of view published by HRAC.

B.3.2 Data on application relevant to the plant protection product (Annex IIIA 3)

B.3.2.1 Field of use envisaged

The herbicide BAS 635 00 H is a water dispersible granules (WG). The active ingredient is 714 g/kg tritosulfuron. The product is intended to be used in agriculture.

B.3.2.2 Effects on harmful organisms

The herbicidal action is mainly over the leaves. Upon uptake by the leaves, BAS 635 00 H, is to a limited extent, systemically translocated in the plant (i.e. acropetally and basipetally). The application of the sulfonylurea tritosulfuron results in the blockage of the enzyme acetolactate-synthase (ALS) also referred to as acetohydroxy acid synthase. The inhibition of ALS activity leads to amino acid starvation and to the accumulation of toxic precursors. The primary effect of the herbicide is the restraint of new growth and cell development of susceptible weeds. The product is most effective if applied on young growing dicotyledonous weeds. BAS 635 00 H at the recommended application rates is well tolerated in all tested cereals and maize varieties.

B.3.2.3 Details of intended uses

BAS 635 00 H is intended to be used in cereals (autumn and spring sown) and maize. It is a post-emergence herbicide with systemic action. BAS 635 00 H must be used as a mixture with an additive (e.g. Citowett New) at a rate of 70 g/ha BAS 635 00 H and 1.25 l/ha Citowett New. The recommended spray (water) volume is from 150 to 400 l/ha. The maximum number of applications is one. The timing is between BBCH 12-18 (maize) and 13-39 (cereals). Application is confined to the spring season.

B.3.2.4 Application rate per unit treated

The application rate is 70 g/ha BAS 635 00 H, corresponding 50 g as/ha tritosulfuron. The recommended spray (water) volume is from 150 to 400 l/ha. Application will be recommended in mixture with a surfactant.

B.3.2.5 Concentration of active substances

The product BAS 635 00 H is applied at water volumes of 150 to 400 l/ha. At the field rate of 70 g/ha BAS 635 00 H the concentration of tritosulfuron is between 0.33 g/l to 0.13 g/l in the spray liquid.

B.3.2.6 Method of application

The intended method of application is spraying by means of each type of straying equipment which is normally used for applying herbicides in practical agriculture. The diluent is water. The recommended spray (water) volume is from 150 to 400 l/ha.

B.3.2.7 Number and timing of applications and duration of protection

The maximum number of applications is one. The timing is between BBCH 13 and 39 (spring-sown cereals) or between BBCH 21 and 39 (autumn-sown cereals) in cereals. In maize BAS 635 00 H can be applied from the two leaf stage of the crop (BBCH 12) until the 8 leaf stage of the crop (BBCH 18). Application is confined to the spring.

B.3.2.8 Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops

There are no waiting periods necessary to be observed.

B.3.2.9 Proposed instructions for use

The herbicide BAS 635 00 H is a water dispersible granules (WG). The chemical family is sulfonylurea. The active ingredient is 714 g/kg tritosulfuron. The product is intended to be used in agriculture. It is a systemic herbicide for the post-emergence control of a range of dicotyledonous weeds in cereals (winter and spring wheat, winter and spring barley, winter rye, oats, triticale) and maize. BAS 635 00 H **must** be used as a mixture with an additive (e.g. Citowett New) at a rate of 70 g/ha BAS 635 00 H and 1.25 l/ha Citowett New. In winter cereals (TRZAW, HORVW) BAS 635 00 H can be applied from the begin of tillering of the crop (growth stage 21, BBCH Code) until the flag leaf stage (growth stage 39, BBCH Code), in summer cereals (TRZAS, TRZDU, HORVS, AVESA, SECCE, TTLSS) from the three leaf stage of the crop (growth stage 13, BBCH Code) until the flag leaf stage (growth stage 39, BBCH Code) and in maize (ZEAMX) from the two leaf stage of the crop (growth stage 12, BBCH Code) until the 8 leaf stage of the crop (growth stage 18, BBCH Code).

B.3.3 Summary of data on application

List of uses supported by available data

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests Controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of g as/kg (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Maize	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	12-18	1	-	0.013-0.033	150-400	0.05	F	
Maize	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	12-18	1	-	0.013-0.033	150-400	0.05	F	
Cereals, winter	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	21-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, winter	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	21-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, summer	Northern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	13-39	1	-	0.013-0.033	150-400	0.05	F	
Cereals, summer	Southern Europe	BAS 635 00 H	F	Dicotyledonous weeds	WG	714	spraying	13-39	1	-	0.013-0.033	150-400	0.05	F	

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

B.3.4 Further information on the active substance (Annex IIA 3.7 to 3.9)

B.3.4.1 Recommended methods and precautions concerning handling, storage, transport or fire (Annex IIA 3.7)

Ref.: Anonymous, 2000 (CHE2001-505, Material safety data sheet)

B.3.4.1.1 Handling

Information on safe handling:
Avoid dust formation.
Protection against fire and explosion:

Personal Precautions:

The usual precautions for the handling of chemicals must be observed
avoid contact with the skin, eyes and clothing

Respiratory protection:	if dust forms dust mask
Hand protection	chemical resistant gloves
Eye Protection:	safety glasses
Body Protection:	protective suit

B.3.4.1.2 Storage

Stow/store/load separately from food, feed and consumable items. Keep in dry place.

B.3.4.1.3 Transport

Not classified as hazardous under transport regulations.

B.3.4.1.4 Fire fighting measures

Suitable extinguishing media:
water spray, dry extinguishing media, carbon dioxide

The following can be given off in fire:
carbon monoxide, nitrogen oxides, sulphur dioxides, hydrogen fluoride

Special protective equipment:
in case of fire, wear a self contained breathing apparatus.
Fire/explosion fumes should not be inhaled.

Further information:
Collect separately contaminated extinguishing water, do not allow to reach sewerage or effluent systems.
Dispose of fire debris and contaminated extinguishing water in accordance with local regulations.

B.3.4.2 Procedures for destruction or decontamination (Annex IIA 3.8)

Unwanted amounts of tritosulfuron TC can be destroyed best by combustion in a licensed incinerator.

Decontamination of equipment, packing a.s.o. is achieved by washing with water. Packs that can not be cleaned should be disposed in the same manner as the contents.

B.3.4.3 Controlled incineration

The halogen content of tritosulfuron TC is below 60 %. Approximately 1100 °C are advised as incineration temperature. Expected combustion products are CO/CO_2, H_2O, N_2/NO_x, SO_2 and HF.

B.3.4.4 Others

Combustion in a licensed incinerator is the only disposal recommended, if tritosulfuron TC can not be used according to its purpose: the production of herbicides.

B.3.4.5 Emergency measures in the case of an accident (Annex IIA 3.9)

Incineration of the contaminated solid product. In case of contamination of water, the aqueous phase is to be collected and the undissolved amount of product has to be separated by filtration or by extraction with a suitable extraction solvent. The organic phase should be incinerated too.

The remaining aqueous phase has to be treated with activated carbon for at least 12 hours. The amount of carbon used should be about 100 times the concentration of the DOC caused by the dissolved tritosulfuron. In general 1.5 g/l of activated carbon are sufficient. After the treatment the separated activated carbon is to be incinerated too. The treated water (pH 6.5 - 9) should be introduced into a public sewer leading to a public owned wastewater treatment works (POTW).

Reference: Schwenk, 2000 (CHE2001-506)

B.3.5 Further information on the plant protection product (Annex IIIA 4)

B.3.5.1 Packaging (type, materials, size, etc.), compatibility of the preparation with proposed packaging materials (Annex IIIA 4.1)

B.3.5.1.1 Description of packaging (Annex IIIA 4.1.1)

BAS 635 00 H is to be marketed in mold blown high-density polyethylene containers (HDPE). They are sealed by foil seals, protected by screw caps of polypropylene.

0.25 litre bottle	material:	HDPE
	shape/size:	cylindrical / approx. 62.5 mm diameter x 126 mm
	opening:	42 mm inner diameter
	closure:	polypropylene screw cap
	seal:	HF-seal
0.5 litre container	material:	HDPE
	shape/size:	rectangular / approx. 69 mm x 186 mm x 362 mm
	opening:	42 mm inner diameter
	closure:	polypropylene screw cap
	seal:	HF-seal
1.0 litre container	material:	HDPE
	shape/size:	cylindrical / approx. 91 mm diameter x 234 mm
	opening:	42 mm inner diameter
	closure:	polypropylene screw cap
	seal:	HF-seal

B.3.5.1.2 Suitability of packaging (Annex IIIA 4.1.2)

The containers and outer packaging meet the ADR requirements. They are labeled individually with all the use instructions. Several bottles are packed in cardboard boxes.

These combination packs meet the requirements of UN 4G/Y (packaging group II) as specified by the ADR/RID regulations for the transport of hazardous goods.

The containers to be used are of sturdy HDPE. Many years of experience with other WG formulations, which are based on the auxiliaries Ufoxane 3A plus Wettol D3, too, have demonstrated that there will be no interaction of the product pearls with the wall material.

B.3.5.1.3 Resistance of packaging material to its contents (Annex IIIA 4.1.3)

Reference number:	III A 4.1.3 / 1
Report:	Kaestel R., 1998 Shelf life in original container of BAS 635 00 H - Physical properties report - [24 month-storage] BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep. unpublished PHY2001-611
Guidelines:	Appendix 1 to § 19 a, Section 1, Chemikaliengesetz of 25th July 1994
GLP:	Yes (laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

A 2-year shelf-life study including evaluation of any interaction of BAS 635 00 H with the PE material showed that BAS 635 00 H is stable for at least 24 months when stored in the unopened original container at 20 °C with 50 % relative humidity and at 30 °C. No adverse interaction between the formulated product and the container occured.

B.3.5.2 Procedures for cleaning application equipment and protective clothing (Annex IIIA 4.2)

Reference number:	III A 4.2 / 1
Report:	Stadler R., 2001 BAS 635 00 H (Tritosulfuron): Effectiveness of procedures for cleaning application equipment and protective clothing BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep. Unpublished PHY2001-613
Guidelines:	none
GLP:	No

When the field sprayer is cleaned with water according to the use instructions after application of BAS 635 00 H, the contamination in the spray immediately afterwards is negligible. Additionally, the effectiveness of cleaning was confirmed by biological tests; no plant damage was caused when the equipment was used subsequently for the treatment of different crops.

Therefore, cleaning the sprayer solely with water is considered completely adequate in the case of BAS 635 00 H. It is not necessary to add cleaning agents.

Protective clothing for applicators of agrochemicals is usually made of cotton. The polar surface of the fiber presents little affinity to the unpolar active ingredients. Therefore, usual laundering with detergents will either suspend or dissolve any contamination efficiently.

B.3.5.3 Re-entry periods, necessary waiting periods or other precautions to protect man, livestock and the environment (Annex IIIA 4.3)

The following safety intervals as defined in Annex IIIA point 4.3 are adequately covered by information described in chapters mentioned below.

- pre-harvest interval for each relevant crop
  see chapters B.7.4 and B.7.10
- re-entry period for livestock to areas to be grazed
  see chapters B.7.4 and B.7.10
- re-entry period for man to crops, building or spaces treated
  see chapter B.6.14
- withholding period from animal feeding stuffs
  see chapters B.7.4 and B.7.10
- waiting period between application and handling to treated products
  see chapters B.7.4 and B.7.10
- waiting period between last application and sowing or planting succeeding crops
  see chapter B.7.

B.3.5.4 Recommended methods and precautions concerning handling, storage, transport or fire (Annex IIIA 4.4)

Handling and storage
(Warehouse-/User level)

General information

The product is classified according to council directive 78/631/EEC.

Hazard Symbol(s)	Xi	Irritant
Hazard designations	R 43	May cause sensitization by skin contact
	S 2	Keep out of reach of children
	S 13	Keep away from food, drink and animal feeding stuffs
	S 20/21	When using, do not eat, drink or smoke
	S 24	Avoid contact with skin

Handling:

Open containers should only be handled in well-ventilated areas. Make provisions for product and fire-fighting water to be retained.

Storage:

Store out of reach of unauthorized persons. Keep away from food, feed and consumable item. Store in original container under usual warehouse conditions, i.e. dry and frost-free avoiding temperatures above 40 °C.

Keep the product away from sources of ignition - no smoking. Good ventilation is required.

For more detailed information see
- Guidelines for the safe handling of pesticides during their formulation, packing, storage and transport (GIFAP).
- Guidelines for the safe warehousing of crop protection produts (GCPF).
- Sichere Lagerung von Pflanzenschutz- und Schädlingsbekämpfungsmitteln (IVA).

Transport:

Follow the general rules and good practice for transport and - if applicable - the Dangerous Goods Regulations. Do not stow the product together with food, feed and consumable items.

General information:

Flammability:	Flash point: not applicable
Irritation:	Irritating to skin and eyes
Temperature limits:	Not applicable

IMDG Code (not yet classified)

UN No.:	Class:	PG:	MPO:
MFAG:	EmS:		
Declaration for sea shipment:		71.4 % Tritosulfuron	

RID/ADR (not yet classified)

ID No.:	Class:	Item No.:
Orange Warning Plate:		(Hazard No.) (Substance No.)

Declaration for land shipment: 71.4 % Tritosulfuron

ADNR (not yet classified)

ID No.:	Class:	Item No.:

Declaration for inland waterways shipment: 71.4 % Tritosulfuron

ICAO/IATA-DGR (not yet classified)

UN or ID No.:	Class:	PG:

Declaration for shipment by air: 71.4 % Tritosulfuron

Protective clothing and equipment proposed:

If product is handled while not enclosed and if skin contact may occur:

Use goggles to protect eyes.
Use respiratory equipment.
Use protective gloves for chemicals to protect hands.

Keep work area clean.
Avoid contact with product.
Keep working clothes separate from other clothing.
Change badly soiled or soaked clothing.
Wash hands before breaks and at end of work.

Procedures to minimise the generation of waste:

Only purchase and store quantities of product required in the short term. Do not mix a volume of spray solution greater than is required for immediate use.

Fire-fighting measures:

Extinguishing media:
Water spray, foam-water mixtures, dry powder, carbon dioxide or sand.
Contain fire-fighting water.
Fight fire if safe to do so.
Wear respiratory equipment,

in well-ventialted areas:	full-face mask with combination filter, e.g. ABEK-P2 (offers no protection from carbon monoxide!)
in enclosed premises:	respirator with independent air supply

Information on combustion products likely to be generated in the event of fire:

In the event of fire the formation of CO/CO_2, H_2O, N_2/NO_x, SO_2 and HF must be anticipated.

B.3.5.5 Emergency measures in case of an accident (Annex IIIA 4.5)

Prevent entry into drains, water or soil. If necessary use personal protective equipment.

Spillage BAS 635 00 H has to be collected with broom and shovel or preferably vacuum cleaner.

Use damp cloth to clean floors and other objects after removal of the product and/or contaminated adsorbent. Adding a detergent will enhance the cleaning process. Place recovered material, contaminated adsorbent and used cleaning materials into closeable receptacles.

Protection of emergency workers and bystanders:

Bystanders are requested to leave the emergency site.

For emergency workers it is a standard safety precaution to wear during clean-up operations goggles, rubber gloves, mouth-and-nose-mask and protective clothing.

First aid measures:

General Advice
Remove person from danger zone.
Remove contaminated clothing.

Upon Inhalation
Bring person to the fresh air.
Call medical help.

Following Skin Contact:
Wash skin thoroughly with soap and water.
Call medical help.

Following Eye Contact:
Wash affected eyes for at least 15 minutes under running water with eyelids held open.
Consult an eye specialist.

Upon Ingestion:
Immediately rinse mouth and then drink plenty of water.
Call medical help.

B.3.5.6 Procedures for destruction or decontamination of the plant protection product and its packaging (Annex IIIA 4.6)

Neutralisation procedures (e.g. reaction with alkali to form less toxic compounds) for use in the event of accidental spillage

Neutralisation procedure: see Annex II, 3.9

Pyrolytic behavior of the active substance under controlled conditions at 800°C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis

Due to a halogen content in the active ingredient of less than 60 % combustion in a waste incinerator plant does not raise concern about the formation of halogenated dibenzodioxins/-furans.

- Detailed instructions for safe disposal of the plant protection product and its packaging

For purposes of disposal, combustion of BAS 635 00 H in a licensed incinerator is recommended. This method of disposal applies also to contaminated packages, which cannot be cleaned or reused.

Although it is possible to incinerate the product at lower temperatures, a combustion at approx. 1100 °C with a residence time of about 2 sec. is advised.

By doing so, i.e., operating the incinerator according to the conditions laid down in council directive 94/67/EEC, one will achieve complete combustion and minimise the formation of undesired by-products in the off-gases.

Users are requested to triple rinse empty primary packages as described in the ECPA "Guidelines for the rinsing of agrochemical containers", 1993.

Pressure rinsing or integrated pressure rinsing of the packaging material achieves a similar or even better result. The rinsate must be added to the spray liquid.

To minimise waste of packages it is recommended that empty and rinsed containers are delivered to local container collection stations. If these are not existing, empty and rinsed containers must be rendered unusable and disposed of according to local regulations.

Methods other than controlled incineration for disposal of the plant protection product, contaminated packaging and contaminated material

No other methods for disposal of BAS 635 00 H than those described above are available.

B.3.6 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[3]
AIIA-3.6	Anonymous	1999	Detecting herbicide resistance Guidelines for conducting diagnostic tests and interpreting results. HRAC. www.plantprotection.org/HRAC/detecting.html (2001-09-14), 1999 not GLP, published BIO2001-311	N	-
AIIA-3.6	Anonymous	2001	Herbicide Resistance Action Committee. Partnership in the management of resistance. HRAC. www.plantprotection.org/HRAC/ Partnership.html(2001-09-14) not GLP, published BIO2001-310	N	-
AIIA-3.6	Anonymous	2001	Guideline to the management of herbicide resistance, HRAC guidelines. www.plantprotection.org/HRAC/ Guideline.html(2001-09-14) not GLP, published BIO2001-309	N	-

[3] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[3]
AIIA-3.6	Claude, J.-P., Cornes, D.	1999	Status of ALS-Resistance in Europe (Poster). 11. EWRS Symposium, Basel, 1999, 1999 not GLP, published BIO2001-304	N	-
AIIA-3.6	Devine, M. D., Preston, C.	2000	The molecular basis of herbicide resistance. Sheffield Academic Press, England, Cobb, A. H., Kirkwood, R. C., Herbicides and their mechanism of action, 2000, 73-104 not GLP, published BIO2001-303	N	-
AIIA-3.6	Heap, I.	2001	Herbicide resistant weed summary table (2001-01-08). www. weedresearch.com/Case/reference.asp(2001-09-14), 2001 not GLP, published BIO2001-306	N	-
AIIA-3.6	Heap, I.	2001	Herbicide resistant weed summary table (2001-01-08). www. weedresearch.com/summary/ MOAsummary.asp(2001-09-14), 2001 not GLP, published BIO2001-305	N	-
AIIA-3.6	Kudsk, P. et al.	1995	Sulfunylurea resistance in Stellaria media L. Weed research, 35, 1995, 19-24 not GLP, published BIO2001-307	N	-
AIIA-3.6	Powles, S. B., Preston, C.	1995	Herbicide cross-resistance and multiple resistance in plants, Monograph 2, HRAC publications. www.plantprotection.org/HRAC/ mono2.html(2001-09-14), 1995 not GLP, published BIO2001-308	N	-
AIIA-3.7	Gerlach, H.	2001	Safety data sheet - BAS 635 H. 2001/1004138 not GLP, unpublished CHE2001-505	Y	BAS
AIIA-3.9	Schenk, W.	2000	Possible Procedures of the Decontamination of Water from BAS 635 H. 2000/1013207 not GLP, unpublished CHE2001-506	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[3]
AIIIA-2.1; AIIIA-2.4; AIIIA-2.7; AIIIA-2.8.1; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.6; AIIIA-4.1	Kaestel, R.	1998	Shelf Life in Original Container of BAS 635 00 H Physical Properties Report [24 month-storage]. 98/10679 GLP, unpublished PHY2001-611	Y	BAS
AIIIA-4.2	Stadler, R.	2001	"BAS 635 00 H" (Tritosulfuron); Effectiveness of Procedures for Cleaning Application Equipment and Protective Clothing. 2001/1001640 not GLP, unpublished PHY2001-613	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-4: Proposals for the classification and labelling

B.4 Proposals for the classification and labelling

B.4.1 Proposals for the classification and labelling of the active substance (Annex IIA 10)

The following is proposed in accordance with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC):

Tritosulfuron (AMTT content ≤ 0.02 %)

Hazard symbol:	Xi	
	N	dangerous for the environment
Indication of danger:	Irritating	
Risk phrases:	R43	May cause sensitisation by skin contact
	R50/53	very toxic for aquatic species/can cause long-term concerns in water ecosystems

Reasons for classification
For justification of R43 see B.6.2.6 Skin sensitisation.

For justification of R50/53 see B.9.2 Effects on aquatic species.

B.4.2 Proposals for the classification and labelling of preparations (Annex IIIA 12.3 and 12.4)

The following is proposed in accordance with Directive 78/631/EEC in combination with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC):

BAS 635 00 H

Hazard symbol:	N	dangerous for the environment
Indication of danger:	None	
Risk phrase:	R50/53	very toxic for aquatic species /can cause long-term concerns in water ecosystems

Reasons for classification
For justification see B.6.11: Acute toxicity including irritancy and skin sensitization of preparations.

B.4.3 References relied on

No references submitted.

Annex B

Tritosulfuron

B-5: Methods of analysis

B.5 Methods of analysis

B.5.1 Analytical methods for formulation analysis (Annex IIA 4.1; Annex IIIA 5.1)

B.5.1.1 Analytical methods for the determination of pure active substance in the active substance as manufactured (Annex IIA 4.1)

The method uses reversed-phase (RP18) HPLC with UV-detection at 230 nm and external calibration to determine tritosulfuron in the active substance as manufactured. The product is dissolved in acetonitrile/1 % formic acid. The solutions are directly injected into the HPLC system for separation and detection.

Ref.: Doetzer, 1994 (CHE2002-11)

Specificity, linearity, accuracy and repeatability

Specificity

Identification of the active ingredient is based on comparison of the respective HPLC retention time of the reference substance to that of the test substance. No interferences were observed.

Linearity

There is linearity in the specified measuring range. The results do not show any significant deviation from the linearity, i.e., the coefficient of correlation (r) is > 0.9999. Typical results for the linear equation were: slope (m) 26400 and intercept (B) 51600.

Accuracy

Based on five replicates of a sample of the active substance as manufactured, the recovery of tritosulfuron was in the range of 100.1 to 101.9 %.

Repeatapility

Based on the analysis of five samples of pure active substance the repeatability (% RSD) was 0.2 %. Five subsamples of a typical technical active substance as well as five samples of technical active substance fortified with pure active substance yielded less than 0.3 % RSD. The acceptance of the results is confirmed by applying the modified Horwitz equation.

Ref.: Doetzer, 1994 (CHE2002-12)
Hassink, 2000 (CHE2002-15)

Conclusions

Data on specificity, linearity, accuracy and repeatability indicate this method is suitable for the determination of tritosulfuron in BAS 635 H.

Methods for the determination of significant and/or relevant impurities and additives (e.g. sabiliser) in the active substance as manufactured

Confidential information, see Annex C.

CIPAC Methods

To date, no CIPAC methods exist for the analysis of tritosulfuron in either technical or formulated material.

B.5.1.2 Analytical methods for formulation analysis (plant protection product) (Annex IIIA 5.1)

Method CF-A 506/1

The method uses reversed-phase (RP18) HPLC with UV-detection at 230 nm and external calibration to determine tritosulfuron in water dispersible granules (BAS 635 00 H). The product is dissolved in acetonitrile/0.01 N ammoniumhydroxide (1:1, v/v) and directly injected into the HPLC system for separation and detection.

Ref.: Ziegler, 1997 (CHE2002-16)

Specificity, linearity, accuracy and repeatability

Test parameters: Six fortifications of active substance to BAS 635 00 H.
Six analysis of a typical BAS 635 00 H sample.
Determination at five concentration levels from about 0.5 ppm to 1.5 of the analyte concentration
Testing of potential interferences.

Specificity

Identification of the active ingredient is based on comparison of the respective HPLC retention time and UV-spectra of the reference substance to those of the test substance. No interferences were observed. The chromatogram of the blank formulation did not show any further substances at the site of the active ingredient peak.

Linearity

There is linearity in the specified measuring range. The results do not show any significant deviation from the linearity, i.e. the coefficient of correlation (r) is 1.0000 for the active substance. Typical results for the linear equation were: slope (m) 308 and intercept (B) -3

Accuracy

Based on six replicates of a sample of blank formulation of BAS 635 00 H fortified with reference grade active substance, the mean recovery has been determined to be 100.16 % (BAS 635 H).

Repeatability

Based on the analysis of six samples of typical BAS 635 00 H the repeatability (% RSD) was determined to be 0.251 % (BAS 635 H).

Ref.: Ziegler, 1998 (CHE2002-17)

Conclusions

Data on specificity, linearity, accuracy, and repeatability indicate this method is suitable for the determination of tritosulfuron in water dispersible granules (BAS 635 00 H).

CIPAC Methods

To date, no CIPAC methods exist for the analysis of BAS 635 H in either technical or formulated material.

Method(s) for relevant breakdown products, isomers, impurities and additives

Method CF-A 588 for impurity Reg.No. 231 700

The method uses reversed-phase (RP18) HPLC with UV-detection at 260 nm and external calibration to determine impurity Reg.-No. 231700 in water dispersible granules (BAS 635 00 H). The product is dissolved in a solution of acetonitrile and ammonia and directly injected into the HPLC system for separation and detection.

Ref.: Ziegler, 1999 (CHE2002-18)

Specificity, linearity, accuracy and repeatability

Test parameters: Six fortifications of Reg.-No. 231700 to BAS 635 00 H.
Six analysis of a typical BAS 635 00 H sample.
Determination at five concentration levels from about 0.1 ppm to 4 ppm Reg.No. 231700.
Testing of potential interferences.

Specificity

Identification of Reg.-No. 231700 is based on comparison of the respective HPLC retention time and UV-spectra of the reference substance to those of the component peak. No interferences were observed. The chromatogram of the blank formulation did not show any further substances at the site of the component peak.

Linearity

There is linearity in the specified measuring range. The results do not show any significant deviation from the linearity, i.e. the coefficient of correlation (r) is 1.0000 for Reg.-No. 231700. Typical results for the linear equation were: slope (m) 421443 and intercept (B) 131.

Accuracy

Based on six replicates of a sample of blank formulation of BAS 635 00 H fortified with reference grade Reg.-No. 231700, the mean recovery has been determined to be 99.75 % (Reg.-No. 231700).

Repeatability

Based on the analysis of six samples of typical BAS 635 00 H the repeatability (% RSD) was determined to be 0.568 % (Reg.-No. 231700).

Ref.: Ziegler, 2000 (CHE2002-19)

Conclusions

Data on specificity, linearity, accuracy, and repeatability indicate this method is suitable for the determination of Reg.-No. 231700 in water dispersible granules (BAS 635 00 H).

B.5.2 Analytical methods (residue) for plants, plant products, foodstuffs of plant and animal origin, feedingstuffs (Annex IIA 4.2.1; Annex IIIA 5.2)

B.5.2.1 Plant material

According to method no. 405/1 (Sasturain et al, 2001) residues of tritosulfuron are extracted from maize and wheat matrices with acetone/water (9:1). After addition of pH 6.5 buffer and saturated NaCl solution the extract is partitioned versus *i*-octane. The organic phase is discarded. The water phase is acidified to pH $\leq$ 1 and again partitioned versus *i*-octane. The aqueous phase is discarded and the organic phase is evaporated to dryness and further purified by SPE phenyl- and C_{18}-columns. The final eluate of the second column is evaporated to dryness and dissolved in 0.5 ml of an acetonitrile/phosphate buffer. The final determination is performed by HPLC-UV (260 nm; pre-column: Phenyl-Nucleosil, separation column: C_{18}-Nucleosil; mobile phase: water/acetonitrile/phosphoric acid, gradient).
In the method is stated for the extraction step, that if the recovery is low, 5 ml of the buffer solution must be added prior extraction. Clarification is needed for the cases where unknown samples will be analysed.
For validation data see Table B.5.2-1.

Table B.5.2-1: Validation data for analytical method for the determination of residues in plant material

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Sasturain et al., 2001 (method no. 405/1)	wheat, plant	0.01*	87	79-105	11.9	5
		0.1	81	79-83	2.3	5
		1.0	78	77-79	1.4	5
	wheat, grain	0.01*	82	74-91	7.8	5
		0.1	89	86-93	3.2	5
		1.0	86	83-94	5.4	5
	wheat, straw	0.01*	84	82-86	1.8	5
		0.1	82	73-86	6.5	5
		1.0	80	79-81	1.0	5
	maize, plant	0.01*	94	89-102	5.8	5
		0.1	87	83-90	3.2	5
		1.0	83	80-87	3.9	5
	maize, grain	0.01*	85	82-89	3.5	5
		0.1	84	80-88	5.1	5
		1.0	78	75-82	3.9	5
	maize, straw	0.01*	77	69-84	7.8	5
		0.1	88	87-89	1.2	5
		1.0	75	74-78	2.2	5

* limit of quantification

In order to check the extraction efficiency of the cold method no. 405/1, maize samples generated in the course of the metabolism studies were extracted with acetone/water and the total radioactive residue (TRR) was determine. The results of the present study show that 62.5 % to 97.5 % TRR were released by the acetone/water mixture. This corresponds to the extraction yields from the metabolism study.

Study No. IF-97/22870-00 (Schulz, 1999) can be regarded as independent laboratory validation of method 405/1, which is proposed for enforcement purposes. However, in the clean up procedure in the phase partitioning at acidic conditions ethyl acetate is used instead of *i*-octane for grain samples.
The US independent laboratory validation, study no. 98052 (Binski and Perez, 2000) of previous method No. 405/1 is submitted additionally as supplementary data.
For validation data see Table B.5.2-2

Table B.5.2-2: Independent laboratory validation for the determination of residues in plant material

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	Recovery rate [%] range	RSD [%]	n
Schulz, 1999 (study no. IF-97-22870-00)	wheat, plant	0.01*	83	76-89	6.2	5
		1.0	74	60-80	11.1	5
	wheat, grain	0.01*	90	86-94	5.3	5
		1.0	91	87-93	2.5	5
	wheat, straw	0.01*	79	69-94	14.8	5
		1.0	70	57-84	15.3	5
Binski and Perez, 2000 (study no. 98052)	wheat, grain	0.01*	81	80+82	-	2
		0.1	77	76+77	-	2

* limit of quantification

As a confirmatory method LC-MS/MS detection (method D0003/1, Stewart, 2001) are demonstrated to be suitable.
Residues of tritosulfuron are extracted from the plant material with 90/10 acetone/water. For grains and grain process fractions an aliquot of the extract is cleaned with a quaternary amine column and analysed using LC-MS/MS. For other matrices an aliquot of the extract is analysed directly using LC-MS/MS (column: Prism RP; mobile phase: water/methanol/ ammonium formate/formic acid, gradient; negative ionisation mode, *m/z*: 446 → 195)
For validation data Table B.5.2-3

Table B.5.2-3: Confirmatory method for the determination of residues in plant material

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Stewart, 2001 (method D0003/1)	corn, grain	0.001*	70	67-73	4.2	4
		0.2	84	58-101	20.4	6
	wheat, grain	0.001*	94	77-112	17.0	4
		0.2	97	94-100	3.2	6
	wheat, straw	0.01	113	98-125	10.0	4
		0.2	118	112-128	7.2	3
		0.4	82	82	-	1
		1.0*	106	97-114	8.3	4
	wheat, forage	0.01*	91	86-101	7.6	4
		0.5	94	92-97	2.2	4
		5.0	92	91-93	1.0	4
	wheat, hay	0.01*	98	89-105	6.7	4
		0.5	108	98-112	6.0	4
		5.0	97	94-103	4.2	4
	wheat, middlings	0.001	121	111-128	5.0	8

* limit of quantification

A multi-residue method is not applicable (Weeren and Pelz, 1998) to the determination of tritosulfuron due to the unpredictable behaviour of tritosulfuron during GC analysis (the German S19 method was tested).

B.5.2.2 Animal matrices

According to method 413/0 (Grosshans, 1998) a 25 g sample is extracted with acetonitrile (in the case of liver, kidney, and muscle) or with a mixture of acetonitrile/*i*-hexane (in the case of fat, milk, and eggs). The extracts are partitioned versus *i*-hexane. The acetonitrile phase is evaporated to dryness and redissolved in 100 ml water. The water phase is acidified and partitioned with ethyl acetate. The organic phase is evaporated to dryness and purified on a silica gel column followed by a clean-up on SPE phenyl- and C_{18}-columns. The final determination is performed by HPLC with UV detection (260 nm; clean-up column: Zorbax-Phenyl; analytical column: Zorbax ODS; mobile phase: water/acetonitrile/formic acid, gradient).
For validation data see Table B.5.2-4

As confirmatory method a mass selective detection of residues of tritosulfuron is described (LC-MS: column: Zorbax-Phenyl; mobile phase: 40 % acetonitrile / 0.1 % formic acid, isocratic; positive single ionisation mode, m/z: 446).

Table B.5.2-4: Validation data for analytical method for the determination of residues in animal matrices

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Grosshans, 1998 (method 413/0)	cow, milk	0.01*	89	87-90	1.5	5
		0.1	88	84-91	3.3	5
	cow, muscle	0.01*	87	81-92	4.5	5
		0.1	84	77-88	5.1	5
	cow, fat	0.01*	93	92-96	2.1	5
		0.1	89	86-92	2.4	5
	cow, kidney	0.01*	87	80-96	7.4	5
		0.1	81	76-87	4.9	5
		1.0	94	91-97	2.3	5
	cow, liver	0.01*	90	88-91	1.3	5
		0.1	90	86-94	3.8	5
		1.0	88	85-90	2.3	5
	hen, egg	0.01*	95	93-96	1.7	5
		0.1	100	99-102	1.3	5

* limit of quantification

The applicability of method no. 413/0 is confirmed by an independent laboratory, study no. 98127, (Malinsky, 2000).
For validation data see Table B.5.2-5

Table B.5.2-5: Independent laboratory validation for the determination of residues in animal matrices

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Malinsky, 2000 (study no. 98127)	cow, milk	0.01*	102	95-108	5.1	5
		0.1	82	66-92	11.8	5
	cow, muscle	0.01*	98	80-107	12.1	5
		0.1	91	89-94	2.2	5
	cow, fat	0.01*	92	84-95	4.8	5
		0.1	93	91-95	2.0	5
	cow, kidney	0.01*	88	85-93	3.4	5
		0.1	83	74-89	9.1	5
		1.0	77	67-80	7.1	5
	cow, liver	0.01*	77	68-87	10.7	5
		0.1	83	73-90	9.0	5
		1.0	73	71-76	2.7	5
	hen, egg	0.01*	108	104-110	2.4	5
		0.1	81	77-84	3.6	5

* limit of quantification

B.5.2.3 Additional Study

According to method D0002 (Jordan and Malinsky, 2001) residues of metabolite AMTT (BH 635-5) are extracted from plant matrices with acetone/water-tris buffer mixture and from animal matrices with acetonitrile. An aliquot of the extract is removed and cleaned by quaternary amine, HLB and silica mini-column chromatography. The final chromatography analysis of AMTT is performed by GC-MS (single ionisation mode, m/z 194 and 164).
For validation data see Table B.5.2-6

Table B.5.2-6: Validation data for analytical method for the determination of residues of metabolite BH 635-5 in plant and animal matrices

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Jordan and Malinsky, 2001 (method D0002)	wheat, grain	0.001*	93	90-95	2.1	5
		0.01	89	84-96	5.9	4
	wheat, forage	0.001*	88	63-102	16.7	5
		0.01	96	86-101	6.4	5
	wheat, hay	0.001*	104	96-114	6.3	5
		0.01	81	50-90	21.4	5
	wheat, straw	0.001	114	101-124	8.1	5
		0.01*	91	86-95	5.0	5
	wheat, shorts	0.001*	96	90-106	6.9	5
		0.01	85	75-93	9.1	5
	corn, grain	0.001*	90	79-101	9.3	5
		0.01	90	75-96	9.7	5
	kidney	0.001*	81	77-85	4.5	5
		0.01	76	65-80	8.2	5
	liver	0.001*	77	70-80	5.3	5
		0.01	74	61-78	10.1	5
	muscle	0.001*	84	80-89	4.1	5
		0.01	76	70-78	5.2	5
	fat	0.001*	77	70-78	5.4	5
		0.01	74	70-78	4.6	5
	milk	0.001*	78	74-86	6.3	5
		0.01	77	68-88	10.6	4

* limit of quantification

B.5.3 Analytical methods (residue) soil, water, air (Annex IIA 4.2. 2 to 4.2.4; Annex IIIA 5.2)

B.5.3.1 Soil

According to method 406/0 (Richter, 2001a) residues of tritosulfuron, BH 635-2 (M02), BH 635-3 (M03) and BH 635-4 (M01) are extracted from soil with acetonitrile/water 80/20. After separating the extract from solids by filtration an aliquot is reduced to 5 ml. Tritosulfuron, BH 635-3 and BH 635-4 are determined directly without further clean-up by HPLC-MS/MS (column: Betasil C18; mobile phase: water/acetonitrile, gradient, tritosulfuron: *m/z* 446 → 195; BH 635-3: 311 → 86; BH 635-4: 354 → 86). For the determination of BH 635-2, 3 ml of the aqueous final extract for HPLC determination are partitioned with dichloromethane. The organic phase is purified by a silica gel column, reduced to dryness and dissolved in acetone containing *meta*-BH 635-2 as an internal standard substance. The determination is conducted by GC-MS (*m/z* 145).
For validation data see Table B.5.3-1.

Table B.5.3-1: Validation data for analytical method for the determination of residues in soil by LC-MS/MS

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Richter, 2001a (method 406/0) **tritosulfuron**	standard soil 2.1	0.001*	80	76-85	4.9	5
		0.01	94	93-97	1.8	5
		0.1	98	93-106	4.8	5
BH 635-4 (M01)		0.001*	93	88-98	4.1	5
		0.01	90	88-91	1.3	5
		0.1	86	71-92	10.6	5
BH 635-3 (M03)		0.001*	105	101-108	3.0	5
		0.01	96	94-99	2.0	5
		0.1	87	84-89	2.3	4
BH 635-2 (M02)		0.001*	93	92-95	1.4	5
		0.01	77	70-81	5.5	5
		0.1	92	85-104	8.8	5

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
tritosulfuron	standard soil 2.2	0.001*	84	73-90	8.2	5
		0.01	86	85-86	0.7	5
		0.1	81	77-85	3.5	5
BH 635-4 (M01)		0.001*	82	77-91	6.6	5
		0.01	97	93-99	2.3	5
		0.1	91	90-93	1.4	5
BH 635-3 (M03)		0.001*	93	91-95	1.9	5
		0.01	96	92-100	3.0	5
		0.1	94	92-95	1.5	5
BH 635-2 (M02)		0.001*	77	58-87	15.9	5
		0.01	88	80-95	5.9	5
		0.1	87	81-93	6.6	5

* limit of quantification

According to method D9907 (Smith and Cluoser-Rouche, 2001) residues of tritosulfuron, BH 635-2 (M02), BH 635-3 (M03), BH 635-4 (M01) and BH 635-5 (AMTT) are extracted with acetonitrile/water (80:20). An aliquot of the extract is reduced by rotary evaporation, brought to volume, filtered and quantitated by HPLC-MS/MS (column: Betasil C18; mobile phase: water, ammonium formate, 0.1 % formic acid/ methanol, ammonium formate, 0.1 % formic acid, gradient; tritosulfuron: *m/z* 446 → 195; BH 635-3: 311 → 86; BH 635-4: 354 → 86; BH 635-2: 223.9 → 159.8; AMTT: 195 → 110). Tritosulfuron, BH 635-3 and BH 635-4 are quantitated in one injection and BH 635-2 and BH 635-5 are quantitated in individual injections.
For validation data see Table B.5.3-2.

Table B.5.3-2: Validation data for analytical method for the determination of residues in soil by LC-MS/MS (recoveries during validation)

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Smith and Clouser-Rouche, 2001 (method D9907) **tritosulfuron**	soil, Indiana	0.001*	93	89+96	-	2
		0.01	89	86+92	-	2
		0.1	78	75+80	-	2
		0.3	74	70+78	-	2
BH 635-3 (M03)		0.001*	97	95+99	-	2
		0.01	92	89+95	-	2
		0.1	88	85+90	-	2
BH 635-4 (M01)		0.001*	94	91+96	-	2
		0.01	89	87+91	-	2
		0.1	86	83+89	-	2
BH 635-5 (AMTT)		0.001	83	83	-	1
		0.01*	86	83+88	-	2
		0.1	86	82+89	-	2
BH 635-2 (M02)		0.001	61	55+67	-	2
		0.01*	106	98+113	-	2
		0.1	68	63+72	-	2
tritosulfuron	soil, Texas	0.001*	97	92-103	5.7	3
		0.01	102	101-104	1.5	3
		0.1	81	80-82	1.4	3
		0.3	84	79-88	5.6	3
BH 635-3 (M03)		0.001*	101	96-106	5.0	3
		0.01	98	97-99	1.2	3
		0.1	90	90-91	0.6	3
BH 635-4 (M01)		0.001*	101	95-105	5.2	3
		0.01	98	96-100	2.1	3
		0.1	89	89-90	0.6	3
BH 635-5 (AMTT)		0.001*	90	79-100	11.7	3
		0.01	92	89-94	2.7	3
		0.1	90	88-94	3.6	3
BH 635-2 (M02)		0.001*	103	95-107	6.7	3
		0.01	101	84-119	17.2	3
		0.1	89	84-92	4.8	3

* limit of quantification

According to method 390 (Keller, 1998) residues of tritosulfuron, BH 635-2 (M02), BH 635-3 (M03) and BH 635-4 (M01) are determined by a common moiety method. Residues are extracted from soil by shaking with 100 ml 50 % aqueous methanol. After filtration, the cleared extracts are reduced to the aqueous phase by rotary evaporation. The remaining concentrated aqueous phase is acidified with sulphuric acid and refluxed for 30 minutes. At this hydrolysis step tritosulfuron, BH 635-3 and BH 635-4 were hydrolysed to BH 635-2. This compound is then partitioned from Extrelut columns into dichloromethane/ethyl acetate followed by solid phase extraction using a silica cartridge and determined by GC-ECD. As a confirmatory technique, BH 635-2 can be detected by GC/MS at *m/z* 145.
For validation data see Table B.5.3-3.

Table B.5.3-3: Validation data for analytical method for the determination of residues in soil by GC-ECD (common moiety method)

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Keller, 1998 (method 390) tritosulfuron	standard soil 2.1	0.001*	94	80-105	11.3	5
		0.01	84	70-91	10.4	5
		0.1	90	78-101	10.4	5
	standard soil 2.2	0.001*	93	84-102	9.0	5
		0.01	97	86-107	7.7	5
		0.1	99	94-106	4.9	5
BH 635-2 (M02)		0.01	101	86+116	-	2
BH 635-3 (M03)		0.01	76	68+84	-	2
BH 635-4 (M01)		0.01	98	98+107	-	2

* limit of quantification

B.5.3.2 Water (incl. drinking water and surface water)

According to method 433/0 (Richter, 2001b) residues of tritosulfuron, BH 635-3 (M03), BH 635-4 (M01) and BH 635-5 (AMTT) are concentrated on a LiChrolut EN SPE column and eluted with 10 ml of *n*-hexane/ethyl acetate (90:10) and 25 ml of methanol. The first eluate contains BH 635-5. After evaporating the solvent, the final determination of BH 635-5 is conducted by GC-MS (*m/z* 163-165) and an isopropoxy-triazin derivative as an internal standard. The methanol eluate contains the parent compound, BH 635-3 and BH 635-4. They are determined by HPLC-MS/MS (column: Betasil C18; mobile phase: water/acetonitrile/ formic acid, gradient; turbo ion spray ionisation, tritosulfuron: *m/z* 446 → 195; BH 635-3: 311 → 86; BH 635-4: 354 → 86).

For the determination of BH 635-2 another water sample aliquot is extracted three times with 15 ml dichloromethane. The organic phases are combined and concentrated and cleared by a NH_2 SPE column clean-up step. Finally the analyte is dissolved in acetone containing *meta*-BH 635-2 as an internal standard substance and is determined by GC-MS (*m/z* 144-146).
For validation data see Table B.5.3-4.

Table B.5.3-4: Validation data for analytical method for the determination of residues in water

Reference	Matrix	Fortification level [µg/l]	Recovery rate [%] mean	range	RSD [%]	n
Richter, 2001b	tap water	0.05*	80	77-84	3.9	5
(method 433/0)		0.5	86	81-91	4.4	5
tritosulfuron	(LC-MS/MS)	5.0	84	80-86	3.0	5
BH 635-2 (M02)	(GC-MS)	0.05	69	65-72	4.0	5
		0.5*	74	72-77	2.9	5
		5.0	77	71-82	5.2	5
BH 635-3 (M03)	(LC-MS/MS)	0.05*	98	92-103	5.4	5
		0.5	96	95-99	1.9	5
		5.0	98	95-102	2.6	5
BH 635-4 (M01)	(LC-MS/MS)	0.05*	108	101-117	7.1	5
		0.5	102	100-105	2.1	5
		5.0	99	96-102	2.2	5
BH 635-5 (AMTT)	(GC-MS)	0.05*	83	67-98	14.3	5
		0.5	79	74-83	4.5	5
		5.0	95	91-102	4.5	5
	surface water					
tritosulfuron	(LC-MS/MS)	0.05*	78	76-79	1.7	5
		0.5	76	71-80	5.3	5
		5.0	84	82-87	2.8	5
BH 635-2 (M02)	(GC-MS)	0.05	65	60-69	5.7	5
		0.5*	72	68-74	4.0	5
		5.0	79	77-82	2.4	5
BH 635-3 (M03)	(LC-MS/MS)	0.05*	93	88-95	4.9	5
		0.5	95	90-98	3.2	5
		5.0	98	97-99	0.9	5
BH 635-4 (M01)	(LC-MS/MS)	0.05*	99	94-106	4.7	5
		0.5	96	91-99	3.2	5
		5.0	102	100-103	1.1	5
BH 635-5 (AMTT)	(GC-MS)	0.05*	81	77-93	8.3	5
		0.5	88	85-89	2.7	5
		5.0	113	97-145	17.4	5

* limit of quantification

Residues of tritosulfuron, BH 635-3 (M03) and BH 635-4 (M01) can be determined by common moiety method no. 401 (Ziegler, 1998) using GC-MS. Water samples are acidified with phosphoric acid and refluxed for one hour. During this hydrolysis BH 635-2 (M02) is

built from tritosulfuron, BH 635-3 and BH 635-4. After neutralisation with sodium hydroxide, BH 635-2 is partitioned into dichloromethane which is cleaned up by a silica gel column. The solvent is evaporated and the residue is dissolved in acetone or toluene/methanol (90:10). The final determination is conducted by GC-MS (*m/z* 145). As a confirmatory technique determination by GC-ECD is described.
For validation data see Table B. 5.3-5.

Table B. 5.3-5: Validation data for analytical method for the determination of residues in water (common moiety method)

Reference	Matrix	Fortification level [µg/l]	Recovery rate [%] mean	range	RSD [%]	n
Ziegler, 1998	tap water	0.05*	77	66-87	11.3	4
(method 401)		0.5	90	81-102	9.1	5
tritosulfuron		5.0	89	85-90	2.5	5
BH 635-2 (M02)		0.05	89	86+91	-	2
BH 635-3 (M03)		0.05	77	75+78	-	2
BH 635-4 (M01)		0.05	100	94+105	-	2
tritosulfuron	leachate water	0.05*	104	92-112	9.4	5
		0.5	99	71-114	19.2	5
		5.0	82	78-84	3.5	5

* limit of quantification

B.5.3.3 Air

According to method 394 (Zangmeister, 1998) a defined air volume (540 and 550 l) is passed through Tenax adsorption tubes spiked with tritosulfuron. After extraction with acetone residues are determined by HPLC with UV-detection (254 nm, column: Supelcosil ABZ+plus; mobile phase: water/acetonitrile/formic acid, gradient).
As confirmatory method HPLC-MS is described.
For validation data see Table B.5.3-6.

Table B.5.3-6: Validation data for analytical method for the determination of residues in air

Reference	Matrix	Fortification level [µg/m³]	Recovery rate [%] mean	range	RSD [%]	n
Zangmeister, 1998	air	2.8*	79	64-90	11.5	6
		57.5	84	79-91	4.8	6
35 °C and 80 % rel. humidity						

* limit of quantification

B.5.4 Analytical methods (residue) for body fluids and tissues (Annex IIA 4.2.5; Annex IIIA 5.2)

The submission of an analytical method for the determination of residues in body fluids and tissues is not necessary, because the active substance tritosulfuron is not classified as toxic or highly toxic.

B.5.5 Evaluation and assessment

B.5.5.1 Formulation analysis

Analytical methodology is available for the determination of the active substance and the impurities in the technical material as manufactured and for the active substance in the formulation.

Tritosulfuron in the active substance as manufactured is determined by a HPLC external standard method on a reversed phase column with UV detection.

Organic impurities in the technical active substance are determined by a HPLC external standard method on a reversed phase column with UV detection.

Tritosulfuron and one impurity in the formulation are determined by HPLC external standard methods on reversed phase columns with UV detection.

The methods are fully validated.

B.5.5.2 Residue analysis

For the assessment of the analytical methods for the determination of tritosulfuron residues the following criteria were used:

- The submitted methods enable the enforcement of the following relevant residue limits (at the time of evaluation):

plants and plant products	0.01	mg/kg	proposed MRL for cereal and maize grain and other food of plant origin
soil	1.0	µg/kg	phytotoxic concentration of tritosulfuron to rape seed
drinking water	0.1	µg/l	EU drinking water limit
surface water	25.5	µg/l	higher aquatic plant
air	225	µg/m³	based on a proposed $AOEL_{systemisch}$ of 0.75 mg/kg bw/d

- Mean recovery rates at each fortification level in the range of 70 to 110 % with a relative standard deviation of ≤ 20 %
- No interfering blanks (< 30 % of the LOQ)
- Methods must employ the simplest approach, involve the minimum cost, and require commonly available equipment.

- The enforcement method for food must be suitable for the determination of all compounds included in the residue definition (see B 7.3), using an additional confirmatory method if appropriate.
- The enforcement methods for environmental matrices must be able to analyse for all compounds of toxicological and/or ecotoxicological significance in soil, water and air (see B 8.9), using an additional confirmatory method if appropriate.

According to these criteria adequate analytical methods are available for the determination of tritosulfuron in plant material, soil, drinking water and air (for a summary see Table B.5.5-1).

Table B.5.5-1: Methods for the determination of residues

	Matrix	Method	Limit of quantification		Reference
crops	wheat: grain, plant, straw maize: grain, plant, straw	HPLC-UV	0.01	mg/kg	Sasturain et al, 2001
	corn, grain	LC-MS/MS	0.001	mg/kg	Stewart, 2001
	wheat: grain, middlings		0.001	mg/kg	
	wheat: straw, forage, hay		0.01	mg/kg	
	metabolite AMTT				
	wheat corn	GC-MS	0.001	mg/kg	Jordan and Malinsky, 2001
animal matrices	milk, muscle, fat, kidney, liver egg	HPLC-UV	0.01	mg/kg	Grosshans, 1998
	metabolite AMTT				
	milk, muscle, fat, kidney, liver	GC-MS	0.001	mg/kg	Jordan and Malinsky, 2001
soil	as + M01, 02, 03	LC-MS/MS	0.001	mg/kg	Richter, 2001a
	as + M01, 02, 03, AMTT	LC-MS/MS	0.001	mg/kg	Smith and Clouser-Rouche, 2001
	as M01, 02, 03	GC-ECD	0.001 0.01	mg/kg mg/kg	Keller, 1998

	Matrix	Method	Limit of quantification		Reference
water	drinking/surface				Richter, 2001b
	as + M01, 03	LC-MS/MS	0.05	µg/l	
	M02 + AMTT	GC-MS	0.05	µg/l	
	drinking/leachate as + M01, 02, 03	GC-MS	0.05	µg/l	Ziegler, 1998
air		HPLC-UV	2.8	µg/m^3	Zangmeister, 1998

B.5.6 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
AIIA-4.1	Dötzer, R.	1994	Validation of HPLC method CP 217 for determination of BAS 635 H (Reg.-No. 271 272) in BAS 635 H technical Laboratory Study Code: PCP03052. 1994/10405 GLP, unpublished CHE2002-12	Y	BAS
AIIA-4.1	Dötzer, R.	1994	Analytical method CP-No. 217: Determination of Reg.-No. 271 271 (BAS 635 H) in technical Reg.-No. 271 272 by HPLC. 1994/1000351 not GLP, unpublished CHE2002-11	Y	BAS
AIIA-4.1	Hassink, J.	2000	Additional analyses for statistical verification of analytical method CP 217. 2000/1018732 GLP, unpublished CHE2002-15	Y	BAS
AIIA-4.1	Hassink J.	2001	Validation of analytical method CP 300: Determination of technical by-products in BASF technical grade BAS 635 H (Reg.-No. 271 272). 2001/1001004 GLP, unpublished CHE2002-9	Y	BAS

[4] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
AIIA-4.1	Hassink J.	2001	Analytical Method CP 300 Determination of by-products in technical BAS 635 H using HPLC. 2001/1001008 not GLP, unpublished CHE2002-7	Y	BAS
AIIA-4.2.1	Binski, C. and Perez, R.	2000	Independent Method Validation of BASF Technical Procedure 405/1 (April 1998 Draft) for BAS 635 H Residues in Corn and Wheat Study No. 98052. 2000/5219 GLP, unpublished MET2001-374	Y	BAS
AIIA-4.2.1	Grosshans, F.	1998	The Validation of BASF Method 413/0: Determination of BAS 635 H (Reg.-No. 271272) in Animal Matrices Study Code 19468. 98/10979 GLP, unpublished MET2001-375	Y	BAS
AIIA-4.2.1	Jordan, J. and Malinsky, S.	2001	Method Validation of BASF Analytical Method D0002 entitled "Method for the Determination of BH 635-5 (AMTT) 2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5 triazine Residues in Plant and Animal Matrices by GC/MS" Study No. 59280. 2001/5000983 GLP, unpublished MET2001-371	Y	BAS
AIIA-4.2.1	Malinsky, S.	2000	Independent Method Validation of BASF Analytical Method No. 413/0: "Determination of BAS 635 H in Animal Matrices" at BASF Study No. 98127. 1999/5054 GLP, unpublished MET2001-376	Y	BAS
AIIA-4.2.1; AIIIA-5.2	Sasturain, J.	1999	Validation of BASF Method No. 438/0: Determination of Bentazon and its Metabolites 6-OH-Bentazon and 8-OH-Bentazon in Maize Matrices Study Code 59041. 99/11014 not GLP, unpublished MET2000-68	N	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
AIIA-4.2.1	Sasturain, J.; Bross, M. and Mackenroth, C.	2001	Validation of BASF Method No. 405/1: Method for the Determination of BAS 635 H (LAB 271 272) in Plant Matrices (Wheat, Maize) Study Code 19438. 2001/1000996 GLP, unpublished MET2001-369	Y	BAS
AIIA-4.2.1	Schulz, H.	1999	Determination of BAS 635 H in Wheat - Validation of the BASF Method No. 405/1 Study No. IF-97/22870-00. 99/11493 GLP, unpublished MET2001-373	Y	BAS
AIIA-4.2.1	Stewart, J.	2001	Validation of BASF Method D0003/1: Analytical Method for Determination of Residues of BAS 635 H in Plant Matrices using LC/MS/MS Study No. 64186. 2001/5001043 GLP, unpublished MET2001-370	Y	BAS
AIIA-4.2.1	Weeren, R. D. and Pelz, S.	1998	Examination of the Applicability of DFG Method S19 for the Determination of BAS 635 H Final report BAS-9804V, Az. 67460/98. 98/11322 GLP, unpublished MET2001-372	Y	BAS
AIIA-4.2.2	Keller, W.	1998	Validation of Analytical Method No. 390 Total Method for Determination of BAS 635 H Residues in Soil Study No. 24395. 98/10097 GLP, unpublished MET2001-377	Y	BAS
AIIA-4.2.2	Richter, T.	2001	Validation of Analytical Method 406/0 for the Determination of BAS 635 H and the following Metabolites in Soil: BH 635-2 (Reg.-No. 292564), BH 635-3 (Reg.-No. 335182), BH 635-4 (Reg.-No. 335184) Study code 39262. 2000/1013299 GLP, unpublished MET2001-378	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
AIIA-4.2.2	Smith, K. and Clouser-Roche, A.	2001	Determination of BAS 635 H and Metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in Soil by LC/MS/MS Method No. D9907. 1999/5128 GLP, unpublished MET2001-379	Y	BAS
AIIA-4.2.3	Richter, T.	2001	Method 433/0; Validatiion of Analytical Method 433/0 for the determination of BAS 635 H (Reg.-No. 271272), BH 635-2 (Reg.-No. 292564), BH 635-3 (Reg.-No. 335182), BH 635-4 (Reg.-No. 335184) and BH 635-5 (Reg.-No.231700) in tap and surface water Study Code 37274. 2000/1013298 GLP, unpublished MET2001-381	Y	BAS
AIIA-4.2.3	Ziegler, G.	1998	Validation of Analytical Method No. 401 Total Method for the Determination of BAS 635 H (271 272) Residues and its Metabolites 292 564, 335 182 and 335 184 in Water Study Code 24398. 98/10663 GLP, unpublished MET2001-380	Y	BAS
AIIA-4.2.4	Zangmeister, W.	1998	Validation of BASF Analytical Method 394 - Determination of BAS 635 H in Air by HPLC Study No. 24402. 98/10659 GLP, unpublished MET2001-382	Y	BAS
AIIIA-5.1	Ziegler, H.	1999	Analytical Method CF-A 588: Quantitative determination of the substance Reg.-No. 231700 in BAS 635 00 H by HPLC. 1999/1004107 not GLP, unpublished CHE2002-18	Y	BAS
AIIIA-5.1	Ziegler, H.	2000	Development and validation of the analytical method CF-A 588: Determination of Reg.-No. 231 700 in water dispersible granules (BAS 635 00 H). 2000/1000323 GLP, unpublished CHE2002-19	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[4]
AIIIA-5.1	Ziegler, H.	1998	Validation of the analytical method CF-A 506/1: Determination of Reg.-No. 271 272 in water dispersible granules (BAS 635 00 H). 1998/10813 GLP, unpublished CHE2002-17	Y	BAS
AIIIA-5.1	Ziegler, H.	1997	Analytical Method CF-A 506/1: Quantitative determination of active ingredient Reg.-No. 271 272 in BAS 635 00 by HPLC. 1997/1000591 not GLP, unpublished CHE2002-16	Y	BAS
AIIIA-5.2	Benz, A. and Mackenroth, C.	2001	Validation of BASF Method No. 472/0: Determination of BAS 615 H and BH 615-3 in Cereal Forage, Grain and Straw Study Code 96355. 2001/1000994 GLP, unpublished MET2001-383	Y	BAS
AIIIA-5.2	Sasturain, J.	1999	Validation of BASF Method No. 444/0: Determination of Dicamba and its Metabolite 5-OH Dicamba in Maize Matrices Study Code 59649. 99/11013 not GLP, unpublished MET2001-384	N	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-6: Toxicology and metabolism

B.6 Toxicology and metabolism

B.6.1 Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA 5.1)

Tritosulfuron was rapidly and almost completely absorbed after oral administration to male and female rats at dose levels of 50 and 500 mg/kg bw. The radioactivity was preferably excreted via the renal route (approx. 70 – 80 % within 48 hours). The bioavailabilty was in the range of 90 - 100 %. The initial plasma half-life was short at both dose levels (5 - 6 hours). At the low dose level a slower terminal phase (19 - 24 hours) followed. Highest tissue concentrations were found in the gastro-intestinal tract and the excretion organs. There was no indication of accumulation of radioactivity in fat or other tissues. The test substance was metabolised to the sulfonamide 635M02 of the trifluoromethyl-phenyl ring and its sulfonic acid 635M23. After hydroxylation at the 4-position of the phenyl ring this compound was further conjugated with glucuronic acid or sulfate. No significant amounts of AMTT were produced in the rat by metabolism of tritosulfuron.

B.6.1.1 Absorption, distribution and excretion following oral and intravenous administration to rats

Report: Leibold E. et al. 1998
^{14}C-BAS 635 H - Study of the biokinetics in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10506

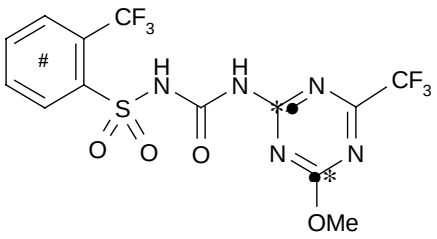
GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 417

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test animals: Wistar rats (Chbb:THOM (SPF))
Test material:
Radiolabelled tritosulfuron (triazine-14C); batch 437 - 32; radiochemical purity > 99 %, chemical purity > 99 % and batch 537 - 01; radiochemical purity > 99 %, chemical purity > 98 %.
Radiolabelled tritosulfuron (phenyl-14C); batch 436 - 23; radiochemical purity > 97 %, chemical purity > 96 % and batch 538 - 01; radiochemical purity > 99 %, chemical purity > 98 %.
13C-labelled tritosulfuron; batch 481 - 05; chemical purity > 99 %.
Non radiolabelled tritosulfuron; batch N14; chemical purity > 96 %



[14C-Phenyl label],
* [14C-Triazine label], • [13C- Triazine label]

The biokinetics of 14C-tritosulfuron in male and female Wistar rats were investigated at dose levels of 50 mg/kg bw and 500 mg/kg bw ("low" and "high" dose, respectively). The experiments, which are summarised in Table B.6.1-1, were performed with 14C-tritosulfuron labelled in the triazine ring and 14C-tritosulfuron labelled in the phenyl ring. The radiolabelled test compound was diluted with the non-labelled compound to achieve the desired specific activity. In the case of the excretion experiments (urine, faeces, bile), 13C-labelled compound was added to the triazine labelled test compound (12C/13C ratio 2:1). The aim of the addition of the 13C-label was to generate a characteristic isotope pattern to improve a potential mass spectrometry identification of metabolites. For the oral administration, the test compound was dissolved in Cremophor EL and Pluriol E200, and then mixed with 0.5 % Tylose suspension. For the intravenous administration, a 0.9 % aq. NaCl solution was used instead of Cremophor and Tylose. The stability, homogeneity and correctness of the test substance preparation was analytically verified.

For the excretion balance experiments, the animals were housed in all-glass metabolism cages. For the biliary excretion experiment, restriction cages were used and for tissue distribution and blood/plasma level determination, the animals were placed in steel wire mesh cages. The animals were fed on a standard rodent diet and had access to water ad libitum. For the determination of the excretion balance, urine and faeces were collected separately at appropriate time points. During Experiment 1 (high dose), exhaled air was also collected. At the end of the excretion balance experiments the following organs and tissues were collected: heart, liver, kidney, spleen, bone and bone marrow, skin, lung, ovaries and uterus, or testes, brain, pancreas, thyroid, adrenal glands, fat tissue, muscle, blood/plasma, stomach and contents, intestinal tract and contents, and carcass. For the determination of blood/plasma levels, blood was taken retro-orbitally. For the determination of the time-dependent tissue distribution, animals were sacrificed at time points close to maximum plasma concentration (MPC) and at ½ MPC, ¼ MPC and ⅛ MPC. The same organs and tissues were removed as described above. For the determination of the biliary excretion, the bile duct of the animals was cannulated and bile was collected in 3 hour intervals.

Total radioactivity in urine, faeces, bile, blood/plasma and tissues was determined by liquid scintillation counting; in the case of solid samples, after preceding solubilisation in a tissue solubiliser. Biokinetic data were analysed using the TOPFIT V 2.0 Program Package. The isolation and identification of metabolites is described in B.6.1.2.

Table B.6.1-1: Summary of biokinetic experiments performed at dose levels of 50 mg/kg ("low dose") and 500 mg/kg ("high dose") ^{14}C- tritosulfuron

Experiment no.	1	2	3	4	5	6	7	8	9	10
Description	excret. balance	excret. balance	excret. balance	excret. balance	blood/ plasma levels	blood/ plasma levels	tissue distrib.	tissue distrib.	biliary excret.	biliary excret.
Dosing	oral high	oral low	i.v. low	oral low (14 x non-labelled, 1 x labelled)	oral high	oral low	oral high	oral low	oral high	oral low
No. of animals per label (m/f)	5/5	5/5	5/5	5/5	5/5	5/5	12/12 (3/3 per time point)	12/12 (3/3 per time point)	4/4	4/4
Labels	triazine phenyl	triazine phenyl	triazine phenyl	triazinep henyl	triazine phenyl	triazine phenyl	triazine phenyl	triazine phenyl	triazine phenyl	triazine phenyl
Duration	120 h	120 h	120 h	120 h	72 h	72 h	0.5, 4, 8, 24 h	0.5, 4, 8, 18 h	48 h	48 h
Analysis	urine, faeces, exhaled air, tissues	urine, faeces, tissues	urine, faeces, tissues	urine, faeces, tissues	blood, plasma	blood, plasma	tissues	tissues	bile	bile

excret.: excretion; distrib.: distribution; m: male; f: female

Findings:

Excretion balance

After 120 hours the total amount of radioactivity was almost completely excreted, predominantly via the renal route: in urine 72 - 86 % of the administered dose were recovered and in faeces 9 - 22 %, irrespective of the labelling position, the route of application and the dose level. No radioactivity was detectable in the exhaled air. Already within the first 24 hours after dosing, 56 - 82 % of the administered radioactivity was excreted via urine and 7 - 18 % via the faeces. Radioactivity remaining in tissues and organs 120 hours post dosing was below 1 µg eq/g at the low dose level and below 8 µg eq/g at the high dose level. The overall recovery of radioactivity was in the range of 91 - 108 %.

Within 48 hours after administration of 50 and 500 mg/kg bw of both 14C-labelled forms of tritosulfuron, approximately 10 - 27 % of the administered radioactivity were excreted with the bile. If it is assumed that the amount of radioactivity excreted via bile and urine represents the bioavailable amount of 14C-tritosulfuron, the bioavailability is approximately 90 - 100 %.

Table B.6.1-2: Excretion balance (in percent of dose) after administration of [triazine-^{14}C]-tritosulfuron to male and female rats (including biliary excretion)

Dose		50 mg/kg bw i.v.		50 mg/kg bw p.o.		50 mg/kg bw multiple p.o.*		500 mg/kg bw p.o.	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
Urine	0 – 24 h	80.9	77.3	77.3	77.4	74.0	73.6	66.8	63.8
	24 – 48 h	2.9	3.0	2.9	2.5	3.3	2.9	10.6	4.5
	48 – 120 h	1.9	2.1	1.3	1.2	1.9	2.1	1.4	1.2
Cagewash		-	-	-	-	-	-	3.8	16.9
Subtotal urine		85.6	82.4	81.5	81.1	79.2	78.6	80.3	79.5
Faeces	0 – 24 h	7.2	7.5	10.7	10.1	6.7	7.4	12.2	7.5
	24 – 48 h	2.3	0.6	1.7	1.1	2.7	1.4	8.7	2.8
	48 – 120 h	0.6	0.9	0.4	0.6	1.2	3.1	1.2	0.4
Subtotal faeces		10.1	9.0	12.7	11.8	10.5	11.9	22.1	10.7
Cagewash		2.7	4.2	1.3	4.4	1.3	5.6	1.5	2.9
Tissues/carcass		2.0	0.8	0.5	0.5	0.4	0.3	0.7	0.3
Total	0 – 120 h	100.4	96.4	96.0	97.8	91.5	96.4	104.5	93.5
Bile	0 - 48 h	-	-	11.6	9.6	-	-	26.7	9.7

* 14 x non-labelled plus one radiolabelled dose

Table B.6.1-3: Excretion balance (in percent of dose) after administration of [phenyl-^{14}C]-tritosulfuron to male and female rats (including biliary excretion)

Dose		50 mg/kg bw i.v.		50 mg/kg bw p.o.		50 mg/kg bw multiple p.o.*		500 mg/kg bw p.o.	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
Urine	0 - 24 h	80.3	78.2	81.8	71.9	73.0	65.5	55.9	64.2
	24 - 48 h	1.6	1.5	2.7	2.3	3.6	3.7	6.2	2.6
	48 - 120 h	1.4	2.2	1.5	1.0	1.3	2.9	1.6	0.8
Cagewash		-	-	1.1	1.9	-	-	19.3	11.1
Subtotal urine		83.3	81.9	86.3	76.8	77.9	72.1	79.1	78.7
Faeces	0 - 24 h	9.0	7.4	17.5	16.3	8.1	9.8	9.8	10.7
	24 - 48 h	1.1	0.6	1.5	1.7	2.6	1.7	4.8	1.3
	48 - 120 h	0.5	0.6	1.5	0.3	0.6	0.8	1.5	0.2
Subtotal faeces		10.6	8.6	20.5	18.3	11.3	12.3	16.1	12.2
Cagewash		2.0	2.2	1.1	0.5	1.7	7.6	1.6	0.7
Tissues/carcass		2.2	0.4	0.4	0.4	0.2	0.3	0.5	0.2
Total	0 - 120 h	98.1	93.0	108.2	96.0	91.1	92.3	97.2	91.9
Bile	0 - 48 h	-	-	13.0	13.0	-	-	9.7	22.3

* 14 x non-labelled plus one radiolabelled dose

Kinetic parameters

Key biokinetic parameters are summarised in Table B.6.1-4. After oral administration of 50 mg/kg bw peak plasma levels were 36.4 – 37.6 µg eq/g (Triazine Label) and 30.1 – 30.8 µg eq/g (Phenyl Label). After oral administration of 500 mg/kg bw. peak plasma levels were 357.5 – 394.3 µg eq/g (Triazine Label) and 275.9 – 327.1 µg eq/g (Phenyl Label). The maximum concentrations were reached already 0.5 hours after dosing. In some cases a second maximum was observed 2 – 4 hours after application. The concentrations in whole blood were

only about 45 – 63 % of the plasma concentrations and thus indicate that the radioactivity preferably stayed in the plasma and was not bound to erythrocytes or other blood cells.

After dosing of 50 mg/kg bw, the plasma levels declined biphasically with an initial half-life of 5.3 – 6.0 hours and a terminal half-life of 18.6 – 23.8 hours. After dosing of 500 mg/kg, a monophasic decline was observed with half-lives of 8.7 – 18.6 hours.

The plasma AUC-values increased over-proportionally with the dose. This was more pronounced in male rats after dosing with the Triazine Label, where the AUC increased by a factor of 18 after a ten-fold increase of dose, than in female rats or after dosing of the Phenyl Label where the factor was only 12 – 14. This finding might be ascribed to a dose dependent distribution into deeper body compartments or a saturation of excretion processes.

Table B.6.1-4: Biokinetic parameters derived from plasma level vs. time curves after oral administration of [triazine-^{14}C]- and [phenyl-^{14}C]-tritosulfuron to male and female rats

Dose level	50 mg/kg p.o.		500 mg/kg p.o.	
Sex	Male	Female	Male	Female
	Triazine Label			
c_{max} [µg/g]	37.6	36.4	394.3	357.5
t_{max} [h]	0.5	0.5	0.5	0.5
$t1/2_{initial}$ [h]	5.6	6.0	8.7	18.6
$t_{1/2\ terminal}$ [h]	22.6	23.8	-	-
AUC [µg*h/g]	304.0	351.6	5548.4	4888.5
Cl [g/min]	2.74	2.4	1.50	1.70
	Phenyl Label			
c_{max} [µg/g]	30.1	30.8	275.9	327.1
t_{max} [h]	0.5	0.5	0.5	0.5
$t1/2_{initial}$ [h]	5.3	5.7	10.2	10.2
$t_{1/2\ terminal}$ [h]	22.1	18.6	-	-
AUC [µg*h/g]	323.1	241.1	3818.2	2871.0
Cl [g/min]	2.58	3.46	2.18	2.90

Tissue distribution

At all dose levels and with both radiolabels, animals that were sacrificed 0.5 hours after dosing (at the presumed maximum plasma concentration) showed highest radioactivity concentrations in the stomach and the stomach content. Tissues and organs which showed radioactivity concentrations higher than or close to the plasma concentration were the gut, the gut content, the kidney and the liver. Concentrations were lowest in the brain, the muscle, fat tissue, bones and bone marrow, and the testes. Animals that were sacrificed 4 hours after dosing (at assumed 50 % maximum plasma concentration) showed high concentrations in the stomach contents indicating that there was still some non-absorbed test material left. In most tissues the concentration had decreased, but in gut and liver concentrations had increased in some cases (due to excretion).

In tissues removed 8 hours after dosing, the situation was not significantly different. At the last time point (18 hours for the low dose level and 24 hours for the high dose level), the radioactivity concentration had decreased to very low levels in all organs and tissues.

The isolation and identification of metabolites is described in B.6.1.2. The dose group with intravenous administration of the test substance was not further analysed for metabolite patterns and identities, because there were no differences observed concerning excretion rates compared to other dose groups.

Conclusion:
14C-tritosulfuron labelled in the triazine and the phenyl ring was rapidly and almost completely absorbed after oral administration to male and female rats at dose levels of 50 mg/kg and 500 mg/kg bw. The radioactivity was preferably excreted via the renal route (approx. 70 – 80 % within 48 hours). The excretion pattern was similar after single oral dosing, intravenous dosing and after multiple oral dosing for 14 days with non-labelled material and for one day with radio-labelled material. The initial plasma half-life was short at both dose levels (5 - 10 hours). At the low dose level a slower terminal phase (19 - 24 hours) followed. Highest tissue concentrations were found in the gastro-intestinal tract and the excretion organs. There was no indication of accumulation of radioactivity in fat or other tissues. There were no marked differences with regard to both genders or labelling positions. The bioavailabilty was in the range of 90 - 100 %.

B.6.1.2 Metabolism in rats

The main metabolism study of tritosulfuron (see B.6.1.2.1 below) was performed with a product specification that did not represent the final composition in respect to the impurity AMTT (2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine). Therefore, the dose group of 50 mg/kg bw was repeated with specified quantities of AMTT in the dosing solution and metabolites were analysed with specific focus on the relative quantities of AMTT in excreta (see B.6.1.2.2). However, for elucidation of the metabolic pathway of tritosulfuron and for quantification of metabolites produced, the main study is completely valid.

B.6.1.2.1 Metabolism of tritosulfuron with initial product specification

Report: Hafemann C. 2000
The metabolism of ^{14}C-BAS 635 H (Reg.-No. 271 272) in rats
BASF AG, Agrarzentrum Limburgerhof, Limburgerhof,
Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1013501

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B

Deviations: None

Acceptability: The study is considered to be acceptable.

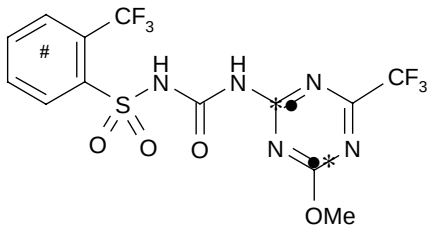
Material and Methods:

Test material: Tritosulfuron - Batch/radiochemical purity: 437 – 32 (14C-triazine ring): 99.2 %; 436 - 23 (14C-phenyl-ring): 97.0 %; 481 - 05 (13C-triazine ring): > 99 %; 691-33-1 (unlabelled): 99.8 % (chemical)

Test animals: Wistar rats (Chbb-THOM (SPF))

Tritosulfuron was fed to male and female Wistar rats including two types of radiolabelled and 13C-labelled active ingredient. The Phenyl label showed the phenyl ring uniformly radiolabelled, while the triazine ring was 13C-labelled in the 2- and 4-position. In case of the Triazine label, the 14C-label and the 13C-label were both incorporated at the 2- and 4-position of the triazine ring. The mixture of radiolabelled and 13C-labelled active ingredient was solubilised in Cremophor EL and Pluriol E 200, and Tylose (0.5 %) was added to a final volume. The dose solution for each label was administered to ten animals of each gender as a single oral dose at a nominal dose level of 500 mg/kg body weight.

Figure B.6.1-1: Structure and position of the $^{14}C/^{13}C$-label for both phenyl and triazine labelled tritosulfuron



[14C-Phenyl label],
* [14C-Triazine label], • [13C- Triazine label]

Metabolite patterns were investigated by radio-HPLC (high pressure liqid chromatography) from urine, faeces extracts and bile as well as from plasma, liver and kidney, the latter were obtained from dose group XX at the time point of the maximum plasma level. All metabolites of equal to or greater than five percent of the dose, but also a few metabolites at quantities down to less than one percent of the dose were isolated and identified by mass spectrometry, in few cases by 1H-NMR (nuclear magnetic resonance). The metabolite patterns of the metabolism group DX (500 mg/kg bw) were compared with those of urine and faeces of the low dose group B (50 mg/kg bw) and the repeat-dose group C (14 non-labelled plus one radiolabelled daily oral doses at 50 mg/kg bw) obtained from a separate biokinetic study (see B.6.1.1).

Table B.6.1-5: Summary of dose groups and analysed samples of male and female rats

Dose group	B, R1)	C	D, DX, S1)	XX
Dose level	50 mg/kg bw	50 mg/kg bw	500 mg/kg bw	50 mg/kg bw
Samples from biokinetics experiment no. 2)	2 (urine, faeces) 10 (bile)	4	1 (urine, faeces), 9 (bile)	-
Number of doses	1 p.o.	14 + 1 p.o.	1 p.o.	1 p.o.
Label	Triazine + Phenyl	Triazine + Phenyl	Triazine + Phenyl	Triazine + Phenyl
Samples analysed	Urine, Faeces, Bile	Urine, Faeces	Urine, Faeces, Bile	Plasma, Liver, Kidney

1) Dose groups R and S were related to the collection of bile at the low dose and the high dose level, respectively.
2) Cf. B.6.1.1

Findings:

Absorption, distribution and excretion of radioactivity

The amounts of radioactivity excreted via urine and faeces in the metabolism group (DX) were comparable to the findings of the biokinetic study (see B.6.1.1). This study had shown that the test substance was very rapidly absorbed from the gastrointestinal tract. In all dose groups the radioactivity was mainly excreted via urine (60 % to 86 % of the oral dose after 120 hours). The major portion of the radioactivity excreted via urine was determined at 56 % to 82 % of the dose within the first 24 hours after dosing. Faeces contained 11 % to 23 % of the dose within 120 hours post-dose. Bile contributed from 10 % to 27 % of the dose (group R and S). No significant differences were detected for male and female rats regarding biokinetics.

Metabolite patterns

For isolation of metabolites, all matrices were analysed using the same HPLC system, either in their original form or as organic extracts. The resulting metabolite patterns were well comparable within each matrix and throughout the dose groups because of reproducible retention times of the relevant compounds. The metabolite patterns of each matrix showed no major quantitative differences throughout all dose groups. Since this was particularly true for the metabolite patterns of excreta of dose group B (one single oral dose at the low dose level) and those of dose group C (15 consecutive daily oral doses), no induction of metabolic enzymes by the test substance was indicated. There were no significant deviations comparing male and female animals.

Isolation and identification of metabolites

Dose group DX was used for isolation and identification of metabolites of excreta, while dose group S was taken for identification work of bile metabolites. The reproducible retention times in the metabolite patterns after HPLC analysis allowed to transfer metabolite identities within a specific matrix from dose group DX and dose group S to the other dose groups.
All metabolite identities are based on mass spectrometric analyses. In case of the major metabolites 635M15 (hydroxylated parent compound at the 4-position of the phenyl ring) and 635M01 (triazine ring-opened parent), additional 1H-NMR spectroscopic data are available. For a summary of all identified structures and their designations see Table B.6.1-12.

The major metabolites in urine and faeces were 635M15 and 635M01 for both labels besides an excess of parent. The same is true for bile, however, the glucuronic acid conjugate of parent

635M24 was additionally detected at increasing amounts in bile samples of consecutive 9-hour time intervals post-dose. After analysis of plasma, liver and kidney almost exclusively parent was identified [see Table B.6.1-6 to
Table B.6.1-11].

There were several minor metabolites found in excreta and bile which resulted in a fairly complex metabolic pathway scheme (see below and Figure B.6.1-2). The limit of identification for individual metabolites was down to 0.1 % of the dose or less.

Table B.6.1-6: Summary of identified metabolites in urine, faeces and bile after administration of a single oral dose of [triazine-^{14}C]- tritosulfuron at 500 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)		Bile (0-36 h)	
T-Label	Male	Female	Male	Female	Male	Female
Tritosulfuron	76.3	66.3	14.5	7.7	13.9	7.6
635M01	2.1	1.5	1.4	0.9	0.3	0.2
635M04	-	-	0.3	0.2	-	-
635M11	0.1	< 0.05	-	-	-	-
635M15	0.7	0.1	4.4	0.9	6.8	2.1
635M16	-	-	-	-	0.1	< 0.05
635M19	0.1	< 0.05	-	-	-	-
635M21	-	< 0.05	-	-	-	-
635M24	-	-	-	-	1.4	< 0.05
635M24/635M30	-	-	-	-	< 0.4	0.3
635M28	-	-	-	-	< 0.05	-
635M29	-	-	-	-	0.3	0.2
635M31	-	-	-	-	0.2	0.2
635M32	-	-	-	-	< 1.7	0.7
635M34	-	-	-	-	0.1	< 0.05

Table B.6.1-7: Summary of identified metabolites in urine, faeces and bile after administration of a single oral dose of [phenyl-^{14}C]-tritosulfuron at 500 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)		Bile (0-36 h)	
P-Label	Male	Female	Male	Female	Male	Female
Tritosulfuron	56.1	62.6	10.2	8.5	5.3	8.4
635M01	2.6	1.5	0.8	0.9	0.2	0.4
635M02	0.5	0.8	0.1	0.3	0.2	0.2
635M08	-	-	-	0.2	-	-
635M15	1.4	0.5	2.5	0.7	2.2	3.1
635M17	-	-	0.3	0.4	-	-
635M23	0.2	0.2	-	-	0.2	-
635M25	0.7	0.7	-	-	-	-

Table B.6.1-8: Summary of identified metabolites in urine, faeces and bile after administration of a single oral dose of [triazine-^{14}C]-tritosulfuron at 50 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)		Bile (0-36 h)	
T-Label	Male	Female	Male	Female	Male	Female
Tritosulfuron	72.7	97.8	8.1	7.9	6.3	6.9
635M01	3.9	-	1.5	1.2	0.2	0.2
635M04	-	-	0.3	0.2	-	-
635M11	0.1	-	-	-	-	-
635M15	1.6	-	1.7	1.2	1.8	1.5
635M21	0.4	-	-	-	-	-
635M24	-	-	-	-	-	0.5
635M28	-	-	-	-	-	< 0.05
635M29	-	-	-	-	0.2	0.1
635M30	-	-	-	-	0.1	0.1
635M31	-	-	-	-	< 0.05	< 0.05
635M32	-	-	-	-	0.3	0.4

Table B.6.1-9: Summary of identified metabolites in urine, faeces and bile after administration of a single oral dose of [phenyl-^{14}C]-tritosulfuron at 50 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)		Bile (0-36 h)	
P-Label	Male	Female	Male	Female	Male	Female
Tritosulfuron	78.6	70.7	14.5	12.8	11.5	8.1
635M01	2.9	1.5	1.0	1.4	2.2	0.6
635M02	1.1	0.7	0.5	0.4	1.3	0.5
635M08	-	-	0.3	< 0.05	-	-
635M15	0.9	0.7	1.3	1.2	4.4	2.2
635M17	-	-	0.5	0.5	-	-
635M23	0.3	0.2	-	-	0.3	< 0.05

Table B.6.1-10: Summary of identified metabolites in urine and faeces after repeated administrations of daily oral doses of tritosulfuron at 50 mg/kg bw (14 days non-labelled plus one day [triazine-^{14}C]-labelled tritosulfuron). Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)	
T-Label	Male	Female	Male	Female
Tritosulfuron	60.7	57.6	5.2	5.2
635M01	2.3	1.0	1.0	1.4
635M04	-	-	0.3	0.3
635M08	-	-	-	< 0.05
635M11	0.1	0.1	-	-
635M15	11.9	12.8	1.4	0.4
635M21	0.1	2.7	-	-

Table B.6.1-11: Summary of identified metabolites in urine and faeces after repeated administrations of daily oral doses of tritosulfuron at 50 mg/kg bw (14 days non-labelled plus one day [phenyl-^{14}C]-labelled tritosulfuron). Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)	
P-Label	Male	Female	Male	Female
Tritosulfuron	71.4	63.9	5.7	8.0
635M01	2.4	-	1.2	1.2
635M02	1.0	-	0.3	0.4
635M08	-	-	0.2	-
635M15	1.3	-	1.5	0.8
635M17	-	-	0.5	0.4
635M23	0.3	-	-	-

Metabolic pathway

After oral administration of tritosulfuron the unchanged parent compound was predominantly found in all matrices. Little quantities of parent were metabolised. Two major metabolic pathway branches were observed. For one, the parent compound was hydroxylated at the 4-position of the phenyl ring followed by conjugation reactions with glucuronic acid or sulfate. These conjugates were also found with an additional methyl ether group in 5-position of the phenyl ring, and they also appeared in the triazine ring-opened form. A cysteine conjugate of parent and of its triazine ring-opened metabolite resulted from previous glutathione conjugation at the phenyl ring. On the other hand, parent was transformed via the demethylated compound by hydrolytic cleavage of the triazine ring and by further degradation of the guanidine side chain resulting in the sulfonamide and the sulfonate of the trifluoromethyl-phenyl part of the parent molecule. A conjugate of the sulfonamide with glucuronic acid was detected. The substitution of the methoxy group of parent by an amino group was found to be a chemical transformation catalysed by artificially high concentrations of ammonia in urine samples. One of the minor metabolites resulted from hydroxylation in 5-position of the phenyl ring. This compound was known as major plant metabolite.

In case of the compounds only containing the triazine ring (635M04 and 635M11), it was not unequivocally clarified within this study whether they represented endogenous metabolites. The quantities determined for these compounds also allowed the hypothesis that 635M04 had been present at very small amounts in the original test substance fed to the animals. The compound 635M11 would then be a transformation product of 635M04.

Figure B.6.1-2: Metabolic pathway of tritosulfuron in rats

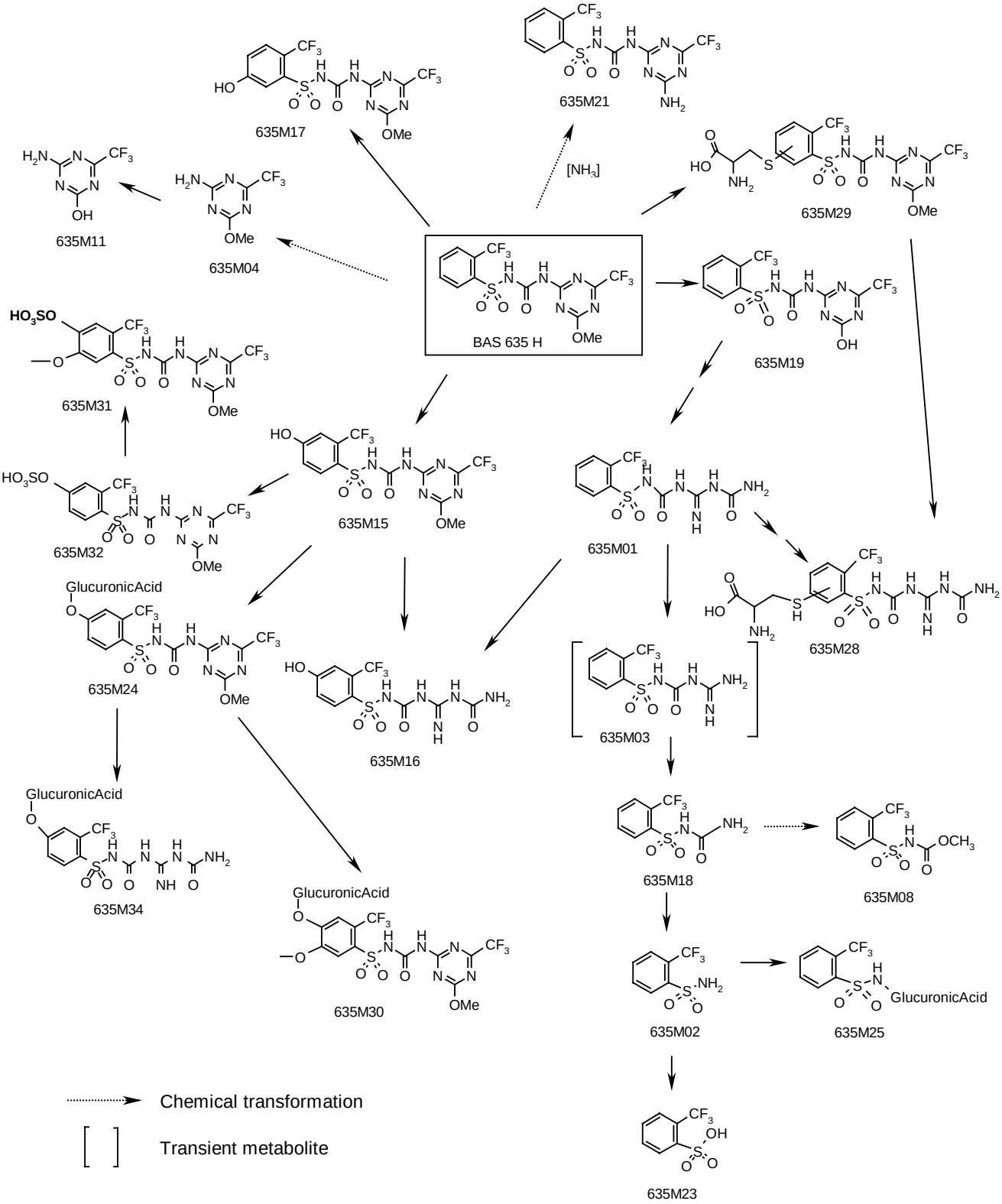
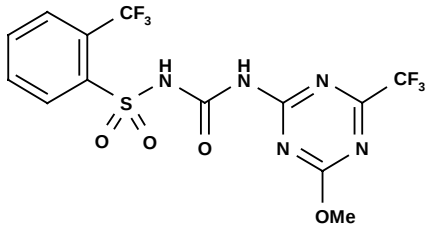
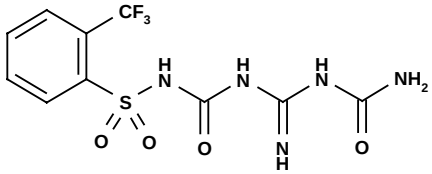
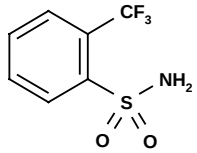
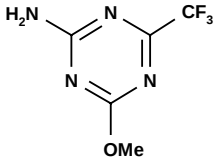
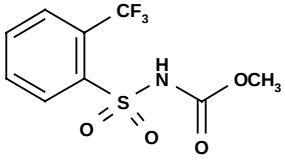
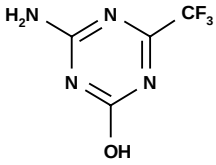
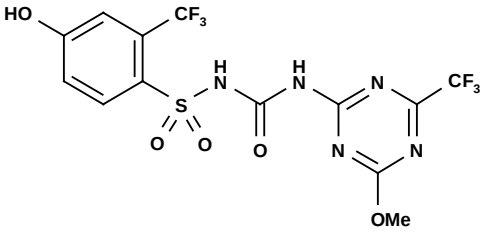
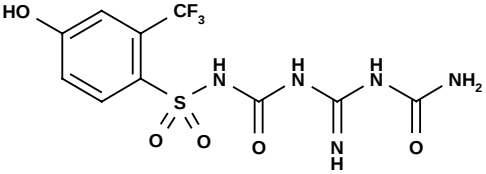
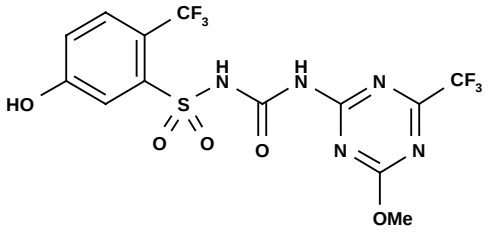
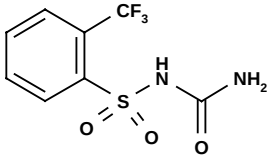
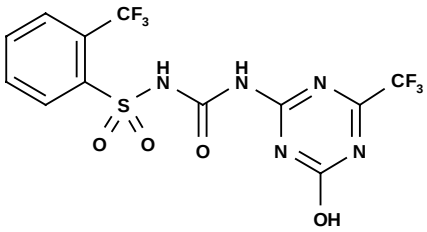
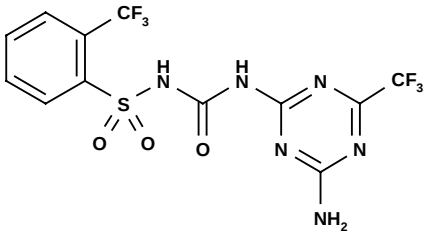
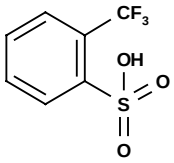
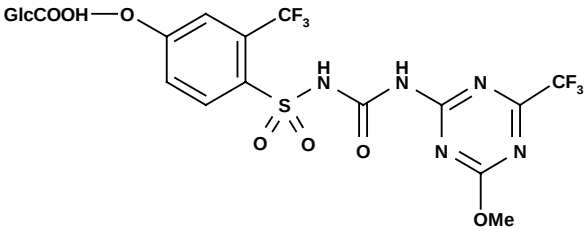
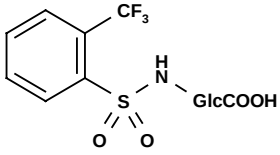
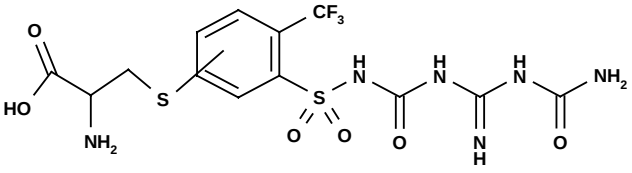
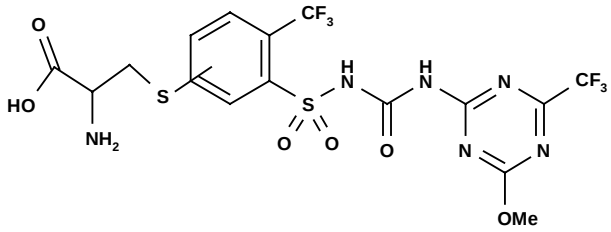
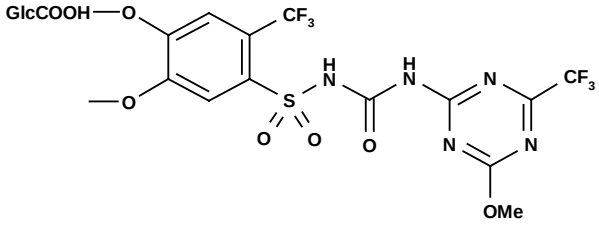
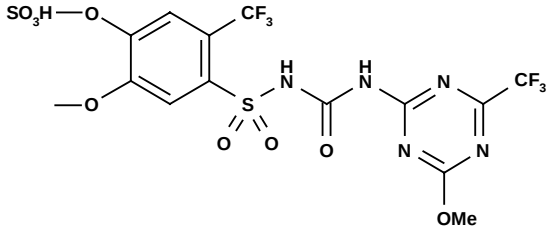
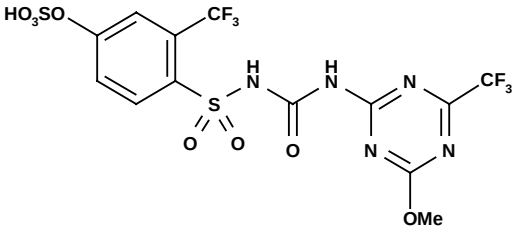
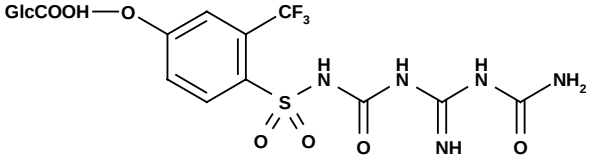


Table B.6.1-12: Structures of identified metabolites in rat urine, faeces, bile, plasma, liver, and kidney

Metabolite designation		Structure
Code; Reg.-No. (BH code)		
Tritosulfuron 271 272 (BAS 635 H)	Urine, feces, bile, plasma, liver, kidney	
635M01 335 184 (BH 635-4)	Urine, feces, bile, plasma, kidney	
635M02 292 564 (BH 635-2)	Urine, feces, bile	
635M04 231 700 (BH 635-5) AMTT	Feces	
635M08 n.a. (BH 635-9)	Feces	
635M11 n.a. AHTT	Urine	
635M15 n.a.	Urine, feces, bile, plasma, liver, kidney	
635M16 n.a.	Bile	

Metabolite designation		Structure
Code; Reg.-No. (BH code)		
635M17 n.a.	Feces	
635M18 n.a.	Urine	
635M19 n.a.	Urine	
635M21 n.a.	Urine	
635M23 324 543 (BH 635-1 as Na-Salt)	Urine, bile	
635M24 n.a.	Feces, bile	
635M25 n.a.	Urine	
635M28 n.a.	Bile	

Metabolite designation		Structure
Code; Reg.-No. (BH code)		
635M29 n.a.	Bile	
635M30 n.a.	Bile	
635M31 n.a.	Bile	
635M32 n.a.	Bile	
635M34 n.a.	Bile	

Conclusion:
Tritosulfuron does not accumulate in rats, but gets effectively excreted. The biotransformation essentially degrades the test substance to the sulfonamide 635M02 of the trifluoromethyl-phenyl ring and its sulfonic acid 635M23. The hydroxylation at the 4-position of the phenyl ring of parent leads to further conjugates with glucuronic acid or sulfate.

B.6.1.2.2 Metabolism of tritosulfuron with defined quantities of AMTT

Report: Leibold E. et al. 2001
Investigations of the formation of AMTT after oral administration of ^{14}C-BAS 635 H in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed.Rep.
unpublished
BASF RegDoc# 2000/1013503

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

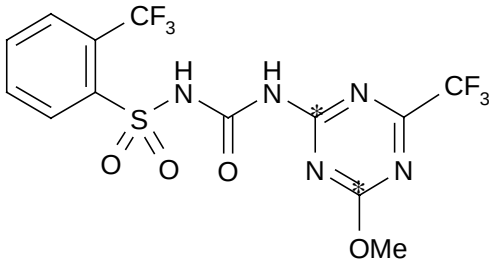
Guideline: Due to the special purpose, the study was not performed according to the guidelines.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 14C-tritosulfuron; batch: 437 - 1406: (triazin-2,4-14C); chemical purity: 97 %; radiochemical purity: > 99 %.
Test animals: Wistar rats (Chbb-THOM (SPF))

14C-triazine-labelled tritosulfuron was fed to male and female Wistar rats at a nominal dose of 50 mg/kg bw. The radiolabelled test substance was solubilised in a definite mixture of Cremophor EL, Pluriol E 200, and Tylose (0.5 % in water). The dose solution was administered as a single oral dose to two groups of eight animals, four males and females per group (dose groups B and R). In dose group B urine und faeces was collected daily for five days, and in dose group R bile was collected up to 48 hours post-dose [see Table B.6.1-15]. AMTT (BH 635-5 (2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine), as an impurity of tritosulfuron was determined in the dosing solution at an initial concentration of 0.5 % of the dose (see Table B.6.1-16). The purpose of this study was to determine the relative quantities of AMTT and its potential metabolite AHTT (2-amino-4-hydroxy-6-(trifluoromethyl)-1,3,5-triazine) in excreta and bile, in order to investigate a potential transformation of tritosulfuron to AMTT in the rat.

Figure B.6.1-3: Structure and position of the 14C-label for triazine-labelled tritosulfuron



* [14C-Triazine label]

Table B.6.1-13: Summary of dose groups and analysed samples of male and female rats

Dose group	B	R
Dose level	50 mg/kg bw	50 mg/kg bw
Number of doses	1 p.o.	1 p.o.
Label	Triazine	Triazine
Samples analysed	Urine, Faeces	Bile

Findings:

Balance and excretion pattern of 14C-tritosulfuron

The excretion pattern was comparable to that found in the corresponding dose group of the biokinetics study (see B.6.1.1 and Table B.6.1-2). Male and female rats excreted 76 % and 84 % of the dose, respectively, via urine, and they excreted around 12 % of the dose via faeces. The total balance including cage wash amounted to 89 % and 96 % of the dose for male and female rats, respectively.

Quantification of AMTT and AHTT in excreta

The chromatographic analyses of urine and faeces showed the major metabolites 635M15 and 635M01 besides dominant quantities of tritosulfuron [see Table B.6.1-14].

Table B.6.1-14: Identified metabolites in urine and faeces after administration of a single oral dose of [triazine-^{14}C]-tritosulfuron at 50 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-48 h)		Faeces (0-48 h)	
T-Label	Male	Female	Male	Female
Tritosulfuron	72.70	81.87	10.37	10.08
635M01	0.49	0.24	0.35	0.32
635M15	0.66	0.29	0.65	0.33
AMTT	0.10	0.10	0.04	0.05
AHTT	0.41	0.30	0.00	0.00

The relative quantities of AMTT excreted via urine amounted to 0.10 % of the dose after 48 hours for both sexes [see Table B.6.1-15]. Via faeces, 0.04 % and 0.05 % of the dose were excreted after 48 hours by male and female rats, respectively. AHTT as relevant metabolite of AMTT was essentially detected in urine. The proportions excreted after 48 hours accounted for 0.41 % and 0.30 % of the dose for male and female rats, respectively.

Table B.6.1-15: Total balance in % dose including quantification of AMTT and AHTT in the excretion experiment

Matrix	Time interval [h]	Dose group B					
		Nominal dose of 50 mg/kg p.o.					
		Male	Female	Male	Female	Male	Female
		Total % dose		AMTT % dose		AHTT % dose	
Urine	0-24	74.3	82.4	0.09	0.08	0.26	0.18
	24-48	1.6	1.3	0.01	0.02	0.13	0.12
	48-72	0.3	0.3	n.d.	n.d.	n.d.	n.d.
	72-96	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	96-120	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0-120	76.2	84.0	0.10	0.10	0.39	0.30
Faeces	0-24	11.6	10.7	0.04	0.04	0.00	0.00
	24-48	0.6	0.5	0.01	0.01	0.00	0.00
	48-72	0.1	0.1	n.d.	n.d.	n.d.	n.d.
	72-96	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	96-120	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0-120	12.3	11.3	0.04	0.05	0.00	0.00
Cage	0-24	0.8	1.0	n.d.	n.d.	n.d.	n.d.
Wash	24-48	0.1	0.1	n.d.	n.d.	n.d.	n.d.
	0-48	0.9	1.1	n.d.	n.d.	n.d.	n.d.
Total	0-120	89.4	96.4	0.15	0.15	0.39	0.30

After dosing rats with 50 mg/kg bw, the proportion of of AMTT and AHTT in total were determined at 0.54 % and 0.46 % of the dose in excreta of male and female rats, respectively.

The quantification results of AMTT and AHTT in the bile experiment (dose group R) are depicted in Table B.6.1-16. The bile of male and female rats contained AMTT at 0.22 % and 0.34 % of the dose, respectively. Its potential metabolite AHTT was detected at 0.16 % and 0.11 % of the dose in bile of male and female animals, respectively.

Table B.6.1-16: Total balance in % dose including quantification of AMTT and AHTT in the bile experiment

Matrix	Time interval [h]	Dose group R [1)]					
		nominal dose of 50 mg/kg p.o.					
		Male	Female	Male	Female	Male	Female
		Total % dose		AMTT % dose		AHTT % dose	
Bile	0-48	8.3	10.8	0.22	0.34	0.16	0.11

1) The dosing solution of 50 mg/kg bw tritosulfuron contained 1.9 % AMTT in case of dosing the male rats and 3.2 % AMTT in case of dosing the female rats.

Summarising the bile experiment, 0.38 % of the dose and 0.45 % of the dose accounted for AMTT and AHTT in total in the bile of male and female rats, respectively.

Conclusion:
The relative quantities of AMTT originally contained in the dosing solution of tritosulfuron were followed in excreta after single oral administration to male and female rats. The initial proportions of AMTT in the dosing solution accounted for 0.5 % of the dose. The proportions of AMTT including its metabolite AHTT identified in urine and faeces throughout five days were determined at the same order of magnitude as the relative amounts of AMTT initially fed to the animals. The relative quantities of AMTT and AHTT in the bile compared to those

found in faeces indicate an enterohepatic circulation of these compounds. Alternatively, the relatively high amounts of AMTT and AHTT in the bile may depend on the higher initial concentrations of AMTT in the dosing solution. It was concluded that no significant amounts of AMTT were produced in the rat by transformation of tritosulfuron.

B.6.2 Acute toxicity including irritancy and skin sensitization (Annex IIA 5.2)

Tritosulfuron (batch no. N12) is characterised by a low acute oral, dermal and inhalation toxicity. The substance is neither irritating to the skin nor to the eyes. It is a skin sensitiser in the Maximisation Test. The results of the acute toxicity studies with tritosulfuron are summarised in the table below.

Table B.6.2-1: Acute toxicity of tritosulfuron

Study type	Species/doses/batch no.	Comments	Results
Acute oral toxicity	Wistar rat 1000; 2000; 3000, 5000 mg/kg bw N12	Mortality: 5 at 5000 mg/kg bw; 3 at 3000 mg/kg bw; 1 at 2000 mg/kg bw	LD_{50}: 4700 mg/kg bw
Acute dermal toxicity	Wistar rat 2000 mg/kg bw N12	No mortality	LD_{50}: > 2000 mg/kg bw
Acute inhalation toxicity	Wistar rat 5.4 mg/l (4 h) dust N12	No mortality	LC_{50}: > 5.4 mg/l
Dermal irritation	New Zealand White rabbit N12	No skin reaction	Not irritating
Eye irritation	New Zealand White rabbit N12	Very slight and reversible conjunctival irritation.	Not irritating
Skin sensitisation maximisation test	Pirbright White guinea pig N12	Slight edema (5/20), well-defined erythema (2/20)	Sensitising

B.6.2.1 Oral

Report: Kirsch P., Hildebrand B. 1995
Study on the acute oral toxicity of Reg.-No. 271 272 in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10634

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 401, EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N 12: 95.6 %.

Test animals: Wistar rats Chbb:THOM (SPF)
Single administration of a test substance preparation in 0.5 % aqueous tylose by gavage to five male and five female fasted Wistar rats at dose levels of 1000; 2000; 3000 and 5000 mg/kg bw, using an application volume of 10 ml/kg bw. The observation period was 14 days.

Findings:
The stability of the test substance over the study period was proven by reanalysis. The stability of the test substance in the vehicle was confirmed by analysis. The concentration and the homogeneity of the test substance in the vehicle were analytically confirmed.

2 male and 3 female animals of the 5000 mg/kg dose group, 1 male and 2 female animals of the 3000 mg/kg dose group and 1 female animal of the 2000 mg/kg dose group died within 1 or 2 days after the application. Signs of toxicity noted in the 5000; 3000 and 2000 mg/kg dose group comprised impaired or poor general state and dyspnoea. The animals of the 1000 mg/kg dose group did not show any symptoms. The surviving animals appeared normal within 6 days after application. Body weight development appeared to be normal in the course of the study. Necropsy finding of the animals that died was agonal congestion. No abnormalities were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The oral LD_{50} was found to be 4700 mg/kg bw for male and female animals.

B.6.2.2 Percutaneous

Report: Kirsch P., Hildebrand B., 1995
Study on the acute dermal toxicity of Reg. No. 271 272 in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10635

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 402, EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N12: 95.6 %.
Test animals: Wistar rats Chbb: THOM (SPF)

The test material was applied dermally as a suspension in 0.5 % solution of Tylose in aqua bidest. to five male and five female Wistar rats for 24 hours under semiocclusive dressing at a

dose level of 2000 mg/kg bw. The application area was about 50 cm². The observation period was 14 days.

Findings:
The stability and homogeneity of the test substance over the study period was proven by analysis. The stability of the test substance in the vehicle was confirmed by analysis; the homogeneity was provided by stirring.
No mortality occurred. No signs of systemic toxicity were noticed. Body weight development appeared to be normal. After removal of the patches very slight erythema could be observed in 3 male and 4 female animals. 1 female animal showed well-defined erythema. No abnormalities were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The dermal LD_{50} was found to be > 2000 mg/kg bw for male and female animals.

B.6.2.3 Inhalation

Report: Gamer A. O., Hoffmann H. D., 1995
Study on the acute inhalation toxicity LC_{50} of Reg.-No. 271 272 as a dust aerosol in rats. 4-hour exposure
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10410

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 403, EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N12: 95.6 %.
Test animals: Wistar rats Chbb:THOM (SPF)

Five male and five female Wistar rats were exposed to a dust aerosol of the test material for four hours in a head/nose inhalation system at the mean analytical concentration and limit dose of 5.4 mg/l. The observation time was 14 days.

Findings:
The stability of the test substance was ensured over the study period, the homogeneity was confirmed. The homogenous distribution of atmospheres in this inhalation system has been proven. The particle size distribution revealed a mass median aerodynamic diameter (MMAD) of 9.2 µm. In spite of several technical measures, no smaller particle size could be achieved.
No lethality occurred at the limit concentration. Clinical examination showed accelerated respiration during exposure and bloody basal crust formation in 3 male animals on day 2. No

abnormalities were observed from post exposure day 3 onward. Body weight development of the animals was not influenced. No pathologic findings were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The inhalation LC_{50} was found to be > 5.4 mg/l (4 h) for males and females.

B.6.2.4 Skin irritation

Report: Rossbacher R., Hellwig J., 1995
Study on the acute dermal irritation/corrosion of Reg.-No. 271 272 in rabbits
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10533

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 404, EEC 92/69, B 4

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N12: 95.6 %.
Test animals: White New Zealand rabbits

The undiluted test material (0.5 g) was applied dermally to the intact skin of three male and three female White New Zealand rabbits for 4 hours on a 2.5 cm x 2.5 cm test patch under a semiocclusive dressing. After the patches were removed the treated area was rinsed with Lutrol and Lutrol/water (1:1). The animals were observed for skin irritation for 72 hours after removal of the patch. Skin readings were performed at 1 h, 24 h, 48 h and 72 h after removal of the patch.

Findings:
The stability of the test substance over the study period was analytically confirmed. The homogeneity of the test substance was confirmed by analysis. No skin reaction could be observed in all animals.

Conclusion:
Tritosulfuron is not irritant to the skin.

B.6.2.5 Eye irritation

Report: Rossbacher R., Hellwig J, 1995
Study on the acute eye irritation of Reg.-No. 271 272 in rabbits
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10532

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 405, EEC 92/69, B 5

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N12: 95.6 %.
Test animals: White New Zealand rabbits

The test substance (about 16 mg, 0.1 ml bulk volume) was applied once to the conjunctival sac of two male and four female White New Zealand rabbits. The application volume was about 0.1 ml. The test substance was not washed out. Readings of the eyes were carried out at 1 hour and 1, 2, 3 days after the application of the test material.

Findings:
The stability of the test substance over the study period was analytically confirmed. The homogeneity of the test substance was confirmed by analysis.

Table B.6.2-2: Eye irritation; mean readings and symptoms

			Conjunctiva	
Animal No.	Opacity	Iris	Redness	Swelling
1	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0
3	0.0	0.0	0.3	0.3
4	0.0	0.0	0.0	0.0
5	0.0	0.0	0.3	0.3
6	0.0	0.0	0.0	0.0
Mean	0.0	0.0	0.1	0.1

The mean value (readings of 24, 48 and 72 hours) for corneal opacity and iris was 0.0, for conjunctivae redness and chemosis it was 0.1. The findings were reversible in all animals within 48 hours.

Conclusion:
Tritosulfuron is not irritant to the eye.

B.6.2.6 Skin sensitisation

Report: Rossbacher R., Hellwig J., 1995
Report on the Maximization test for the sensitizing potential of Reg.-No. 271 272 in guinea pigs
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/10523

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69, OECD 406

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N12: 95.6 %.
Test animals: Pirbright White (Dunkin-Hartley) guinea pigs

Tritosulfuron was tested for its skin sensitising effect in Pirbright White (Dunkin-Hartley) guinea pigs using the Maximisation Test based on the method of Magnusson and Kligman. Twenty female animals were used for the test group and ten female animals in each of two control groups.
The concentrations of the test substance suitable for use in the main experiment were determined in a pretest: Two 24-hour percutaneous occlusive applications within 96 hours were performed. No sign of skin irritation could be observed for up to 50 % test substance preparation. It was possible to inject a 5 % test substance preparation in 0.5 % Tylose CB 30.000 in aqua bidest. or in Freund's adjuvant / 0.9 % aqueous NaCl-solution (1 : 1) with a syringe.

The following concentrations for induction and challenge were selected on the basis of the pretests.

Table B.6.2-3: Test substance preparations for Maximisation test

Intradermal induction	Test substance 5 % in 0.5 % Tylose CB 30.000 in aqua bidest. or in Freund's adjuvant / 0.9 % aqueous NaCl-solution (1 : 1)
Percutaneous induction	Test substance 50 % in 0.5 % Tylose CB 30.000 in aqua bidest.
Challenge	Test substance 50 % in 0.5 % Tylose CB 30.000 in aqua bidest.

The induction phase consisted of both intradermal and percutaneous exposures. First, six intradermal injections in groups of two were given to each animal. One week later a percutaneous induction exposure was conducted. 2 x 4 cm filter paper strips coated with the test substance formulation were applied to the skin of the shoulder under an occlusive dressing for 48 h. The test animals were treated with the preparations as indicated in the table above. Control animals received the same treatment but without test material. The challenge was conducted 14 days after the percutaneous induction with a test substance preparation as

indicated in the above table. Control group two received the same treatment but without test substance. 2 x 2 cm filter paper strips coated with the test substance formulation were applied to the skin of the flank under an occlusive dressing for 24 h. Skin irritation readings were made at 24 and 48 hours after removal of the paper strips. Separate tests using 1-chloro-2,4-dinitrobenzene as a positive control are conducted twice a year in the laboratory to determine the ability of the test procedures to detect sensitising compounds.

Findings:
The stability of the test substance over the study period was proven by reanalysis. The homogeneity of the test substance was confirmed by analysis. The stability of the test substance in the vehicle was confirmed by analysis. Homogeneity of the preparation was ensured by stirring. The number of animals with skin findings after the challenge is summarised in the table below.

Table B.6.2-4: Results of Maximisation Test after challenge application

Total number of animals with positive reactions at 24 and/or 48 h / number of animals tested:	
Control group 1	0/10
Control group 2	No application of test substance
Test group	7/20

The intradermal induction of test substance preparation in 0.5 % aqueous solution of Tylose caused well-defined erythema and very slight edema. After injection of a 5 % test substance preparation in Freund's adjuvant / 0.9 % aqueous NaCl solution (1:1) the test group animals exhibited well-defined erythema and slight edema. The control group animals did not show any skin reactions.

The percutaneous induction with 50 % test substance preparation led to incrustation, partially open, in addition to well-defined erythema and slight edema in the test group. The animals of the control groups treated with 0.5 % solution of Tylose in aqua bidest. exhibited the same skin reactions as the test group animals.

After the challenge with 50 % test substance preparation 5 out of 20 test group animals showed very slight erythema, while well-defined erythema were observed in 2 out of 20. The animals of control group 1 did not show any skin reaction.

Conclusion:
Tritosulfuron has a sensitising effect on the skin of the guinea pig in the Maximisation test.

B.6.3 Short-term toxicity (Annex IIA 5.3)

The short-term toxicity of tritosulfuron was investigated in dietary 4-week studies in rats and mice, 3-month studies in rats, mice and dogs and in a 12-month study in dogs. In addition, the short-term toxicity following dermal exposure was determined in a 28-day study in rats.
The 3-month and 12-month dog studies as well as the 28-day dermal study in rats were conducted with tritosulfuron containing high amounts of AMTT (batch no. N24). The dietary 4-week and 3-month studies in rats and mice were performed with batch no. N14 (purity 96.4 %).
The signs of toxicity in the mouse were minor and consisted mainly of some clinical chemical changes (after 3 months: increased urea and decreased serum triglyceride levels in males), as

well as decreased body weights and increased water consumption. In the 3-month toxicity study cystitis was noted in 3/10 female mice and in one male mouse as well as decreased adrenal weights in females. Both, in the 28-day study and in the 3-month study the NOAEL was found to be 3000 ppm (equal to 547 mg/kg bw/d in male mice/692 mg/kg bw/d in female mice and 770 mg/kg bw/d in male mice/938 mg/kg bw/d in female mice).

The main target organs in the rat were liver and kidney. After 28 days of tritosulfuron administration the signs of toxicity consisted of decreased body weight gain, increased water consumption and urinary volume with decreased urinary specific gravity, altered clinical-chemical parameters, i.e. decreases in glucose, triiodthyronine and triglycerides and an increase in total bilirubin levels. Histopathological evaluation revealed papillary necrosis and nephropathies. The NOAEL was found to be 3000 ppm (equal to 296 mg/kg bw/d in males, 313 mg/kg bw/d in females).
After 3 months of administration to rats, increased liver weights, centrilobular hypertrophy in hepatocytes as well as altered clinical-chemical and hematological parameters and altered enzyme activities were noted in addition to the results obtained after the 4-week administration. At the dose level of 15000 ppm, premature deaths were noted in female rats, most likely due to the occurrence of severe nephropathies. The NOAEL was found to be 1000 ppm (equal to 75 mg/kg bw/d in males, 85 mg/kg bw/d in females).

Overall, the signs of toxicity observed in the dogs were similar to rats and mainly consisted of centrilobular hypertrophy of liver hepatocytes and single cell necrosis accompanied by increased organ weights and altered clinical-chemical parameters, i.e. higher platelet counts, shorter partial thromboplastin times, higher activities of alkaline phosphatase and alanine aminotransferase, lower levels of triglycerides, cholesterol, creatinine, potassium, calcium, lower concentrations of total proteins, mainly due to lower albumin levels and higher levels of inorganic phosphate. In the kidneys, a degeneration of renal tubular epithelium was noted after the 3-month administration period. Weights of adrenal and thyroid glands were increased. The NOAEL was found to be 500 ppm (equal to 15 mg/kg bw/d in males, 17 mg/kg bw/d in females).
Feeding of tritosulfuron to dogs for one year resulted in clinical chemical changes mainly at the high dose level of 5000 ppm. At this dose level and to a lesser extent at 1000 ppm there was decreased body weight gain at the beginning of the study. Functional and/or morphological changes of the liver consisted of decreased urea levels and increased activities of alkaline phosphatase in female dogs, increased organ weights together with necrosis of hepatocytes in two males and inflammatory reactions in the liver of females. The NOAEL in this 12-month dog study was 200 ppm (equal to 6 mg/kg bw/d). The overall NOAEL in dogs was considered to be 500 ppm (equal to 15 mg/kg bw/d from the 90-day study) based on the LOAEL from the 12-month study.

In a 4-week dermal toxicity study in rats no substance-related systemic adverse effects were detected up to the highest dose level tested of 1000 mg/kg bw. There were no signs of local irritation in this study.
A summary of short-term toxicity studies is given in Table B.6.3-1.

Table B.6.3-1: Summary of short-term toxicity studies

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
28-day feeding Chbb:THOM Wistar rat 0, 3000, 8000, 15000 (m) / 20000 (f) ppm N14	3000 ppm [296]	8000 ppm: Increased water consumption and urinary volume, lower sodium, chloride and triglyceride values. At 15000 ppm (m): Reduced bw, bw gain and food consumption. 20000 ppm (f): Papillary necrosis, multifocal vacuolar degeneration of renal tubules in one female, altered hematological parameters.
28-day feeding B6C3F1 CrlBr mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [547]	8000 ppm: Increased water consumption
28-day dermal Chbb:THOM Wistar rat 0, 50, 200, 1000 mg/kg bw/d N24	[1000]	No systemic adverse effects. No signs of local irritation.
90-day feeding study Chbb:THOM Wistar rat 0, 1000, 5000, 15000 ppm N14	1000 ppm [75]	5000 ppm: Increased water consumption, slightly lower red blood cell parameters; centrilobular hypertrophy in hepatocytes; increased liver weights, nephropathies (slight). 15000 ppm: Premature deaths (5/10 f), reduced bw and bw gain, altered clinical-chemical and hematological parameters; altered enzyme activities; papillary necrosis; nephropathies (severe)
90-day feeding study B6C3F1 CrlBR mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [770]	8000 ppm: Increased water consumption, reduced bw and bw gain (m), increased urea/decreased triglyceride levels (m), increased adrenal gland weights and cystitis (f)
90-day feeding study Beagle dogs 0, 500, 3000, 9000 ppm N24	500 ppm [15]	3000 ppm: Increased platelet count (f day 41); decreased albumin concentration (f day 41); increased alkaline phosphatase activity (m day 91), increased rel. adrenal gland weights (f), centrilobular hypertrophy (m) 9000 ppm: Decreased bw and bw gain, altered clinical chemical and hematological parameters (increase in alkaline phosphatase and alanine aminotransferase activity, decreased albumin conc.), increased weights of liver, kidney, adrenal and thyroid glands, centrilobular hypertrophy and degeneration of hepatocytes; focal and multifocal lesions in kidneys; degenerative changes of tubular epithelium with reactive inflammatory response in cortical region of kidneys.
12-month feeding study Beagle dogs 0, 200, 1000, 5000 ppm N24	200 ppm [6]	1000 ppm: Initial bw loss (m), increased activity of alkaline phosphatase (f), decreased urea concentrations (f) 5000 ppm: Initial bw loss (m), retarded bw development (f), altered clinical chemical and hematological parameters, increased liver weights, centrilobular necrosis of hepatocytes (m), inflammatory reactions in livers (f), increased adrenal gland weights (m)

m: male; f: female; bw: body weight; d: day

B.6.3.1 Oral administration (28-day study)

B.6.3.1.1 Rat

Report: Mellert W. et al., 1997
Reg.-No. 271 272 - Repeated dose oral toxicity study in Wistar rats. Administration in the diet for 4 weeks
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/10819

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69, OECD 407

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N14: 96.4 %.
Test animals: Groups of 5 male and 5 female Wistar rats Chbb:THOM (SPF), 42 days old at start of the administration period, 172-189 g (males), 136-150 g (females), supplied by Dr. Karl Thomae GmbH, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0 ppm; 3000 ppm; 8000 ppm; 15000 ppm (males only) and 20000 ppm (females only) for four weeks. This was equal to 296, 819, and 1601 mg/kg bw/d for males and 313, 872, and 2198 mg/kg bw/d for females. The concentrations in the diet were selected based on the results of a palatability study. In high dose males (20000 ppm for 2 weeks) food consumption was decreased by 10 % and body weight by 20 % was noted whereas in females no decrease was observed.
Food consumption, body weight and water consumption was determined weekly. The animals were examined for mortality or signs of toxicity at least once a day. During the weekly weighing, the animals were subjected to an additional comprehensive clinical examination. Urinalysis as well as clinico-chemical and hematological examinations were carried out during the last week of dosing. All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures (Table B.6.3-2)
The stability of the test substance was proven by reanalysis. The stability and homogenous distribution of the test substance in the diet was proven over the study period. The correctness of the test substance concentrations was analytically confirmed.

Table B.6.3-2: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
3000	296	313
8000	819	872
15000	1601	
20000		2198

Mortality and clinical signs:
No mortalities occurred in the study. In one high and one mid dose female rat the anogenital region was smeared with urine.

Body weight, body weight gain, food and water consumption (Table B.6.3-3)
Body weight and body weight gain was decreased in high dose females during the entire administration period, resulting in reduced values of about 12 % when compared to controls on day 28. In male rats body weight gain was transiently reduced on day 7 in the mid and high dose group. Food consumption was reduced in high dose females, the values being up to 17 % below control (statistically significant on days 7 and 21). Water consumption was increased in male and female rats of the mid and high dose (up to 74 % and 38 % above controls, respectively).

Table B.6.3-3: Body weight, body weight gain, food and water consumption

Dose level (ppm)	0	3000	8000	15000 (males) 20000 (females)
Body weight (g)				
Day 7 (females)	173.9	173.4	171.6	152.1**
Day 14 (females)	194.0	193.5	190.5	176.2**
Day 21 (females)	206.8	207.9	203.1	181.1**
Day 28 (females)	222.6	224.1	219.9	194.9**
Body weight change (g)				
Day 7 (males)	54.8	53.1	45.4*	37.8**
Day 7 (females)	29.3	29.6	26.7	6.7**
Day 14 (females)	49.5	49.6	45.6	30.9**
Day 21 (females)	62.3	64.0	58.2	35.7**
Day 28 (females)	78.0	80.3	75.0	49.6**
Food consumption (g/animal/day)				
Day 7 (females)		20.7	21.0	18.5**
Day 21 (females)		20.2	21.2	17.6**
	21.0			
	21.2			
Water consumption (g/animal/day)				
Day 7 (males)		25.3	32.0**	41.2**
Day 14 (males)		27.9	34.8**	42.8**
Day 21 (males)		26.7	32.5	42.2**
Day 28 (males)	25.0	27.5	34.3**	43.2**
Day 7 (females)		21.5	29.4	35.1**
Day 14 (females)	26.8	24.2	27.9*	36.7**
Day 21 (females)		18.4	29.1*	32.6**
Day 28 (females)		23.1	32.0	40.6**
	26.3			
	24.8			
	21.6			
	21.0			
	22.3			
	24.3			

* P < 0.05; ** P < 0.02 (Kruskal-Wallis + Mann-Whitney u-tests)

Hematology

Hematological examinations showed a mild leukocytosis and lymphocytosis at 20000 ppm (females).

Blood chemistry (Table B.6.3-4)
At the end of the treatment period sodium, chloride, glucose and triglyceride levels were decreased and total bilirubin was increased in the in high dose animals, although attaining statistical significance mainly in male rats. Triiodthyronine (T3) was decreased in females of the high dose. Male rats at 8000 ppm also had lower sodium, chloride and triglyceride values. These changes were considered treatment-related.
The statistically significant increase of total bilirubin in female rats of the low and intermediate group was not considered treatment-related, since no dose-response relationship could be established.

Table B.6.3-4: Blood chemistry parameters

Sex	Male				Female			
Dose (ppm)	**0**	**3000**	**8000**	**15000**	**0**	**3000**	**8000**	**20000**
Sodium (mmol/l)	143.2	142.7	141.4*	140.6**	141.8	141.8	141.9	140.8
Chloride (mmol/l)	101.8	101.8	101.0	101.0	104.0	104.0	103.4	101.8
Glucose (mmol/l)	9.09	8.73	8.82	8.21**	8.45	8.48	8.23	7.82
Total bilirubin (µmol/l)	2.33	2.23	3.15	3.47	1.96	2.86**	2.84**	4.03**
Triglycerides (mmol/l)	3.17	2.72	1.84**	1.51**	1.99	1.42	1.87	1.34
Triiodthyronine (nmol/l)	1.96	2.00	1.95	1.88	2.14	2.05	2.07	1.76**

* $P < 0.05$; ** $P < 0.02$ (Kruskal-Wallis + Mann-Whitney u-tests)

Urinalysis
The urinary specific gravity was decreased at 20000 ppm (females) and the urinary volume increased at 20000 ppm and 8000 ppm (females). Furthermore, females of the 20000 ppm group revealed occurrence of bacteria in the sediment.
Organ weights and pathology
Changes in organ weights (decreased thymus weight, increased heart, adrenal glands, spleen, liver and brain weights) were not considered treatment-related because changes were due to lower terminal body weights or there were no histopathological findings. The target organ was the kidney. Histopathological investigations demonstrated papillary necrosis and multifocal vacuolar degeneration of renal tubules in the kidneys of one female animal at 20000 ppm. This animal also showed a moderate inflammation with a reactive hyperplastic change of the transitional epithelium of the urinary bladder.
There were no test substance related changes at 8000 and 3000 ppm.

Conclusion:
The NOAEL under the conditions of this study was 3000 ppm (equal to 296 mg/kg bw/d in males, 313 mg/kg bw/d in females) based on increased water consumption and urinary volume, as well as lower sodium, chloride and triglyceride values at 8000 ppm.

B.6.3.1.2 Mouse

Report: Mellert W. et al., 1996
Reg.-No. 271 272 - Repeated dose oral toxicity study in B6C3F1 CrlBr mice. Administration in the diet for 4 weeks
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1996/10430

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 84/449, OECD 407

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N14: 96.4 %.
Test animals: Groups of 5 male and 5 female B6C3F1 CrlBr mice, 48-50 days old at start of the administration period, 27-30 g (males), 22-24 g (females), supplied by Charles River Wiga GmbH, Sulzfeld, FRG.
The mice received the test material by dietary administration at concentrations of 0, 1000, 3000 and 8000 ppm for four weeks. This was equal to 174, 547, and 1311 mg/kg bw/d for males and 228, 692, and 1832 mg/kg bw/d for females. The concentrations in the diet were selected based on the results of a 2-week palatability study. In the highest dose of 8000 ppm no substance-related effects were observed.
Food consumption, body weight and water consumption was determined weekly. The animals were examined for mortality or signs of toxicity at least once a day. During the weekly weighing, the animals were subjected to an additional comprehensive clinical examination. Clinico-chemical and hematological examinations were carried out during the last week of dosing. All animals were subjected to gross-pathological assessment, followed by histo-pathological examinations.

Findings:
Analysis of the dietary mixtures (Table B.6.3-5)
The stability of the test substance was proven by reanalysis. The stability and homogenous distribution of the test substance in the diet was proven over the study period. The correctness of the test substance concentrations was analytically confirmed.

Table B.6.3-5: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
1000	174	228
3000	547	692
8000	1311	1832

The only finding considered treatment-related was an increase in water consumption at 8000 ppm (up to 38 % above controls) (see Table B.6.3-6).

Table B.6.3-6: Water consumption

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**3000**	**8000**	**0**	**1000**	**3000**	**8000**
Water consumption (g/animal/d)								
day 7	5.1	5.4	5.5	6.2	5.2	5.2	5.3	6.5**
day 14	5.3	4.4	4.4	5.6	5.1	4.9	4.7	6.1
day 21	5.0	4.8	5.0	5.8	4.9	5.3	4.8	5.7**
day 28	5.0	4.7	4.7	6.9*	4.8	5.2	4.8	5.9**

* P < 0.05; ** P < 0.02 (Kruskal-Wallis + Mann-Whitney u-tests)

Conclusion:
The NOAEL under the conditions of this study was 3000 ppm (equal to 547 mg/kg bw/d in males; 692 mg/kg bw/d in females) based on an increase in water consumption at 8000 ppm.

B.6.3.2 Dermal route (28-day study)

B.6.3.2.1 Rat

Report: Mellert W. et AL., 1998
BAS 635 H - Repeated dose dermal toxicity study in Wistar rats. Administration for 4 weeks
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10479

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 92/69, OECD 410, EPA/FIFRA 82-2

Deviations: The study was conducted with a batch containing 2.45 % AMTT.
The homogeneity and correctness of the concentration of tritosulfuron in 0.1 % Tylose® solution could not be demonstrated for all samples.
Values for water consumption were not available in the dossier. These deviations are not considered to affect the integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N24: 95.9 %.
Test animals: Groups of 5 male and 5 female Wistar rats Chbb:THOM (SPF), 9-11 weeks old at the start of the administration period, 270 - 298 g (males), 214 - 240 g (females), supplied by Dr. Karl Thomae GmbH, Biberach/Riss, FRG.

Tritosulfuron was administered to the rats by dermal route (6 hours/day; 5 days/week, semiocclusive dressing) at concentrations of 0 (vehicle control; 0.1 % aqueous CMC solution), 50, 200 and 1000 mg/kg bw/d for 4 weeks.
Food consumption and body weight were determined weekly. The animals were examined for signs of toxicity or mortality at least once a day. Urinalysis, clinico-chemical and hematological examinations were carried out at the end of the administration period. All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The stability of the test substance in the vehicle was verified. The homogeneity and correctness of the concentration of tritosulfuron in 0.1 % Tylose® solution could only be demonstrated at one of the three samplings for the low concentration (1 g/100 ml) and for two of the three samplings for the mid concentration (4 g/100 ml). For the high concentration (20 g/100 ml) the results demonstrated the homogeneity and correctness of tritosulfuron in 0.1 % Tylose® solution for all three samples.
Clinical findings
No mortalities occurred in the study. In three high dose females the finding "Erosion/Ulcus, Focal" was noted towards the end of study. This finding was also observed in one control animal.
Body weight, body weight gain, and food consumption
Body weight, body weight gain, and food consumption were considered unaffected by treatment.
Hematology and clinical chemistry
Hematology and clinical chemistry examinations revealed no changes, which were related to the test compound administered.
Urinalysis
Urinalytical determinations showed an increased occurrence of crystals of unknown origin in the urine of isolated animals at 1000 mg/kg. Since in the 4-week oral toxicity study in rats the occurrence of crystals in the urinary sediment was not increased in a persuasive manner and a dermal absorption study revealed an absorption rate below 3 % of the dose the finding is considered unlikely to be of toxicological relevance.
Organ weights and pathology
Concerning pathology, no significant or otherwise suspect weight changes were detected; all gross lesions and microscopic findings noted gave no indication for a treatment-related effect.

Conclusion:
The NOAEL for systemic toxicity after a 28-day dermal administration in rats was 1000 mg/kg bw/d in both sexes.

B.6.3.3 Oral administration (90-day study)

B.6.3.3.1 Rat

Report: Mellert W. et al., 2000
BAS 635 H - Subchronic oral toxicity study in Wistar rats. Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1003966

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 408, EEC 87/302, EPA/FIFRA 82-1, JMAFF

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N14: 96.4 %.
Test animals: Groups of 10 male and 10 female Wistar rats Chbb:THOM (SPF), 42 days old at start of the administration period, 164-181 g (males), 135-149 g (females), supplied by Dr. Karl Thomae GmbH, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0; 1000; 5000 and 15000 ppm for 3 months. This was equal to 75, 376 and 1238 mg/kg bw/d for males and 85, 441 and 1310 mg/kg bw/d for females.
Food and water consumption and body weight were determined each week. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations were performed once a week.
Ophthalmological examinations were carried out prior to the start and towards the end of dosing. Urinalysis, clinico-chemical and hematological examinations were carried out in the mid and at the end of the administration period. All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures (Table B.6.3-7)
The stability of the test substance was proven by reanalysis. The stability of the test substance in the diet was verified. The homogeneity of the mixtures was proven. The correctness of the concentrations was demonstrated.

Table B.6.3-7: Test substance intake intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
1000	75	85
5000	376	441
15000	1238	1310

Clinical findings
Five females of the high dose group (15000 ppm) died prematurely towards the end of the in-life phase of the study. They all showed as the main finding a marked papillary necrosis in the kidneys and a nephropathy. A general reduced cellularity and hemosiderosis of the spleen, a thymic atrophy, and a hypocellular marrow are further findings in some animals which are considered to be secondary effects in close connection with an end-stage renal disease (see Pathology). Discoloration of the urine was seen in 7/10 males and 4/10 females of the high dose group, accompanied by smeared fur in 3/10 males, 4/10 females. The latter finding was also noted in 1/10 females of the mid-dose group (5000 ppm).
Food and water consumption, body weight and body weight gain (Table B.6.3-8)
Food consumption was decreased in high dose animals only on day 7 of treatment, the values being 13.5 % (males) and 17.6 % (females) below controls. Water consumption was increased in high dose animals over the entire treatment period, values being up to 189.6 % (males) and 118.8 % (females) above controls. Also in the mid dose animals, there was a trend towards increased values, reaching statistical significance on day 91 in females.
Body weight was reduced at 15000 ppm in males (-21.8 % on day 91) and females (-15.1 % on day 91) during the entire study period; body weight change was reduced in males (-35.2 % on day 91) at 15000 ppm during the entire study period and on most days in females (-31.2 % on day 91) at 15000 ppm.

Table B.6.3-8: Food and water consumption, body weight and body weight gain

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**5000**	**15000**	**0**	**1000**	**5000**	**15000**
Food consumption (g/animal/day 7)	25.0	26.6	24.8	21.6**	18.6	19.2	18.5	15.4**
Water consumption (g/animal/day 91)	25.0	27.1	29.8	67.2**	22.5	23.8	30.1*	49.0**
Body weight; day 91 (g)	453.6	473.4	451.5	354.8**	258.6	267.2	266.3	219.5**
Body weight change, day 91 (g)	281.4	299.1	278.7	182.3**	115.5	124.9	122.7	79.5*

* $P < 0.05$; ** $P < 0.01$ (Anova + Dunnett's test)

Ophthalmological observations
No substance-related effects were seen.
Hematology (Table B.6.3-9)
White blood cell count was increased in animals at 15000 ppm. This was mainly due to an increase in neutrophils and lymphocytes. In addition, female rats of the high dose group had lower values of red blood cell count, hemoglobin concentration and hematocrit, obvious mainly at the investigation at day 92.
In female rats of the 5000 ppm group a statistically significant decrease of hematocrit was noted at day 44 investigation. Values for red blood cells and hemoglobin concentration were also lower but without significance. At the day 92 investigation, again all red blood cell parameters were lower compared to control and low dose group. These changes were considered substance-related.

Table B.6.3-9: Hematology

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**5000**	**15000**	**0**	**1000**	**5000**	**15000**
Red blood cells (tera/l)								
Day 44	8.36	8.21	8.29	8.37	8.09	8.02	7.66	7.75
Day 92	8.61	8.60	8.60	8.73	8.40	8.33	8.05	7.79**
Hemoglobin (mmol/l)								
Day 44	9.5	9.4	9.4	9.5	9.4	9.4	9.0	8.9*
Day 92	9.6	9.4	9.5	9.4	9.6	9.6	9.2	8.7**
Hematocrit (l/l)								
Day 44	0.437	0.429	0.434	0.432	0.427	0.422	0.405*	0.403*
Day 92	0.433	0.431	0.430	0.429	0.427	0.424	0.412	0.385**
White blood cells (giga/l)								
Day 44	9.81	9.71	10.18	12.45**	5.27	5.09	5.74	6.75*
Day 92	8.51	8.45	8.50	10.18*	4.51	4.76	4.95	7.29**

* P < 0.05, ** P < 0.02 (Kruskal-Wallis+Mann-Whitney u-tests)

Clinical chemistry (Table B.6.3-10)

In the high dose group (15000 ppm) increased total bilirubin, urea, creatinine, potassium and magnesium concentrations were found in the sera of both sexes. Decreased sodium and chloride levels were mainly noted in females, but a tendency to lower values were also noted in male animals of the 15000 ppm group. Inorganic phosphate concentrations were higher in females and triglyceride values were decreased in males especially at the 13-week interval.

In males of the high dose group increased alanine aminotransferase and alkaline phosphatase activities were found at the 13-week interval. In females of this dose group a trend towards higher alanine aminotransferase and significantly elevated aspartate aminotransferase activities were measured at study end.

Table B.6.3-10: Clinical chemistry

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**5000**	**15000**	**0**	**1000**	**5000**	**15000**
Bilirubin tot. (µmol/l)								
Day 44	3.43	2.92	3.51	5.52**	3.01	3.04	3.74	5.22**
Day 92	3.86	3.39	4.12	6.61**	3.67	3.62	4.08	6.87**
Urea (mmol/l)								
Day 44	6.91	6.88	7.07	11.34**	7.14	7.27	7.61	10.58*
Day 92	6.35	6.30	6.26	11.67**	6.31	6.76	6.66	10.86**
Creatinine (µmol/l)								
Day 44	53.5	49.0	53.3	68.4**	55.9	55.4	54.4	62.9
Day 92	49.3	48.0	50.3	67.6**	49.7	50.6	52.7	58.3*
Chloride (mmol/l)								
Day 44	102.6	103.3	104.6	101.5	105.6	104.9	105.0	102.3
Day 92	99.7	100.8	101.0	97.3	102.1	102.2	101.4	96.4**
Sodium (mmol/l)								
Day 44	139.9	140.4	140.3	140.6	141.7	140.7	141.0	140.6
Day 92	142.7	143.4	143.0	141.5	143.0	142.7	143.4	137.4**
Potassium (mmol/l)								
Day 44	6.83	6.56	6.47	6.95	6.09	6.32	6.13	6.31
Day 92	6.53	6.47	6.54	7.25**	5.74	6.08	5.87	6.76**
Inorganic phosphate (mmol/l)								
Day 44	2.89	2.76	2.77	2.79	2.54	2.55	2.51	2.67
Day 92	2.29	2.27	2.26	2.47	1.99	1.99	2.04	2.47**
Magnesium (mmol/l)								
Day 44	0.90	0.85	0.87	1.04*	0.94	0.95	0.96	1.02
Day 92	0.86	0.85	0.90	1.09**	0.94	0.94	0.93	1.02
Triglycerides (mmol/l)								
Day 44	2.68	3.38	2.19	1.83	1.61	2.24	1.75	1.66
Day 92	2.84	3.13	2.02	1.50**	1.99	2.49	1.95	1.88
Alanine aminotrans-ferase (µkat/l)								
Day 44	1.61	1.37	1.35	1.77	1.32	1.23	1.20	1.44
Day 92	1.01	0.94	1.01	1.54**	0.92	0.87	0.87	1.25
Alkaline phosphatase (µkat/l)								
Day 44	7.43	7.78	7.55	8.45	6.11	5.93	5.85	5.18
Day 92	5.47	5.84	5.33	6.64*	4.60	4.08	4.01	4.88
Aspartate aminotransferase (µkat/l)								
Day 44	2.33	1.83	1.79	2.18	2.08	1.62	1.95	3.91
Day 92	1.56	1.59	1.96	1.99	1.74	1.72	1.62	2.65*

* $P < 0.05$; ** $P < 0.01$ (Anova + Dunnett's test)

Urinalysis

Males and females of the high dose group (15000 ppm) had increased urinary volume with decreased specific gravity. Furthermore, macrohematuria was detected and a reddish discoloration was noted. Higher incidences of leukocytes and bacteria were found in the urine of animals of the high dose group. Additionally, urobilinogen was detected in the urine of females.

Organ weights (Table B.6.3-11)

The terminal body weight was decreased in animals of the high dose group, reaching statistical significance in male rats only. Therefore and taking into account the deteriorated

health state of the animals, only weight changes of livers in male rats of the high dose group (15000), in female rats of the mid (5000 ppm) and high groups as well as kidney weight changes in males of the mid and high dose groups and in females of the high dose group were considered treatment-related.
The statistical significant weight changes of other organs, i.e. heart, spleen, thymus, epididymides, testes, brain and adrenal glands are seen to be related to the decreased terminal body weights and are considered secondary to the treatment with tritosulfuron.

Table B.6.3-11: Terminal body weights and mean organ weights

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**5000**	**15000**	**0**	**1000**	**5000**	**15000**
Terminal body weight (g)	429.1	447.7	422.8	328.3**	241.6	247.1	245.7	231.3
Liver, absolute (g)	13.15	14.61	13.57	11.73*	7.59	8.01	8.29**	9.36**
Liver, relative (%)	3.06	3.26	3.21*	3.65*	3.15	3.25	3.37*	4.05**
Kidneys, absolute (g)	2.85	3.12**	3.04*	2.87	1.94	1.98	2.03	2.12
Kidneys, relative (%)	0.66	0.7	0.72*	0.89**	0.80	0.80	0.83	0.92**

* $P < 0.05$; ** $P < 0.01$ (Kruskal-Wallis-H + Wilcoxon-Test)

Gross lesions and histopathology (Table B.6.3-12)
In the high dose group (15000 ppm) the kidneys of 6/10 male rats showed a granular surface, each one male and one female had bilateral pelvic dilatation and unilateral retraction, respectively.
Dilatation of the urinary bladder containing discoloured urine was noted in one male with severe kidney changes. Erosion/ulcer of glandular stomach were noted in two female rats and discoloured lungs were additionally observed in females who died prematurely. These changes were considered directly treatment-related.
Histopathological investigations of the kidneys revealed marked papillary necrosis at 15000 ppm (8/10 in males; 5/10 in females), up to severe nephropathy at 15000 ppm (8/10 in males; 9/10 in females) and a gain in minimal up to slight nephropathies in females at 5000 ppm (6/10; control 2/10), a pelvic dilatation in one male at 15000 ppm. No further treatment-related changes were noted for the urinary tract (ureter, urinary bladder).
In the liver, a slight to moderate centrilobular hypertrophy of hepatocytes at 15000 ppm (9/10 in males; 8/10 in females) and a slight centrilobular hypertrophy of hepatocytes in one male at 5000 ppm. Fatty vacuolation if liver hepatocytes was reduced in high dose animals. A focal necrosis of liver tissue (2/10 in males) was noted at 15000 ppm versus none in control and other dose-groups of either sex.

Table B.6.3-12: Incidence/gradings of histopathological changes of kidneys and liver

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**5000**	**15000**	**0**	**1000**	**5000**	**15000**
Total no. examined	10	10	10	10	10	10	10	10
Kidneys								
- Nephropathy	1/1	0	2/1	8/2-4	2/1	3/1	6/1-2	9/1-5
- Dilatation, pelvis	0	0	0	1/3	0	0	0	0
- Papillary necrosis	0	0	0	8/3-4	0	0	0	5/4
Liver								
- Vacuolation, fatty	9/1-3	9/1-2	7/1-3	0	7/1	2/1	1/1	0
- Hypertrophy, central	0	0	1/2	9/2-3	0	0	0	8/1-3

Gradings: 1: Minimal; 2: Slight; 3: Moderate; 4: Marked/Severe; 5: Massive/Extreme

Discussion:
The results of the hematological examinations are treatment-related; however, the mechanism of the mild anemia, slight decrease in hematocrit as well as of the increase in neutrophils and lymphocytes is not fully clear. Possibly, due to severe kidney lesions it is the matter of renal anemia. Since the reticulocyte counts were slightly increased for compensation of the peripheral anemia, a direct effect of tritosulfuron on the bone marrow seems unlikely. The increase of white blood cell count might be a reaction to the inflammatory changes of the kidneys.
The changes in enzyme levels are indicative of mild hepatocellular damage at 15000 ppm. The decrease in triglyceride levels at the end of the study as well as the loss of fatty vacuolation in the hepatocytes is regarded as a result of reduced terminal body weights in these animals.
The centrilobular hypertrophy of hepatocytes in the liver indicates a proliferation of organelles, which is observed in the progression of an enzyme induction and may express an adaptive change in the sense of detoxification. The increase in the mean absolute and relative liver weights indicates a treatment-related effect being in accordance with an enzyme induction. The main target organ is the kidney. The increases in urea, creatinine and magnesium as well as the increased incidence in macrohematuria characterise renal dysfunction or kidney damage. Further indicators of kidney damage are the increases in sera concentrations of potassium and inorganic phosphate and the elevated excretion of urinary volume and urinary leukocytes. The decreases in urinary specific gravity, sodium and chloride are also considered to be associated with renal dysfunction, as well as the increased water consumption. The animals that died prematurely showed as a main finding a marked papillary necrosis in kidneys and at least a moderate, mostly a severe nephropathy. As recorded for the animals which died under study, the kidneys were as well severely altered (papillary necrosis, nephropathy) in most animals at 15000 ppm.
Histopathological changes in the spleen (cellularity reduced, hemosiderosis), hypocellularity of the bone marrow, atrophy of the thymus predominantly noted in high dose females, were considered secondary to the treatment with tritosulfuron (deteriorated health state).
Thus, the oral administration of tritosulfuron to rats resulted in toxic effects at 15000 ppm and 5000 ppm. Target organs were the kidney and the liver. There were no test substance related effects seen at 1000 ppm.

Conclusion:
The NOAEL of this study was 1000 ppm (equal to 75 mg/kg bw/d in males, 85 mg/kg bw/d in females) based on direct effects on the kidneys and liver with subsequent changes of laboratory parameters and organ weights.

B.6.3.3.2 Mouse

Report: Mellert W. et al., 1997
BAS 635 H - Subchronic oral toxicity study in B6C3F1 Crl BR mice. Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/11511

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 87/302, OECD 408, EPA/FIFRA 82-1, JMAFF

Deviations: During the study there was spilling of food by the mice of all group. This deviation is considered to have no impact on the integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N14: 96.4 %.
Test animals: Groups of 10 male and 10 female B6C3F1 CrlBr mice, 49 days old at start of the administration period, 22-27 g (males), 18-22 g (females), supplied by Charles River Wiga GmbH, Sulzfeld, FRG.
The mice received the test material by dietary administration at concentrations of 0, 1000, 3000 and 8000 ppm for three months. This was equal to 227, 770, and 2135 mg/kg bw/d for males and 344, 938, and 3023 mg/kg bw/d for females. The concentrations in the diet were selected based on the results of a 4-week range finding study. The only relevant finding was an increase in water consumption in high dose animals.
Food consumption, water consumption and body weight were determined once a week. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations of the animals were performed once a week. Clinico-chemical and hematological examinations were carried out at the end of the administration period. All animals were subjected to gross-pathological assessment, followed by histopathological examination.

Findings:
Analysis of the dietary mixtures (Table B.6.3-13)
The stability of the test substance was proven by reanalysis. The stability of the test substance in the diet was verified. The homogeneity of the mixtures was proven. The correctness of the concentrations was demonstrated.

Table B.6.3-13: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
1000	227	344
3000	770	938
8000	2135	3023

Clinical findings
Each one female of the 3000 ppm and 8000 ppm group died prematurely.
Food and water consumption, body weight and body weight gain (Table B.6.3-14)
Statistically significantly lower food consumption values were seen in all treated groups on several days. However, no dose-response relationship could be established, therefore these changes were considered not substance-related.
Water consumption was increased in high dose animals on several days, values being up to 22.2 % (males) or 20.3 % (females) above controls.
High dose male mice had lower body weight/body weight change towards the end of study, the value on day 91 being 8.8 % / 28 % below control. In female mice body weight changes were decreased on several days. Since there were no differences at study end, this was assessed as being incidental.

Table B.6.3-14: Water consumption, body weight and body weight gain

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**3000**	**8000**	**0**	**1000**	**3000**	**8000**
Water consumption (g/animal/day)								
day 5	5.2	5.5	5.3	5.9	5.4	5.6	5.9	6.5**
day 61	5.6	5.1	5.4	6.2*	6.0	5.9	6.0	6.6
day 89	5.2	5.1	5.1	6.3**	5.9	5.6	5.7	6.2
Body weight (g)								
day 84	33.8	34.0	32.6	30.7*	26.4	26.2	27.1	26.5
day 91	34.7	35.4	34.1	31.6*	26.6	26.4	27.0	26.6
Body weight change (g)								
day 84	8.8	9.3	8.0	6.0**	6.6	6.2	7.0	6.5
day 91	9.7	10.7	9.4	7.0**	6.8	6.5	7.0	6.6

* P < 0.05; ** P < 0.01 (Anova + Dunnett's test)

Hematology

There are no treatment-related changes in the hematological parameters measured.

Clinical chemistry

At the end of study, increased urea levels and decreased triglyceride concentrations were found in the sera of high dose males. No treatment-related changes were seen in females.

Table B.6.3-15: Clinical chemistry

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**3000**	**8000**	**0**	**1000**	**3000**	**8000**
Triglycerides (mmol/l) Day 92/93	1.97	1.90	1.72	1.40*	1.22	1.47	1.38	1.29
Urea (mmol/l) Day 92/93	6.34	7.25	7.27	7.47*	7.56	6.86	6.85	6.42

* P < 0.05 (Kruskal-Wallis+Mann-Whitney u-tests)

Organ weights (Table B.6.3-16)

The mean terminal body weight of the high dose males was reduced, when compared to control. In the high dose group (8000 ppm), relative liver weights were increased and absolute kidney weights were decreased in male mice, whereas relative kidney weights and adrenal weights (absolute and relative) were decreased in female mice.

Table B.6.3-16: Terminal body weight and organ weights

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**3000**	**8000**	**0**	**1000**	**3000**	**8000**
Terminal body weight (g)	29.67	30.26	28.75	26.55*	21.76	21.98	22.22	21.87
Liver, absolute (g)	1.288	1.308	1.319	1.288	1.079	1.132	1.155	1.072
Liver, relative (%)	4.354	4.338	4.611	4.864*	4.975	5.146	5.198	4.895
Kidneys, absolute (g)	0.559	0.573	0.55	0.501*	0.385	0.389	0.392	0.36
Kidneys, relative (%)	1.89	1.897	1.917	1.887	1.775	1.766	1.768	1.65*
Adrenal glands, absolute (mg)	5.9	6.3	6.6	6.0	18.9	16.1	17.44	13.0**
Adrenal glands, relative (%)	0.02	0.021	0.023	0.022	0.087	0.073	0.079	0.06**

* P < 0.05; ** P < 0.01 (Dunnett-Test)

Gross lesions and histopathology (Table B.6.3-17)
Histopathological investigations revealed a slight to moderate cystitis in the urinary bladder at 8000 ppm in females (3/10) and in one male animal (1/10). Additionally, in two cases (one male, one female) a reactive transitional cell hyperplasia was noted. These changes were considered treatment-related.
A suppurative pyelonephritis was observed in one female mouse of the 8000 ppm group (found dead on day 35) which led to an involvement of the whole abdominal cavity. Macroscopically observed erosion/ulcer of the glandular stomach was confirmed on histopathological evaluation. Granulomas of the liver Kupffer cells were noted in female mice with higher incidences in the 8000 ppm group. A relation to treatment cannot be excluded with certainty, although no strictly dose-dependent relationship could be established. No histopathological correlate was noted in the adrenal glands, which may have accounted for the decrease in organ weight.
There were no test substance related effects seen at 3000 and 1000 ppm.

Table B.6.3-17: Selected histopathological findings

Sex	Male				Female			
Dose (ppm)	**0**	**1000**	**3000**	**8000**	**0**	**1000**	**3000**	**8000**
Total no. examined	10	10	10	10	10	10	10	10
Kidneys - Pyelonephritis, supp.	0	0	0	0	0	0	0	1 a)
Urinary bladder - Hyperplasia, trans. - Cystitis	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 3
Glandular stomach -Erosion/ulcus	0	1	0	0	1	0	2	2
Liver - Granuloma, Kupff.	0	0	0	0	1	1	1	3

a) with involvement of the whole abdominal cavity

Conclusion:
The NOAEL of this study was 3000 ppm (equal to 770 mg/kg bw/d in males, 938 mg/kg bw/d in females) based on increased water consumption, decreased body weight/body weight changes in males, increased urea and decreased serum triglyceride levels in males, cystitis in females (3/10) and one male as well as decreased absolute/relative weights of the adrenal glands in females at 8000 ppm.

B.6.3.3.3 Dog

Report: Menges S. et al., 2000
BAS 635 H - Subchronic oral toxicity study in Beagle dogs.
Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1012355

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 409, EPA/FIFRA 82-1

Deviations: The study was conducted with a batch containing 2.45 % AMTT.
Due to technical reasons the food consumption in the specific tables is given only up to study day 91 but the dogs received the food/test substance mixtures until the day before necropsy.
Water consumption was not recorded. It is recommended to use 8 animals/dose level.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron; batch/purity: N24: 96.8 %.
Test animals: Groups of six male and six female purebred Beagle dogs, 6 to 9 months old at start of the administration period, 8.8-14.0 kg (males), 7.9-12.2 kg (females), supplied by BASF's own breed. The dogs received the test material by dietary administration at concentrations of 0, 500, 3000 and 9000 ppm for three months. This was equal to 15, 92 and 287 mg/kg bw/d for males and 17, 100, and 308 mg/kg bw/d for females. The concentrations in the diet should aid the dose selection for the subsequent 12-month feeding study.
Food consumption of the animals was determined daily and their body weight once a week. The animals were examined at least once each working day for any signs of toxicity and a check for any moribund or dead animals was made twice a day (Mondays to Fridays) and once a day (Saturdays, Sundays and on public holidays).
Clinical chemistry and hematological examinations as well as urinalyses were carried out once before and two times during the administration period.
Ophthalmological examinations were carried out 6 days before the beginning of the administration period and on study day 90.
All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures (Table B.6.3-18)
The stability of the test substance over a period of 32 days was proven analytically. The stability of the test substance in the diet and dietary preparation was verified. The homogeneity of the mixtures was verified. The correctness of the concentrations was demonstrated by analysis.

Table B.6.3-18: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
500	15	17
3000	92	100
9000	287	308

Clinical findings
There was no test substance related mortality at any dose level.
Vomitus (2/6 male and 3/6 female dogs) and diarrhea (1/6 male dogs) was noted in high dose animals at slightly higher incidences versus none in control and other dose-groups.

Ophthalmoscopy
The ophthalmoscopical examinations revealed no changes, which can be attributed to the test substance administration.
Food consumption, body weight and body weight gain
Food consumption was not affected by administration of the test substance. Male and female dogs of the high dose group (9000 ppm) had reduced body weights of 8 % and 9 % in comparison to the control, although without statistical significance.
At 9000 ppm clinical examinations revealed test substance related decreased body weight changes in both sexes (males on study day 7, 28, females during the entire administration period). The body weight losses were - 0.6 kg in males (control weight gain: + 0.5 kg) and 0.3 kg in females (control weight gain: + 0.8 kg) at the end of the study. Thus reduced food efficiency in both sexes in this dose group were noticed. Also in the males of the 3000 ppm group, body weight gain was decreased almost during the entire administration period (being statistically significant only on study day 7), resulting in body weight loss when compared to the control. These changes were considered treatment-related.
Hematology (Table B.6.3-19)
Hematological examinations revealed higher platelet counts in female dogs at 9000 ppm at the 41 and 91 day intervals and in the mid dose females (3000 ppm) on day 41. Male dogs of the high dose also had slightly higher values, without statistical significance. Slightly shortened partial thromboplastin times were found in the plasma samples of the high dose animals of either sex at all time intervals during the administration period.

Table B.6.3-19: Hematology

Sex	Male				Female			
Dose (ppm)	**0**	**500**	**3000**	**9000**	**0**	**500**	**3000**	**9000**
Platelet counts (giga/l)								
Day 40/41	300	316	348	375	296	310	353 *	409 *
Day 91	272	311	296	368	280	301	325	429 **
Partial thromboplastin time (sec)								
Day 40	11.2	11.3	10.9	10.3	12.3	12.3	12.0	11.2 **
Day 91	12.1	11.4	11.6	10.5**	11.9	11.8	11.8	11.0 *

* $P < 0.05$, ** $P < 0.02$ (Kruskal-Wallis+Mann-Whitney u-tests)

Clinical chemistry (Table B.6.3-20)
Alkaline phosphatase activities were increased in dogs of the high dose group (9000 ppm) at day 41 and 91 investigations. In male dogs at day 91, an increase was also seen at 3000 ppm. In addition, in male dogs of the high dose group slightly higher activities of alanine aminotransferase were recorded at day 91. Total protein values were decreased in dogs of the high dose group. This was mainly due to lower albumin levels, also noted in female dogs at 3000 ppm. Generally lower values were recorded in dogs of the high dose group for triglyceride, cholesterol, creatinine, potassium and calcium levels and higher values for inorganic phosphate concentrations.
The decreased level of albumin concentrations in the sera of the low dose females on day 41 was regarded not to be test substance related since on the day 91 the levels of albumin recovered to normal. Likewise, the decreased levels of triglycerides and total protein, both on day 91 in the females of the 500 ppm dose group were considered not to be substance related since there was no decreased level found in the 3000 ppm dose group and the levels observed in the control group were high at this time point.

Table B.6.3-20: Clinical chemistry

Sex	Male				Female			
Dose (ppm)	**0**	**500**	**3000**	**9000**	**0**	**500**	**3000**	**9000**
Alkaline phosphatase (µkat/l)								
Day 40/41	3.57	3.24	4.17	10.61 **	3.28	3.34	3.90	13.74 **
Day 91	3.53	3.51	5.11 **	14.07 **	3.46	3.73	4.10	20.60 **
Alanine aminotransf. (µkat/l)								
Day 40/41	0.66	1.01	0.55	0.97	0.62	0.61	0.56	0.59
Day 91	0.75	0.89	0.68	2.03	0.76	0.88	0.57	0.86
Total protein (g/l)								
Day 40/41	55.53	54.63	56.31	49.23 **	55.62	52.77	52.70	48.99 **
Day 91	58.93	58.69	59.48	49.55 **	62.57	57.90 *	57.83	51.97 **
Albumin (g/l)								
Day 40/41	31.07	30.47	29.57	24.28 **	32.50	30.84 *	29.48 *	25.55 **
Day 91	33.49	32.20	31.83	23.26 **	35.47	33.78	31.18 *	25.83 **
Triglycerides (mmol/l)								
Day 40/41	0.50	0.40	0.58	0.38	0.53	0.53	0.48	0.33 **
Day 91	0.45	0.44	0.55 *	0.37 **	0.51	0.37 **	0.48	0.37 **
Cholesterol (mmol/l)								
Day 40/41	3.77	3.62	3.68	2.86	3.92	3.72	3.62	2.59 **
Day 91	4.17	4.44	4.43	2.94	4.44	4.62	4.46	3.07 **
Creatinine (µmol/l)								
Day 40/41	78.7	76.7	73.8	66.0**	78.1	77.8	72.8	65.1**
Day 91	88.4	84.3	81.6	66.1**	89.8	88.1	81.0	68.5**
Potassium (mmol/l)								
Day 40/41	4.92	4.76	4.87	4.28**	4.71	4.76	4.78	4.58
Day 91	4.80	4.69	4.64	4.35 **	4.61	4.46	4.50	4.52
Inorganic phosphate (mmol/l)								
Day 40/41	1.81	1.69	1.78	1.77	1.66	1.63	1.71	1.81
Day 91	1.63	1.52	1.65	1.87*	1.55	1.55	1.68	1.79
Calcium (mmol/l)								
Day 40/41	2.69	2.67	2.69	2.60	2.75	2.71	2.71	2.62
Day 91	2.87	2.83	2.86	2.66**	2.93	2.88	2.86	2.72**

* $P < 0.05$, ** $P < 0.02$ (Kruskal-Wallis+Mann-Whitney u-tests)

Urinalysis

Urinalysis revealed no changes, which could be related to the treatment with tritosulfuron.

Organ weights (Table B.6.3-21)

Organ weight determinations showed an increased weight of the liver (9000 and 3000 ppm), and of the kidney (9000 ppm) in male and female dogs. In females the weights of the adrenal glands were increased at 9000 ppm (absolute and relative weights) and at 3000 ppm (relative weights). In males the absolute and relative weights of the thyroid glands in the high dose group was increased.

Increased relative ovary weights as recorded for all dose groups were not considered treatment-related since weight changes did not show a dose-response relationship.

Table B.6.3-21: Organ weights

Sex	Male				Female			
Dose (ppm)	**0**	**500**	**3000**	**9000**	**0**	**500**	**3000**	**9000**
Terminal body weight (kg)	11.63	11.97	11.83	10.98	11.53	11.20	11.15	10.35
Liver, absolute (g)	333.14	346.45	406.35*	512.22**	331.11	332.74	362.35	475.37**
Liver, relative (%)	2.858	2.907	3.43**	4.658**	2.868	2.966	3.251**	4.605**
Kidneys, absolute (g)	54.97	62.79	56.88	67.91	52.69	51.33	52.51	62.09 **
Kidneys, relative (%)	0.472	0.527	0.479	0.619**	0.457	0.458	0.473	0.6 **
Adrenal glands, absolute (g)	1.27	1.25	1.29	1.49	1.27	1.26	1.44	1.5**
Adrenal glands, relative (%)	0.011	0.011	0.011	0.014	0.011	0.011	0.013*	0.015**
Thyroid gland, absolute (g)	0.74	0.8	0.81	1.073**	0.86	0.8	0.95	0.99
Thyroid gland, relative (%)	0.006	0.007	0.007	0.01**	0.007	0.007	0.009	0.01

* $P < 0.05$; ** $P < 0.01$ (Kruskal-Wallis-H + Wilcoxon-Test)

Gross lesions and histopathology (Table B.6.3-22)

In 5/6 male dogs and 6/6 female dog of the 9000 ppm dose group and 1/6 male dog of the 3000 ppm dog centrilobular hypertrophy of hepatocytes were observed during histological examination. Additionally, degeneration of hepatocytes (single liver cell necrosis) was noted in males and females of the high dose group. Thus, weight increase of the liver and the pathomorphological image of the organ matched well and were seen to be related to the test substance. One of the male test animals with a single cell necrosis showed primarily subcapsular, focal hemorrhages. For this and another test animal with the finding single cell necrosis a pigment accumulation was present. The pigment reacts positively in PERL's iron stain (hemosiderin).

In the kidney, macroscopically focal and multifocal lesions were noticed. Histo-morphologically the kidneys showed degenerative changes of the tubular epithelium with a reactive inflammatory response primarily located in the cortical region. The effects in liver and kidney were considered to be test substance related.

Histologically there were no findings in the adrenal glands and the weight increases of the thyroid gland did not find a histomorphological correlate. However, it cannot be ruled out that the weight changes represent an adaptative response to treatment,

Hypospermatogenesis in the testes, oligozoospermia/aspermia in the epididymides and atrophy of prostate were also noted with slightly higher incidences in dogs of the high dose group.

There were no gross or microscopical changes related to the test substance application observed in any of the other organs.

Table B.6.3-22: Treatment-related histopathological changes

Sex	Male				Female			
Dose (ppm)	**0**	**500**	**3000**	**9000**	**0**	**500**	**3000**	**9000**
Total no. examined	6	6	6	6	6	6	6	6
Liver								
- Hemorrhage	0	0	0	1	0	0	0	0
- Pigmentation, focal	0	0	0	2	0	0	0	0
- Single cell necrosis	0	0	0	3	0	0	0	1
- Hypertrophy, centr.	0	0	1	5	0	0	0	6
Kidneys								
- Degeneration, focal	0	0	0	3	0	0	0	5
- Pyelitis, focal	0	0	0	1	0	0	0	0
Testes								
-Hypospermatogenesis	1	0	0	2	-	-	-	-
Epididymides								
- Aspermia	0	0	0	1	-	-	-	-
- Oligozoospermia	1	0	0	1	-	-	-	-
Prostate								
- Atrophy	0	0	2	3	-	-	-	-

Discussion:
There is only partial agreement with the opinion of the notifier that all changes seen in blood chemistry examinations of the high dose animals should be considered as a result of the reduced nutritional status and the decreased body weights. Body weight was only slightly affected in high dose dogs and otherwise clinical examinations revealed only slightly higher incidences of vomitus and diarrhea but no severe toxicity. The increases in alkaline phosphatase were probably due to induction of the microsomal enzyme system in the liver. It is also very likely that the shorter clotting times are associated with enzyme induction. Likewise, the marked decreases in creatinine and albumin levels were clearly related to treatment.
In this study the target organs were the liver and the kidneys as characterised by functional and/or morphological changes. Moreover, on the basis of decreased weights adrenal glands and thyroid glands were affected, too.

Conclusion:
The NOAEL was 500 ppm (equal to 15 mg/kg bw/d in males, 17 mg/kg bw/d in females) based on centrilobular hypertrophy of liver hepatocytes, lower albumin concentrations and higher alkaline phosphatase activities at 3000 ppm.

B.6.3.4 Oral administration (12-month)

B.6.3.4.1 Dog

Report: Menges S. et al., 2000
BAS 635 H - Chronic oral toxicity study in Beagle dogs.
Administration in the diet for 12 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1012356

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, EPA/FIFRA 83-1, OECD 452

Deviations: The study was conducted with a batch containing 2.45 % AMTT.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 6 male and 6 female purebred Beagle dogs, approximately 7 to 8 months old at start of the administration period, 8.5-12.6 kg (males), 6.7-11.5 kg (females), supplied by BASF's own breed.
The dogs received the test material by dietary administration at concentrations of 0, 200, 1000 and 5000 ppm for 12 months. This was equal to 6, 31 and 151 mg/kg bw/d for males and 6, 31 and 175 mg/kg bw/d for females. The concentrations in the diet were selected based on the results of the 3-month feeding study.
Food consumption of the animals was determined daily and their body weight once a week. The animals were examined at least once each working day for any signs of toxicity and a check for any moribund or dead animals was made twice a day (Mondays to Fridays) and once a day (Saturdays, Sundays and on public holidays).
Clinical chemistry and hematological examinations as well as urinalyses were carried out once before and after approximately 3, 6 and 12 months of test substance administration.
Ophthalmological examinations were carried out 15 days before the beginning of the administration period and on study day 364.
All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures (Table B.6.3-23)
The stability of the test substance was proven by reanalysis. The stability of the test substance in the diet, its homogeneous distribution, and correct concentration were confirmed by analysis.

Table B.6.3-23: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
200	6	6
1000	31	31
5000	151	175

Clinical findings
No mortality occurred during the study. There were no clinical findings, which could be related to the treatment with tritosulfuron.
Ophthalmoscopy
The ophthalmoscopical examinations revealed no changes, which can be attributed to the test substance administration.

Food consumption, body weight and body weight gain

At the dose levels of 1000 and 5000 ppm there was body weight losses in male dogs at the beginning of the administration period and therefore a decrease of food efficiency in the male dogs at this time. Afterwards, body weight gain was similar for all dose groups tested. Body weight gain of the male dog control group was superior to all dose groups tested, but this was considered to be due to above mentioned body weight loss, which was not fully compensated during the course of the study. Therefore, only body weight loss lasting from day 1 to day 14 of the treatment period in males at 1000 and 5000 ppm was considered treatment-related.

In the female dogs of the 5000 ppm group body weight development was retarded lasting during the entire administration period.

Hematology (Table B.6.3-24)

There was an increase in total white blood cell count in female dogs at 5000 ppm. This was mainly due to an increase of polymorphonuclear neutrophils and lymphocytes. In addition platelet counts were also higher in the high dose females at all time intervals.

Table B.6.3-24: Hematology

Sex	Male				Female			
Dose (ppm)	**0**	**200**	**1000**	**5000**	**0**	**200**	**1000**	**5000**
WBC (giga/l)								
Day 96/97	8.59	10.08	10.16	11.00	9.20	11.88 **	9.84	13.58 **
Day 187/188	8.93	13.80	11.97	12.03	9.66	13.05 *	10.22	15.02 **
Day 362/363	8.72	11.83**	11.60	10.65	8.85	11.88	10.18	13.22 **
Polymorphonuclear neutrophils (giga/l)								
Day 96/97	5.05	5.79	5.98	5.56	5.16	6.36	5.25	7.16
Day 187/188	5.12	9.60	7.66	6.70	5.64	7.05	5.94	8.33
Day 362/363	5.08	7.27	7.47	5.94	5.02	6.16	5.91	6.77
Lymphocytes (giga/l)								
Day 96/97	2.86	3.47	3.54	4.51	3.27	4.62	3.81	5.23
Day 187/188	3.06	3.16	3.61	4.43	3.25	5.02	3.43	5.57
Day 362/363	2.89	3.45	3.39	3.82	3.08	4.74	3.41	5.33
Platelet counts (giga/l)								
Day 96/97	301	290	319	340	331	316	300	411 **
Day 187/188	287	292	318	330	363	283	317	418
Day 362/363	285	282	329	354	311	330	303	392 **

* $P < 0.05$, ** $P < 0.02$ (Kruskal-Wallis+Mann-Whitney u-tests) / WBC: White blood cell count

Clinical Chemistry (Table B.6.3-25)

Increased activities of alkaline phosphatase were recorded for high dose animals and mid dose females. In both sexes of the 5000 ppm dose group decreased levels of urea and albumin were noted, and decreased levels of calcium, creatinine, total protein, triglycerides and cholesterol were recorded in 5000 ppm females. Additionally decreased levels of urea concentrations were noticed in the 1000 ppm group, although attaining statistical significance only in females at the end of the administration period. These findings were considered treatment-related.

The increase in globulins in males of the low dose group on day 187 was not related to the treatment, since in the same group increased levels of globulins could be observed on day –9, even before application started.

Table B.6.3-25: Main findings in clinical chemistry investigations

Sex	Male				Female			
Dose (ppm)	**0**	**200**	**1000**	**5000**	**0**	**200**	**1000**	**5000**
Alkaline phosphatase (µkat/l)								
Day 96/97	2.62	2.73	3.28	3.98	2.27	2.50	3.39*	5.00 **
Day 187/188	2.01	2.38	2.69	3.89 **	2.05	2.28	3.69 **	5.60 **
Day 362/363	2.02	2.05	2.63	4.10 **	1.75	1.99	3.47 **	4.52 **
Urea (mmol/l)								
Day 96/97	5.51	5.21	5.08	3.90 **	4.85	4.81	4.30	3.97
Day 187/188	4.78	4.69	4.31	3.16 **	4.60	4.72	4.12	3.37 **
Day 362/363	5.07	5.04	4.56	3.90	5.23	5.18	4.18 **	4.12 *
Total protein (g/l)								
Day 96/97	54.61	55.16	52.92	52.54	57.01	54.69	55.99	49.68 **
Day 187/188	57.83	57.87	57.66	57.26	61.63	59.21	61.38	54.47 **
Day 362/363	59.16	58.73	58.95	58.65	62.30	61.63	63.93	55.63 **
Albumin (g/l)								
Day 96/97	31.99	30.81	29.48	27.55 **	34.02	32.65	32.35	25.46 **
Day 187/188	34.62	32.83	32.54	31.14 **	35.83	34.65	34.19	28.49 **
Day 362/363	33.86	31.72	31.77	30.42 **	36.02	34.31	34.98	29.08 **
Globulins (g/l)								
Day -9	22.85	25.24 **	24.95 *	23.71	22.06	21.24	21.75	23.01
Day 96/97	22.62	24.35	23.44	24.98 **	22.99	22.04	23.63	24.22
Day 187/188	23.21	25.04 *	25.12	26.12 **	25.53	24.57	27.19	25.98
Day 362/363	25.30	27.01	27.18 *	28.23 **	26.28	27.32	28.95	26.55

* P < 0.05, ** P < 0.02 (Kruskal-Wallis+Mann-Whitney u-tests)

Urinalysis

There were no treatment-related changes in the urine parameters measured.

Organ weights and histopathology (Table B.6.3-26)

Organ weight determinations revealed an increase of absolute and relative liver weights in 5000 ppm males and a tendency of increase of liver weights in 5000 ppm females. Although there were no histomorphological signs concerning hypertrophy of hepatocytes, the weight gain was considered to be treatment related. Also the slight centrilobular necrosis of hepatocytes in two males of the 5000 ppm dose group and the higher incidence and grading of inflammatory reactions in the liver of the females of the 5000 ppm dose group were assessed to be substance related. Additionally, increased absolute and relative adrenal gland weights were recorded in male dogs of the high dose group. This change was seen to be most probably a treatment-related effect, although a histomorphological correlate was missing.

There were no test substance related effects at 200 ppm.

Table B.6.3-26: Organ weights

Sex	Male				Female			
Dose (ppm)	**0**	**200**	**1000**	**5000**	**0**	**200**	**1000**	**5000**
Terminal body weight (kg)	13.17	12.47	12.13	12.52	11.88	12.20	12.32	11.13
Liver, absolute (g)	370.13	383.64	389.37	437.658 **	345.092	377.192	369.245	424.747
Liver, relative (%)	2.184	3.082	3.233	3.5 **	2.905	3.091	2.993	3.81
Adrenal glands, absolute (g)	1.363	1.42	1.44	1.757 *	1.577	1.855	1.557	1.695
Adrenal glands, relative (%)	0.01	0.011	0.012	0.014 **	0.013	0.015	0.013	0.015

* P < 0.05; ** P < 0.01 (Kruskal-Wallis-H + Wilcoxon-Test)

Conclusion:
The NOAEL in this 12-month dog study was 200 ppm (equal to 6 mg/kg bw/d) based on functional and/or morphological changes of the liver (i.e. initial body weight loss in male dogs, decreased urea levels and increased activities of alkaline phosphatase in female dogs) at 1000 ppm.

B.6.3.5 Other routes

Not applicable.

B.6.4 Genotoxicity (Annex IIA 5.4)

The potential genotoxicity of tritosulfuron (batch no. N24) was investigated in a series of both *in vitro* and *in vivo* studies. Batch no. N12 was additionally tested in a bacterial mutagenicity test. All regular end points for genetic damage (point mutations, chromosome damage and DNA-damage and repair) were assessed. Tritosulfuron was evaluated for its potential genotoxicity *in vitro* using bacterial and mammalian cell mutagenicity tests, a chromosome damage (clastogenicity) test and an unscheduled DNA synthesis test. There was no indication for genotoxic potential. *In vivo*, the test substance was assessed for the induction of micronuclei in mice. The results of this study showed that tritosulfuron (N24) has no chromosome-damaging potential. It is therefore concluded, that tritosulfuron of batches with a high content of AMTT has no mutagenic or genotoxic properties both *in vitro* and *in vivo*.

Table B.6.4-1: Summary of mutagenicity studies

Study/strains/species/batch no.	Test conditions	Results
Ames mutagenicity test; TA 1535, 100, 1537, 98, E. coli WP2 uvrA; N24	without S-9 mix with S-9 mix	Negative Negative
Ames mutagenicity test; TA 1535, 100, 1537, 98, E. coli WP2 uvrA; N12	without S-9 mix with S-9 mix	Negative Negative
CHO/HPRT mutagenicity test; N24	without S-9 mix with S-9 mix	Negative Negative
In vitro cytogenetics: chromosome aberration in Chinese hamster V79 cells; N24	without S-9 mix with S-9 mix	Negative Negative
In vitro UDS, rat hepatocytes; N24	-	Negative
In vivo chromosome aberration: Mouse micronucleus test; N24	0, 125, 250 and 500 mg/kg bw (intraperitoneally)	Negative

B.6.4.1 In vitro testing

B.6.4.1.1 Gene mutation in bacterial cells

B.6.4.1.1.1 Ames mutagenicity test – batch no. N24

Report: Engelhardt G., Hoffmann H. D., 1998
Report on the study of BAS 635 H in the Ames test (Salmonella/Mammalian-Microsome Mutagenicity Test – Standard Plate Test and Preincubation Test)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11634

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test system: *Salmonella typhimurium* strains TA 100, TA 1535, TA 1537 and TA 98

Tritosulfuron was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The *Salmonella typhimurium* strains TA 100, TA 1535, TA 1537 and TA 98 were exposed to the test substance dissolved in acetone at doses ranging from 6.25 - 100 µg/plate (standard plate test) and 3.125 - 50 µg/plate (preincubation test). The study consisted of a standard plate test and preincubation test both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls with S-9 mix (2-aminoanthracene) and without S-9 mix (N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine chloride monohydrate) were tested.

A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate,
- there is a dose-response relationship and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of tritosulfuron in the vehicle acetone and in water has been determined analytically.

No test substance precipitation was found. A bacteriotoxic effect was observed depending on the strain and test conditions from about 12.5 – 25 µg/plate onward. Expected increases in revertant colonies were obtained with the positive controls. The mean number of revertant colonies was not increased in the standard plate test or in the preincubation test both with and without addition of a metabolising system.

Conclusion:
According to the results of the study, tritosulfuron is not mutagenic in the Ames reverse mutation assay. In order to test a different batch of tritosulfuron a second Ames reverse mutation assay was conducted.

B.6.4.1.1.2 Ames mutagenicity test – batch no. N12

Report: Engelhardt G., Hoffmann H. D., 2000
Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with BAS 635 H
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1018507

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 2000/32, B.13 / B. 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N12: 96.1 %.
Test system: *Salmonella typhimurium* strains TA 100, TA 1535, TA 1537 and TA 98 and *Escherichia coli* strain WP2 uvrA

Tritosulfuron was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in DMSO at doses ranging from 0.16 µg - 5,000 µg/plate in the standard plate test and 0.032 µg – 20 µg/plate in the preincubation test. The study consisted of a standard plate test and preincubation test both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system negative controls (soft agar, S-9 mix, buffer, vehicle and test substance) and positive controls with S-9 mix (2-aminoanthracene), without S-9 mix (N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and 4-nitroquinoline-N-oxide).

A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate,
- there is a dose-response relationship and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of tritosulfuron in the vehicle DMSO and in water has been determined analytically. The homogeneity was guaranteed by mixing before preparation of the test substance formulations. No test substance precipitation was found. A bacteriotoxic effect was observed depending on the strain and test conditions from about 20 - 100 µg/plate onward. Expected increases in revertant colonies were obtained with the positive controls. The mean number of revertant colonies was not increased in any strain in the standard plate test and the preincubation test either with or without S-9 activation.

Conclusion:
According to the results of the study, tritosulfuron is not mutagenic in the Ames reverse mutation assay.

B.6.4.1.2 Gene mutation in mammalian cells

Report: Engelhard G., Hoffmann H. D., 1998
In vitro gene mutation test with BAS 635 H in CHO cells (HPRT locus assay)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11436

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 476, EEC 87/302

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test system: Chinese hamster ovary (CHO) cells

Tritosulfuron was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, both with and without the addition of Aroclor induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation).
In an initial range-finding cytotoxicity test, the cloning efficiency was reduced at doses ≥ 1000 µg/ml both with and without S-9 mix. Test substance precipitation was observed at doses ≥ 100.0 µg/ml.

According to these results the following doses were evaluated in the 1st experiment:
without S-9 mix: 0; 62.5; 125; 250; 500; 1000 and 2000 µg/ml.
with S-9 mix: 0; 62.5; 125; 250; 500; 1000 and 1500 µg/ml.

A 2nd experiment for confirmation of the result, the following doses were tested:
without S-9 mix: 0; 125; 250; 500; 1000; 2000 and 3000 µg/ml.
with S-9 mix: 0; 62.5; 125; 250; 500; 1000 and 1500 µg/ml.

After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation, an expression phase of about 7 - 9 days and a selection period of about one week, the colonies of each test group were fixed with methanol, stained with Giemsa and counted.
The criteria for a positive response are:

- Increases of the corrected mutation frequencies above the concurrent negative control values and above 15 mutants per 10^6 clonable cells and/or the evidence of a dose-response relationship in the increase in mutant frequencies.
- Evidence of reproducibility of any increase in mutant frequencies.
- A statistically significant increase in mutant frequencies and the evidence of a dose-response relationship.

Findings:
The stability of the test substance throughout the study has been verified by reanalysis. The stability of tritosulfuron in the vehicle acetone over a period of 4 hours and in water over a period of 7 days was verified analytically. Since a solution was obtained with the vehicle acetone, homogeneity was guaranteed. In pretests for dose selection precipitation was observed at doses ≥ 100.0 µg/ml and the cloning efficacy (with and without S-9 mix) was reduced at doses ≥ 1,000.0 µg/ml. The negative controls (untreated and vehicle controls) gave mutant frequencies within the range expected for the CHO cell line. Both of the positive control chemicals, i.e. EMS (ethyl methane sulfonate) and MCA (methylcholanthrene), led to the expected increase in the frequencies of forward mutations. On the basis from the results of the present study, the test substance did not cause any increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in two experiments performed independently of each other.

Conclusion:
Under the experimental conditions of this assay, tritosulfuron does not induce forward mutations *in vitro* in the CHO/HPRT mutation assay.

B.6.4.1.3 In vitro cytogenetic tests

Report: Engelhardt G., Hoffmann H. D., 1998
In vitro chromosome aberration assay with BAS 635 H in V79 cells
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11437

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 473, EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test system: V79 cells derived from the Chinese hamster

Tritosulfuron was assessed for its potential to induce structural chromosomal aberrations in V79 cells *in vitro* both in the presence and in the absence of a metabolising system (S-9 mix of Aroclor 1254-induced Sprague-Dawley rat liver). According to an initial range-finding cytotoxicity test the following doses were evaluated.

1st experiment:
4 hours exposure, 18 hours harvest time, with and without S-9 mix:
0; 125; 250; 500 and 2000 µg/ml

2nd experiment:
continuous treatment, 18 hours harvest time, without S-9 mix: 0; 125; 250 and 500 µg/ml,
continuous treatment, 28 hours harvest time, without S-9 mix: 0 and 500 µg/ml
4 hours exposure, 18 hours harvest time, with S-9 mix: 0; 500; 1000 and 2000 µg/ml.
4 hours exposure, 28 hours harvest time, with S-9 mix: 0; 1000 and 2000 µg/ml

3rd experiment:
4 hours exposure, 18 hours harvest time, with S-9 mix: 0; 1000 and 2000 µg/ml.
4 hours exposure, 28 hours harvest time, with S-9 mix: 0; 1000 and 2000 µg/ml.

The cell cycle of the untreated V79 cells is about 13 - 14 hours under the selected culture conditions. Thus, the selected 1st sampling time of 18 hours was within the 1 - 1.5 x the normal cell cycle time, as recommended by the OECD Guideline No. 473 (EEC Guidance Note). The later sampling time of 28 hours was chosen to cover a possible cell cycle delay. About 2 - 3 hours prior to harvesting the cells, colcemid was added to arrest cells in a metaphase-like stage of mitosis (c-metaphases). After preparation of the chromosomes and staining with Giemsa, 100 metaphases for each culture in the case of the test substance and vehicle controls, or 50 cells for each culture in the case of the concurrent positive controls, were analysed for chromosomal aberrations. For each experiment two cultures were used.

The criteria for a positive response are:
- A dose-related and reproducible significant increase in the number of structural chromosomal aberrations.
- The proportion of aberrations exceeded both the concurrent negative control range and the negative historical control range.

A test substance is generally considered non-clastogenic in this test system if:
- There is no significant increase in the number of chromosomal damaged cells at any dose above concurrent control frequencies.
- The aberration frequencies are within the historical control range.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of tritosulfuron in the vehicle acetone over a period of 4 hours and in water over a period of 7 days has been determined analytically. Since a solution was obtained with the vehicle acetone, homogeneity was guaranteed.

According to the results of the determination of the mitotic index, suppression of the mitotic activity was observed occasionally at doses ≥ 250 µg/ml depending on the experiment and test conditions. Cell count indicated occasionally that growth inhibition occurred. Cell attachment was slightly reduced (i.e. few cells rounded) from about 2000 µg/ml onward only in the groups with S-9 mix (2nd and 3rd experiment). Osmolality and pH values were not influenced by test substance treatment. The negative controls (vehicle controls) gave frequencies of aberrations within the range expected for the V79 cell line. Both of the positive control chemicals, i.e. EMS (ethyl methane sulfonate) and cyclophosphamide, led to the expected increase in the number of cells containing structural chromosomal aberrations.

On the basis from the results of the present study, the test substance did not cause any biologically relevant and dose-dependent increase in the number of structurally aberrant metaphases including and excluding gaps at both sampling times either without S-9 mix or after adding a metabolising system in two experiments performed independently of each other. No increase in the frequency of cells containing numerical aberrations was demonstrated either.

Conclusion:
Tritosulfuron is considered not to be a chromosome-damaging (clastogenic) agent under *in vitro* conditions in V79 cells.

B.6.4.1.4 DNA damage and repair

Report: Engelhardt G., Hoffmann H. D., 1998
In vitro unscheduled DNA synthesis (UDS) assay with BAS 635 H in primary rat hepatocytes
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10811

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 482, EEC 87/302

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test system: Primary Wistar rat hepatocytes

Tritosulfuron was tested for its ability to induce DNA repair synthesis (unscheduled DNA synthesis (UDS)) in primary Wistar rat hepatocytes *in vitro*. Two independent experiments were carried out. The quantification of UDS was performed microscopically using 2 or 3 slides per test group. 25 – 50 cells in good morphological conditions were randomly selected per slide and examined to achieve a total number of 100 cells/dose group. Both test substance treatment and labelling with 3H-thymidine lasted for about 18 - 20 hours.
For each cell, the following counts were performed with an automatic image analyser (ARTEK):
- the nuclear grain (NG) count (= number of silver grains overlying the nucleus)
- the cytoplasm grain (CG) count (= number of grains in two or three nucleus-equivalent areas adjacent to the nucleus).

In an initial range-finding cytotoxicity test, the LDH release was increased at doses ≥ 500 µg/ml (> 2 fold). According to these results the following doses were evaluated in the 1st experiment: 0; 62.5; 125; 250 and 500 µg/ml
In a 2nd experiment for confirmation of the results of the 1st experiment, the following doses were tested: 0; 15.625; 31.25; 62.5; 125; 250 and 500 µg/ml

A test substance is considered positive if a dose-related increase is demonstrated in both of the following:
- The mean number of NNG (net nuclear grain, i.e. nuclear grain count minus cytoplasm grain count) counts, which must exceed zero at one of the test points.
- The percentage of cells in repair must be equal to or exceed 20, with a NNG of ≥ 5.

A dose-related increase in % cells in repair ≥ 5 outside the values of both the concurrent negative control and the historical control data base (≥ 3 < 20) and a dose-related increase in the mean number of NNG counts near to but without exceeding zero is considered to be an indication for a marginal response which needs to be confirmed / clarified in a further experiment.A test article producing NNG counts and % cells in repair in the range of the negative control data is considered to be negative in the *in vitro* UDS assay.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of tritosulfuron in the vehicle acetone over a period of 4 hours and of a comparable batch (N14) in water over a period of 7 days has been determined analytically. Cytotoxicity was observed from about 500 µg/ml onward. The negative controls (untreated and vehicle controls) gave UDS activities within the range expected for rat hepatocytes. The positive control chemical 2-acetylaminofluorene (2-AAF) revealed a distinct increase in the mean number of nuclear and net grain counts. On the basis of the results from the present study, it is considered that the test substance did not lead to an increase in the mean number of net nuclear grain counts at any dose level in isolated rat hepatocytes in two experiments performed independently of each other.

Conclusion:
The test substance tritosulfuron is considered to be negative in the *in vitro* UDS assay using primary rat hepatocytes.

B.6.4.2 In vivo testing

B.6.4.2.1 In vivo cytogenetic test

Report: Engelhardt G., Hoffmann H. D., 1998
Cytogenetic study *in vivo* with BAS 635 H in the mouse micronucleus test - Single intraperitoneal administration
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10581

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 474, EEC 92/69, B 12

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: NMRI mice

Tritosulfuron was tested for clastogenicity and for the ability to have spindle poison effects in NMRI mice using the micronucleus test method. For this purpose the test substance, suspended in an aqueous 0.5 % CMC (carboxymethyl cellulose) formulation, was administered once intraperitoneally to male and female animals at dose levels of 125 mg/kg, 250 mg/kg and 500 mg/kg body weight in a volume of 10 ml/kg body weight in each case. As a negative control, male and female mice were administered the vehicle, 0.5 % CMC, by the same route. As a positive control, 20 mg of cyclophosphamide (CPP) / kg body weight or 0.15 mg of vincristine sulphate (VCR) / kg body weight, both, dissolved in purified water, were administered to male and female animals once intraperitoneally each in a volume of 10 ml/kg bw.
The animals were sacrificed and the bone marrow of the two femora was prepared 24 hours and 48 hours after administration in the highest dose group of 500 mg/kg body weight and in the vehicle controls. In the test groups of 125 mg/kg and 250 mg/kg body weight and in the positive control groups, the 24-hour sacrifice interval was investigated only. After staining of the preparations, 2000 polychromatic erythrocytes were evaluated per animal and investigated for micronuclei. The normocytes with and without micronuclei occurring per 2000 polychromatic erythrocytes were also registered.

The test chemical is to be considered positive in this assay if the following criteria are met:
- A dose-related and significant increase in the number of micronucleated polychromatic erythrocytes at any of the intervals.
- The proportion of cells containing micronuclei exceed both, the values of the concurrent negative control range and the negative historical control range.

Findings:
The stability of the test substance was verified. The stability of tritosulfuron in the vehicle over a period of 7 days was analytically confirmed. The homogeneity of the test substance in the vehicle was guaranteed by constant stirring during the removal and administration of the test substance formulation. Animals which were administered the vehicle or the positive control substances cyclophosphamide or vincristine did not show any clinical signs of toxicity. The administration of the test substance led to piloerection and squatting posture in all dose groups after about 30 minutes. In the top dose of 500 mg/kg bw these signs were still observed 2 days after treatment and the general state of the animals was poor. The negative control gave frequencies of micronucleated polychromatic erythrocytes within the historical control range. Both of the positive control chemicals, i.e. cyclophosphamide for clastogenicity and vincristine for spindle poison effects, led to the expected increase in the rate of polychromatic erythrocytes containing small or large micronuclei. An inhibition of erythropoiesis determined from the ratio of polychromatic to normocromatic erythrocytes induced by the treatment of mice with tritosulfuron was detected at doses of ≥ 250 mg/kg bw. According to the results of the present study, the single intraperitoneal administration of tritosulfuron did not lead to any increase in the number of polychromatic erythrocytes containing either small or large micronuclei. The rate of micronuclei was always in the same range as that of the negative control in all dose groups and at all sacrifice intervals.

Conclusion:
The test substance tritosulfuron has no chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis.

B.6.4.2.2 DNA damage and repair

Because of the unambiguous negative result of the *in vitro* UDS assay with tritosulfuron, no *in vivo* study was performed.

B.6.4.3 In vivo testing, germ cells

The results of the *in vitro* as well as the *in vivo* studies demonstrated that tritosulfuron has no mutagenic or genotoxic potential. Therefore, there was no necessity to evaluate the test substance in an *in vivo* study using germ cells.

B.6.5 Long-term toxicity and carcinogenicity (Annex IIA 5.5)

The 12-month chronic toxicity study (batches nos. N42, N53, N59) and two 24-month carcinogenicity studies in rats (batches nos. N34, N42, N53, N59) conducted with tritosulfuron containing low quantities of AMTT and the 18-month carcinogenicity study in mice which was conducted with tritosulfuron containing high quantities of AMTT (batch no. N24) did not show a carcinogenic potential.
In the 12-month chronic toxicity study in rats the administration of 7000 ppm of tritosulfuron resulted in an increase in water consumption in both sexes, a mild anemic process as well as clues to slight impairment of renal function in females which was evidenced by increases in urinary volume with decreased urinary specific gravity. Males at this dose level showed slightly increased incidence of chronic interstitial nephritis in the kidneys and slightly

increased incidence of pericholangitis in the liver. Increased number of animals with 'anogenital region smeared with urine' and/or 'inflammation in the anogenital region' was seen at 7000 and 3500 ppm. These findings indicate that the kidney is the main target organ for tritosulfuron toxicity in chronic rat studies, which is in accordance with the subchronic rat toxicity studies. The NOAEL was found to be 1000 ppm (equal to 51.7 mg/kg bw/d in males and 68.4 mg/kg bw/d in females.

In a 24-month carcinogenicity study in rats conducted with tritosulfuron containing low quantities of AMTT the main findings consisted in an increase in water consumption and the clinical finding 'anogenital region smeared with urine' in both sexes at 3500 ppm. The NOAEL was found to be 1000 ppm (equal to 48 mg/kg bw/d in males and 64 mg/kg bw/d in females).

In supplementary 24-month carcinogenicity study in rats conducted with with doses of 0 ppm and 7000 ppm (equal to 327 mg/kg bw/day in males, 463 mg/kg bw/day in females) tritosulfuron containing low quantities of AMTT the main changes consisted in the clinical observation "anogenital region smeared with urine" and/or "inflammation in the anogenital region", an increase in water consumption, as well as changes in certain red blood cell parameters (polychromasia, anisocytosis and microcytosis) in females. In the kidney, papillary necrosis was noted in either sex, pyelonephritis in males and angiectasis in renal papilla in females. In addition, male animals had cystitis and urothelial hyperplasia in the urinary bladder.

A carcinogenicity study in mice was conducted with tritosulfuron containing high quantities of AMTT. Animals of the high dose group (7500 ppm) were prematurely sacrificed after 16 months of treatment without further examinations. At 3750 ppm there was increased water consumption. Decreased body weight gain was seen at all dose levels. The NOAEL was found to be below 250 ppm (equal to < 36 mg/kg bw/d in males, < 44 mg/kg bw/d in females).

In 24-month carcinogenicity studies in rats conducted with a batch of tritosulfuron containing high levels of AMTT (N24: 2.45 %) neoplastic lesions were found in the mammary glands, i.e. adenocarcinomas and fibroadenomas. Non-neoplastic lesions consisted in effects on the testes (degeneration of the germinal epithelium, sperm stasis, focal calcification of seminiferous tubules), on the uterus and mammary gland (diffuse hyperplasia) and in increased haematopoiesis in the bone marrow at 3500 ppm. Rats of the high dose groups (7000 ppm) were prematurely sacrificed after 16 months of treatment without further examinations.

The main toxicological profile of tritosulfuron could also be confirmed in these long-term studies conducted with tritosulfuron containing high levels of AMTT. Water consumption was increased and body weight gain was decreased. Changes of white cell (leukocytosis, mainly lymphocytosis, increased numbers of polymorphonuclear granulocytes) and red cell parameters (anemia, increases in reticulocytes), distinct changes in clinico-chemical parameters (increases in alanine aminotransferase, calcium, cholesterol, decreases in triglycerides, alkaline phosphatase, increases or decreases of proteins, i.e. globulins and albumin) as well as urinary parameters (polyuria with decreased specific gravity, cloudy and/or discoloured urine samples, increased numbers of epithelial cells, granular casts and macrohematuria) were recorded.

It was concluded that tritosulfuron with a high AMTT content did show a carcinogenic potential in Wistar rats.

A summary of long-term toxicity and carcinogenicity studies with tritosulfuron is shown in Table B.6.5-1.

Table B.6.5-1: Summary of long-term toxicity and carcinogenicity studies with tritosulfuron

Study type / species / dose levels /batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
12-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500; 7000 ppm N42, N53, N59	1000 ppm [51.7]	3500 ppm: Anogenital region smeared with urine and/or "inflammation in the anogenital region. 7000 ppm: Increased water consumption and urinary volume (f), decreased urinary specific gravity (f), anemia (f), chronic interstitial nephritis in the kidneys (m), pericholangitis in liver (m)
24-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500 ppm N34, N42, N53, N59	1000 ppm [48]	3500 ppm: Anogenital region smeared with urine, increased water consumption; no carcinogenic properties.
Supplementary 24-month feeding study Wistar rats (Chbb: THOM) 0; 7000 ppm N34, N42, N53, N59	1000 ppm [48]	Anogenital region smeared with urine, inflammation in the anogenital region, increased water consumption, changes in red blood cell parameters (f), papillary necrosis in the kidney, pyelonephritis (m), cystitis and urothelial hyperplasia in urinary bladder (m), angiectasis in renal papilla (f), no carcinogenic properties.
24-month feeding study Wistar rats (Chbb: THOM) 0; 250; 1000; 3500; 7000 ppm N24	< 250 ppm [< 11.8]	250 ppm: Lower body weight, increased incidence of palpable masses in the skin 1000 ppm: Additionally increased water consumption, changes of hematological and clinico-chemical parameters. 3500 ppm: Additionally, increased mortality in females, abnormal clinical signs, changes of urinary parameters, effects on testes, uterus and mammary gland 7000 ppm: Premature sacrifice after 16 months. Mammary gland tumors at all dose levels.
24-month feeding study Wistar rats (Chbb: THOM) 0; 50; 100 ppm N24	100 ppm [5]	No effects
18-month feeding study B6C3F1 CrlBR mice 0; 250; 1000; 3750; 7500 ppm N24	< 250 ppm [< 36]	250 and 1000 ppm: Decreased bw and bw gain. 3750 ppm: Additionally increased water consumption. 7500 ppm: Premature sacrifice after 16 months No carcinogenic properties.

m: male; f: female; bw: body weight; d: day

B.6.5.1 Chronic toxicity rat

Report: Mellert W. et al., 2001
BAS 635 H – Chronic Toxicity Study in Wistar rats. Administration in the diet for 12 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006059

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 452, EEC 87/302, EPA/OPPTS 870.4100

Deviations: Different batches of the test substance were used.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron

Batch No.	Purity	AMTT content	Application period
N42	98.7 %	0.02 %	March 02 - November 09, 1999
N53	99.8 %	0.012 %	November 09, 1999 – January 04, 2000
N59	98.2 %	0.006 %	January 04, 2000 – end of study

Test animals: Groups of 20 male and 20 female Wistar rats Chbb:THOM (SPF), 46 ± 2 days old at start of the administration period, 204.5-268.6 g (males), 143.3-192.6 g (females), supplied by Boehringer Ingelheim Pharma KG, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0, 100, 1000, 3500 and 7000 ppm for 12 months. This was equal to 5.2, 51.7, 181.8 and 363.8 mg/kg bw/d for males and 6.5, 68.4, 235.6, and 478.7 mg/kg bw/d for females.
Food consumption, water consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day. Moreover, detailed clinical examinations in an open field (including palpation) were performed once a week. A functional observational battery and measurement of motor activity was carried out at the end of the in life phase.
Ophthalmological examinations were carried out prior to the start and towards the end of dosing. Vaginal smears for estrus cycle determination of the first 10 surviving animals of high dose and control were prepared and evaluated each day during 3 weeks towards the end of the study. Urinalysis, clinico-chemical and hematological examinations were carried out at approximately 3, 6 and 12 months after start of the administration period. The animals treated for 12 months were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The homogeneous distribution, stability and correct concentration of the test substance in the diet were verified.

Table B.6.5-2: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
100	5.2	6.5
1000	51.7	68.4
3500	181.8	235.6
7000	363.8	478.7

Mortality and clinical findings
The administration of tritosulfuron for 12 months did not affect the mortality of the animals. The incidence was 100 % / 95 % / 100 % / 95 % / 100 % for male and 95 % / 100 % / 100 % / 100 % / 90 % for female animals. Clinical observations showed an increased number of animals with 'anogenital region smeared with urine' and/or "inflammation in the anogenital region" at 3500 and 7000 ppm. The occurrence of this finding in 2 females at 1000 ppm was considered to be of no toxicological relevance because of its low incidence.

Table B.6.5-3: Clinical signs

Sex	Male					Female				
Dose (ppm)	**0**	**100**	**1000**	**3500**	**7000**	**0**	**100**	**1000**	**3500**	**7000**
	Number of affected animals (n= 20)									
Anogenital region smeared with urine and inflammation	0	0	0	5	10	0	0	2	5	12

Food and water consumption:
For food consumption, some significant differences between treated groups and controls were recorded. Due to the lack of a dose-response relationship, these deviations were assessed as being incidental and not treatment-related.
Water consumption was increased at 7000 ppm (up to 34.8 % above control in males; up to 49.1 % above control in females) which was assessed as being treatment-related.
Body weight gain
No significant differences were recorded in any of the treatment groups.
Ophthalmoscopy
No substance-related effects were seen.
Functional observation battery (FOB)
No substance-related effects were seen for "quantitative parameters", i.e. feces, rearing, grip strength, landing foot-splay, and motor activity measurements.
Oestrus Stages
No substance-related effects noted.
Hematological examinations (Table B.6.5-4)
At the end of the treatment period on day 350, female rats at 7000 ppm had lower red blood cell counts, hemoglobin and hematocrit values.

Table B.6.5-4: Chronic rat study: Red blood cell parameters

Sex	Male					Female				
Dose (ppm)	**0**	**100**	**1000**	**3500**	**7000**	**0**	**100**	**1000**	**3500**	**7000**
Red blood cells (Tera/l) day 350	8.16	8.41	8.31	8.30	8.14	7.85	7.94	7.78	7.68	7.15 ***
Hemoglobin (mmol/l) day 350	8.6	8.7	8.6	8.8	8.7	8.8	8.8	8.6	8.6	7.9***
Hematocrit (l/l) day 350	0.406	0.415	0.414	0.415	0.412	0.401	0.405	0.399	0.394	0.366 ***

* P < 0.05; ** P < 0.02; *** P < 0.002 (Kruskal-Wallis + Mann-Whitney u-tests)

Clinical chemistry
No substance-related effects noted.

Urinalysis
At the end of the study on day 356, urinary volume increased and urinary specific gravity was decreased in females at 7000 ppm. In the urinary sediment, crystals of unknown origin were found with minimally increased incidence in animals at 3500 and 7000 ppm.
Organ weights and pathology
All organ weights taken were inconspicuous in all treatment groups.
In male rats at 7000 ppm, a slightly increased incidence of chronic interstitial nephritis in the kidneys and of pericholangitis in the liver was noted upon histopathological examination.

Conclusion:
The NOAEL in this 12-month chronic toxicity study in rats was 1000 ppm (equal to 51.7 mg/kg bw/d in males and 68.4 mg/kg bw/d in females) based on the clinical observation "anogenital region smeared with urine" and/or "inflammation in the anogenital region" with higher incidence at 3500 ppm.
This NOAEL is not in accordance with the proposal of the notifier.

B.6.5.2 Carcinogenicity studies in rats

B.6.5.2.1 First study

Report: Mellert W. et al., 2001
BAS 635 H – Carcinogenicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006062

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 451, EEC 87/302, EPA/OPPTS 870.4200

Deviations: Different batches of the test substance were used.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron

Batch No.	Purity	AMTT content	Application period
N34	99.1 %	0.024 %	July 06, 1998 – February 23, 1999
N42	98.7 %	0.02 %	February 22, 1999 – October 26, 1999
N53	99.8 %	0.012 %	October 25, 1999 – January 04, 2000
N59	98.2 %	0.006 %	January 03, 2000 – July 14, 2000

Test animals: Groups of 50 male and 50 female Wistar rats Chbb:THOM (SPF), 41 ± 2 (males) or 42 ± 2 days old at start of the administration period, 138.1-198.6 g (males), 112.4-165.1 g (females), supplied by Boehringer Ingelheim Pharma KG, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0, 100, 1000 and 3500 ppm for 24 months. This was equal to 4.8, 48.0 and 170.4 mg/kg bw/d for males and 6.3, 64.0 and 224.6 mg/kg bw/d for females.
Food consumption, water consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week. Vaginal smears for oestrus cycle determination of the first 25 surviving animals of high dose and control were prepared and evaluated each day during the last 4 weeks of the study. Differential blood counts were determined for all surviving animals after 12 months, 18 months and at the end of the study and also from all animals killed *in extremis* during the study. After about 24 months, the animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The homogeneity, stability and correct concentration of the test substance in the diet were proven.

Table B.6.5-5: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
100	4.8	6.3
1000	48.0	64.0
3500	170.4	224.6

Mortality and clinical signs
The administration of the test substance did not affect the mortality of the animals.

Table B.6.5-6: Mortality rates

Dose level (ppm)	Mortality males (%)	Mortality females (%)
0	24	28
100	16	26
1000	24	26
3500	16	32

The incidence of the clinical finding “anogenital region smeared with urine” was increased in animals at 3500 ppm.

Table B.6.5-7: Clinical observations

Sex	**Male**				**Female**			
Dose (ppm)	**0**	**100**	**1000**	**3500**	**0**	**100**	**1000**	**3500**
	Number of affected animals (n = 50)							
anogenital region smeared with urine	2	2	2	10	6	2	5	15

Food and water consumption, body weight
There were no treatment-related differences in food consumption in any of the dose groups. Water consumption was increased in animals at 3500 ppm. Body weight gain was minimally lower in males at 3500 ppm, although without reaching statistical significance.

Hematology, weight parameters as well as pathology did not show any substance-related effects.

Conclusion:
The NOAEL in this 24-month carcinogenicity toxicity study in rats was 1000 ppm (equal to 48 mg/kg bw/day in males, 64 mg/kg bw/day in females) based on increased number of animals with clinical symptoms and increased water consumption at 3500 ppm.
Tritosulfuron was not carcinogenic under the conditions of this study.

B.6.5.2.2 Second study

Report: Mellert W. et al., 2001
BAS 635 H – Supplementary carcinogenicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006063

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 451; EEC 87/302; EPA/OPPTS 870.4200

Deviations: Different batches of the test substance were used. Food consumption was not determined on day 119 and therefore substance intake and food efficiency could not be calculated for this day. These deviations are considered not to affect the integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron

Batch No.	Purity	AMTT content	Application period
N34	99.1 %	0.024 %	October 19, 1998 – February 15, 1999
N42	98.7 %	0.02 %	February 15, 1999 – October 25, 1999
N53	99.8 %	0.012 %	October 25, 1999 – December 27, 1999
N59	98.2 %	0.006 %	December 27, 1999 – October 26, 2000

Test animals: Groups of 50 male and 50 female Wistar rats Chbb:THOM (SPF), 42 ± 2 days old at start of the administration period, 164.3-218 g (males), 122.1-168.0 g (females), supplied by Boehringer Ingelheim Pharma KG, Biberach/Riss, FRG.

The study was carried out as a supplementary carcinogenicity study with one high dose level only.
The rats received the test material by dietary administration at concentrations of 0 and 7000 ppm for 24 months. This was equal to 327 mg/kg bw/d for males and 463 mg/kg bw/d for females.
Food consumption, water consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week. Differential blood counts were determined for all surviving animals after 12 months, 18 months and at the end of the study and also from all animals killed *in extremis* during the study. After about 24 months, the animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The homogeneity, stability and correct concentration of the test substance in the diet were proven.

Table B.6.5-8: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
7000	327	463

Mortality and clinical signs
The administration of tritosulfuron did not affect the mortality of the animals.

Table B.6.5-9: Mortality rate on day 728 of study

Dose level (ppm)	Mortality males (%)	Mortality females (%)
0	18	30
7000	20	24

The incidence of the clinical finding “anogenital region smeared with urine” was increased and in some females “inflammation in the anogenital region” was additionally found.

Table B.6.5-10: Clinical observations

Sex	**Male**		**Female**	
Dose (ppm)	**0**	**7000**	**0**	**7000**
Anogenital region smeared with urine	2	35	0	29
Inflammation in the anogenital region	0	0	0	10

Food and water consumption, body weight
During the whole treatment period treated females consumed significantly more food compared to controls. Water consumption was significantly increased in treated animals. The values were up to 39 % (males) and 50.4 % (females) above control. Body weight gain was minimally lower in treated males.

Hematology / Differential blood count
Slight changes in red blood cell parameters such as increases in polychromasia, anisocytosis and microcytosis suggesting an adverse effect on circulating erythrocytes were seen in some females at the end of the study.
No treatment-related changes were observed in the red blood morphology of the males and in the white blood cell differential count of either sex.
Organ weights and pathology
There were no organ weight changes, which could be attributed to the treatment with tritosulfuron.
The mean liver weight was significantly decreased (- 11.5 %) in male rats. In contrast, the mean liver weight in females was increased (+ 8.4 %). These weight changes were interpreted as fortuitous as they were controversial in males and females and as they lacked a morphological correlate.
Non-neoplastic lesions (Table B.6.5-11)**:** Histopathologically, the following treatment-related non-neoplastic findings were seen: Increased number of rats with papillary necrosis in the kidneys and with angiectasis in the renal papillas. In treated male rats, pyelonephritis in the kidneys, and cystitis with urothelial hyperplasia in the urinary bladder occurred with higher incidences.

Table B.6.5-11: Non-neoplastic lesions

	Males		**Females**	
Group	0 ppm	7000 ppm	0 ppm	7000 ppm
No. of rats examined	50	50	50	50
Findings in the kidneys				
Papillary necrosis	4	9	0	4
Angiectasis	1	2	0	8
Pyelonephritis	4	11	1	2
Findings in the urinary bladder				
Cystitis	5	11	1	0
Urothelial hyperplasia	4	7	0	0

Neoplastic lesions: A variety of neoplastic lesions were seen in different organs/tissues but the incidences did not reveal a relation to the treatment with tritosulfuron. Hence, in this study the administration of tritosulfuron did not reveal a carcinogenic potential under the conditions of this study.

Conclusion:
Tritosulfuron is not carcinogenic in rats.

B.6.5.2.3 Third study

Report: Mellert W. et al., 2001
BAS 635 H – Chronic toxicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006060

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B, OECD 452, EPA/FIFRA 83-1

Deviations: This chronic toxicity study was performed with tritosulfuron containing 2.45 % AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine). The 7000 ppm group was discontinued after approximately 17 months of treatment.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 20 male and 20 female Wistar rats Chbb:THOM (SPF), 42 ± 1 days old at start of the administration period, 163-194 g (males), 126-152 g (females), supplied by Dr. Karl THOMAE, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0 , 250 ; 1000 and 3500 ppm for 24 months. The 7000 ppm dose level was discontinued after approximately 17 months of treatment without further examinations.
This was equal to 11.9, 49.5, 174.4, and 393.5 mg/kg bw/d for males and 16.4, 68.0, 247.8, and 531.1 mg/kg bw/d for females.
Food consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week.
Ophthalmological examinations were carried out prior to the start and towards the end of dosing. Urinalysis, clinico-chemical and hematological examinations were carried out at approximately 3, 6, 12, 18, and 24 months after start of the administration period. The animals treated for 24 months were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The homogeneous distribution, stability and correct concentration of the test substance in the diet were confirmed by analysis.

Table B.6.5-12: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
250	11.9	16.4
1000	49.5	68.0
3500	174.4	247.8
7000*	393.5	531.1
* treated for 17 months		

Mortality and clinical signs:
Animals at 7000 ppm were prematurely sacrificed on study days 524-525. The mortality rate was not increased shortly before when compared to rats of other groups. On day 728 the mortality rate for female rats at 3500 ppm was slightly increased.

Table B.6.5-13: Mortality rate on days 455 and 728 of study

	Mortality males (%)		Mortality females (%)	
Dose level (ppm)	Day 455	Day 728	Day 455	Day 728
0	0	20	0	25
250	0	35	0	20
1000	5	25	5	30
3500	0	35	15	55
7000	0	0	5	20

In females at 3500 and 7000 ppm there was an increased incidence of abnormal clinical signs (anogenital region smeared with urine). A reduced general state was noted in females at 3500 ppm with a higher incidence when compared to other groups. Palpabale masses in the skin were noted in females of all dose groups with lowest incidence at 7000 ppm.

Table B.6.5-14: Clinical observations

Sex	**Male**					**Female**				
Dose (ppm)	**0**	**100**	**1000**	**3500**	**7000**	**0**	**100**	**1000**	**3500**	**7000**
	Number of affected animals (n = 20)									
Anogenital region smeared with urine	2	0	1	3	1	0	0	0	4	7
Palpable masses in the skin	3	1	4	1	1	0	7	8	10	4
Reduced general state	2	2	5	2	0	4	4	4	10	4

Food and water consumption
Food consumption was not affected by the treatment. Compared to control water consumption was significantly increased at 7000 ppm (in males up to 46.7 % and in females up to 119.2 %), 3500 ppm (in males up to 34.1 % above control; in females up to 56.7 % above control) and in the 1000 ppm group (in males 22.1 % above control; in females up to 30.9 % above control). At 250 ppm water consumption was increased on several occasions up to 35.6 % in males (day 728) and 21.1 % in females (day 707) although without statistical significance.
Body weight data
Although the difference in males at 250 ppm was not statistically significant, it was assessed as being treatment-related. Body weights were affected as follows:

Table B.6.5-15: Body weight gain compared to controls after 24 months in %

Dietary dose level (ppm)	Males	Females
250	- 9.1	+ 0.9
1000	- 15.1*	+ 1.1
3500	- 20.9**	- 12.9*
7000 (day 511)	- 24.4**	- 11.3**

* $P < 0.05$, ** $P < 0.01$ (Anova + Dunnett's test)

Ophthalmoscopy
No substance-related effects were obtained.
Hematology
Hematology examinations revealed an anemic process, evidenced by lower red blood cell count, hemoglobin concentration, and hematocrit values in females at 7000 ppm and 3500 ppm. Reticulocyte counts were increased in females at 3500 ppm on day 716 investigation. A mild leukocytosis was noted in animals at 7000 ppm and 3500 ppm. Apart from an increase of polymorphonuclear neutrophils in females at 3500 ppm towards the end of the treatment period, the differences were not strictly dose-related and the toxicological relevance remained obscure.

Table B.6.5-16: Hematology

Sex	Male					Female				
Dose (ppm)	**0**	**250**	**1000**	**3500**	**7000**	**0**	**250**	**1000**	**3500**	**7000**
Red blood cells										
(tera/l) day 86/87	8.47	8.54	8.63	8.37	8.20	8.28	8.31	8.16	8.02**	7.93**
day 181/184	8.84	8.90	8.90	8.77	8.73	8.41	8.44	8.14	8.17**	7.90***
day 363/366	8.26	8.23	8.22	8.27	8.15	7.62	7.64	7.41**	7.20**	7.21**
day 713/716	7.29	7.88	7.50	7.84	-	7.00	7.10	7.14	5.77*	-
Hemoglobin										
(mmol/l) day 86/87	9.5	9.6	9.6	9.4	9.3	9.5	9.6	9.4	9.2**	9.1***
day 181/184	9.5	9.6	9.6	9.5	9.5	9.6	9.7	9.3	9.3**	9.0***
day 363/366	9.3	9.3	9.2	9.3	9.2	9.1	9.2	8.9	8.6**	8.5***
day 713/716	8.3	8.9	8.6	8.8	-	8.5	8.6	8.6	7.2	-
Hematocrit (l/l)										0.408***
day 86/87	0.430	0.432	0.436	0.432	0.419	0.428	0.428	0.422	0.412**	0.410***
day 181/184	0.448	0.452	0.450	0.445	0.447	0.439	0.442	0.427	0.425**	0.375***
day 363/366	0.423	0.422	0.418	0.420	0.416	0.397	0.402	0.388*	0.374**	-
day 713/716	0.380	0.412**	0.394	0.402	-	0.375	0.376	0.376	0.328	
Reticulocytes (0/00)										
day 713/716	38	30	26	26	-	25	28	18	104	-
White blood cells										
(giga/l) day 86/87	8.14	8.75	8.81	9.69**	9.14**	4.65	5.06	4.67	5.86***	6.77***
day 181/184	6.84	6.95	7.73*	7.94**	7.76	4.17	4.36	5.21	5.15**	5.92***
day 363/366	6.54	6.55	6.69	6.47	6.55	4.08	4.12	4.60	6.03***	5.93***
day 713/716	8.65	7.53	7.59	6.43	-	5.24	5.87	6.38	10.77***	-

* P < 0.05, ** P < 0.02, *** P < 0.002 (Kruskal-Wallis + Mann-Whitney u-tests)

Clinical chemistry
The following changes of clinical chemistry parameters were considered treatment-related: Higher activities of alanine aminotransferase in females at 7000 ppm. Findings at 3500 and 7000 ppm consisted in increases in total bilirubin and decreases of triglycerides (both sexes), decreased activities of alkaline phosphatase (males), decreased total protein and globulins (males). In females, globulin concentrations were significantly increasing and albumin levels significantly decreasing during the treatment period, resulting in apparently unchanged total protein concentrations. In addition, potassium, chloride and glucose levels were decreased; calcium, cholesterol and magnesium concentrations were increased. Some of these changes were already noted at the 1000 ppm level (decreased potassium, glucose, triglyceride and increased magnesium concentrations) on different investigation points.

Table B.6.5-17: Clinical chemistry

Sex	Male					Female				
Dose (ppm)	**0**	**250**	**1000**	**3500**	**7000**	**0**	**250**	**1000**	**3500**	**7000**
Alanine aminotrans.										
(µkat/l) day 86/87	1.05	1.05	1.04	1.01	1.15	0.80	0.81	0.83	0.86	0.95***
day 363/366	1.05	0.92*	1.00	0.95	1.08	1.03	1.03	1.06	1.12	1.38***
Alkaline phosphat.										
(µkat/l) day 86/87	6.52	6.12	6.14	6.28	6.31	4.64	4.11	4.35	4.32	4.40
day 363/366	5.93	5.53	5.79	4.88***	4.72***	4.35	4.19	4.11	4.16	4.49
Total bilirubin										
(µmol/l) day 86/87	2.69	2.49	2.74	2.94	3.08*	2.69	2.94	2.83	3.17***	3.45***
day 181/184	3.59	3.16	3.47	3.90*	4.08***	2.62	2.76	2.61	3.15**	3.95***
day 363/366	1.96	1.60	1.88	2.17	2.31	1.57	1.99	1.93	3.43**	2.95***
Total Prot. (g/l)										
day 86/87	65.0	64.3	64.7	62.3	61.5**	65.1	65.5	66.2	67.1	65.5
day 181/184	66.4	66.1	65.0	65.1	63.5	66.6	68.7	68.5	70.7	69.9
day 363/366	68.5	67.0	68.3	67.6	65.8	73.1	76.3	73.9	72.1	74.3
Albumine (g/l)										
day 86/87	32.2	32.2	32.3	31.8	31.4	34.6	34.4	35.1	35.6	34.4
day 181/184	32.3	32.5	32.3	32.6	32.1	35.1	35.8	36.5	36.7	36.4
day 363/366	33.9	34.0	34.2	34.3	33.5	39.9	40.9	39.5	36.4**	37.3**
Globulins (g/l)										
day 86/87	32.8	32.1	32.4	30.5**	30.1**	30.5	31.1	31.1	31.5	31.1
day 181/184	34.0	33.6	32.8	32.5	31.5	31.5	32.9	32.0	33.9**	33.5**
day 363/366	34.5	33.1	34.1	33.3	32.3	33.2	35.3*	34.4	35.7*	37.0***
Triglycerides										
(mmol/l) day 86/87	3.87	3.97	3.56	2.35***	1.61***	2.29	2.03	2.04	1.98	1.79
day 181/184	4.62	5.21	4.13	2.22***	2.08***	3.24	3.18	3.32	2.98	1.95**
day 363/366	6.82	7.07	5.67	3.26***	2.46***	6.30	5.54	4.85	2.48***	2.17***

* $P < 0.05$, ** $P < 0.02$, *** $P < 0.002$ (Kruskal-Wallis + Mann-Whitney u-tests)

Urinalysis

An increase in urinary volume with decreased urinary specific gravity was noted in animals at 7000 ppm and in females at 3500 ppm. Additionally, an increase in turbidity was recorded in animals at 7000 ppm and in males at 3500 ppm. Urinary crystals were noted in males at 7000 ppm and 3500 ppm. Urinary blood, urinary erythrocytes, renal epithelial cells, squamous epithelial cells, granular casts, macrohematuria and bacteria were observed in females at 7000 ppm and partly, at 3500 ppm.

Terminal body and organ weights

Terminal body weights were not taken from animals sacrificed prematurely.

The mean terminal body weights were decreased in male rats of all treatment groups and in females at 3500 and 1000 ppm. All organ weight changes were considered to be the result of the lower terminal body weight.

Table B.6.5-18: Terminal body and organ weights

Sex	Male				Female			
Dose (ppm)	0	250	1000	3500	0	250	1000	3500
Terminal body weight (g)	702.12	641.98	593.44**	554.6**	358.83	362.36	365.73	311.66*
Kidneys								
absolute (g)	4.062	4.142	3.705*	3.841*	2.611	2.646	2.647	2.837
relative (%)	0.591	0.654	0.641	0.699	0.738	0.738	0.736	0.91**
Liver								
absolute (g)	18.959	19.938	19.429	17.151**	11.567	11.734	11.244	11.429
relative (%)	2.727	3.119	3.628	3.067	3.217	3.252	3.08	3.649*

* P < 0.05, ** P < 0.01 (Kruskal-Wallis-H- + Wilcoxon-Test)

Gross lesions and histopathological findings

Macropathological and histopathological examinations were not reported/performed for animals at 7000 ppm sacrificed prematurely.

Non-neoplastic findings: Increased hematopoiesis in the spleen was more frequently observed in females at 3500 ppm (9/11/11/17). Diffuse hyperplasia in the mammary gland was noted with higher incidence in females at 3500 ppm (6/6/7/12).

All other findings noted in survivors and/or decedents were seen at comparable incidence in control and treated animals and were regarded to have developed spontaneously and unrelated to treatment.

Neoplastic findings: The macroscopically observed masses in the mammary gland of female rats could be confirmed on histopathological examination where the incidence of fibroadenomas (0/4/7/4) and adenocarcinomas (0/4/1/9) was increased. In comparison with the historical control data it is obvious that the absence of these tumors in the control group reflects an unusual situation. Anyhow, they were considered substance-related in the present study.

Discussion:

Substance–related effects were seen at all dose levels, especially the incidence of mammary tumors was increased in female rats of all treatment groups when compared to controls.

Conclusion:

The NOAEL under the conditions of this study with tritosulfuron containing 2.45 % AMTT was below 250 ppm (equal to < 11.9 mg/kg bw/d in males; < 16.4 mg/kg bw/d in females) based on the occurrence of mammary gland tumors at all dose levels.

B.6.5.2.4 Fourth study

Report: Mellert W. et al., 2001
BAS 635 H – Carcinogenicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006064

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B, OECD 451, EPA/FIFRA 83-2

Deviations: This carcinogenicity study was performed with tritosulfuron containing 2.45 % AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine). Water consumption was not determined on day 35 in males. The 7000 ppm group was discontinued after approximately 17 months of treatment.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 50 male and 50 female Wistar rats Chbb:THOM (SPF), 42±2 days old at start of the administration period, 141-195 g (males), 126-155 g (females), supplied by Dr. Karl THOMAE, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0, 250, 1000 and 3500 ppm for 24 months. The 7000 ppm dose level was discontinued after approximately 16 (females) or 17 (males) months of treatment, respectively, without further examinations. This was equal to 11.8, 48.7, 176.0 and 389.9 mg/kg bw/d for males and 16.2, 67.7, 246.7 and 534.2 mg/kg bw/d for females.
Food consumption, body weight and water consumption was determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week.
Differential blood counts were evaluated from the 3500 ppm group and control animals at the end of the study and also from all animals killed *in extremis* during the study. The animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
Analysis of the dietary mixtures
See BASF RegDoc# 2001/1006060

Mortality and clinical signs:
Female animals at 7000 ppm were prematurely sacrificed after 16 months (study days 496-498), males after 17 months (study days 513-515). The mortality rate was not increased shortly before when compared to rats of other groups. On day 728 the mortality rate for female rats at 3500 ppm was slightly increased.

Table B.6.5-19: Mortality rates on days 455 and 728 of study

	Mortality males (%)		Mortality females (%)	
Dose level (ppm)	Day 455	Day 728	Day 455	Day 728
0	0	22	2	26
250	2	22	2	22
1000	4	26	0	20
3500	0	14	2	40
7000	4	8 (day 515)	4	12 (day 498)

In females at 3500 and 7000 ppm there was an increased incidence of abnormal clinical signs (anogenital region smeared with urine and piloerection). Palpabale masses in the skin were

noted in females of all dose groups. The incidence at 7000 ppm was comparable with those of the control group.

Table B.6.5-20: Clinical observations

Sex	Male					Female				
Dose (ppm)	**0**	**250**	**1000**	**3500**	**7000**	**0**	**250**	**1000**	**3500**	**7000**
	Number of affected animals (n = 50)									
Anogenital region smeared with urine	0	4	2	8	8	2	2	1	4	23
Piloerection	0	2	0	1	2	4	3	4	6	11
Palpable masses in the skin	15	8	9	6	3	15	12	22	24	15
Mamma induration	-	-	-	-	-	4	4	8	10	1

Food and water consumption, body weight

Food consumption was not affected by the treatment. Compared to control water consumption was significantly increased at 7000 ppm (in males up to 71.5 % and in females up to 90.1 %), 3500 ppm (in males up to 42.2 % above control; in females up to 43.4 % above control) and in the 1000 ppm group (in males 25.4 % above control; in females up to 35.1 % above control). At 250 ppm water consumption was increased on several occasions up to 12.9 % in males (day 371). Body weight was decreased in males in all dose groups, and in females from 1000 ppm onwards.

Table B.6.5-21: Body weight gain compared to controls after 24 months in %

Dietary dose level (ppm)	Males	Females
250	- 7.5*	+ 1.3
1000	- 14.6**	- 7.6
3500	- 28.8**	- 22.1**
7000	- 27.6** (day 511)	- 24.7** (day 483)

* $P < 0.05$, ** $P < 0.01$ (Anova + Dunnett's test)

Ophthalmoscopy

See BASF RegDoc# 2001/1006060

Hematology

The differential blood count revealed no differences between the control and the 3500 ppm group.

Terminal body and organ weights

Terminal body weights were not taken from animals sacrificed prematurely.

The mean terminal body weights were significantly decreased in male rats of all treatment groups and in females at 3500 and 1000 ppm, although the latter without statistical significance. All organ weight changes were considered to be the result of the lower terminal body weight. Great differences in absolute and relative ovarial weights as well as lower adrenal weights in males were noticed, the latter with dose dependency. After checking individual histopathological diagnoses it became clear that tumors and/or cysts in the ovary were responsible for the weight changes. Likewise, tumors of the adrenal medulla were observed in individual control and low dose males which were considered responsible for weight increases.

Table B.6.5-22: Terminal body and organ weight

Sex	Male				Female			
Dose (ppm)	**0**	**250**	**1000**	**3500**	**0**	**250**	**1000**	**3500**
Terminal body weight (g)	723	677.6*	640.5**	559.4**	366.4	367.5	346.4	312.6**
Kidneys								
absolute (g)	4.083	4.073	3.966	3.909*	2.871	2.788	2.759	2.869
relative (%)	0.571	0.611	0.624**	0.706**	0.792	0.777	0.805	0.926**
Liver								
absolute (g)	20.731	19.191	18.668**	17.43**	12.277	12.31	11.763	11.422
relative (%)	2.885	2.846	2.934	3.135**	3.349	3.349	3.405	3.687

* P < 0.05, ** P < 0.01 (Kruskal-Wallis-H- + Wilcoxon-Test)

Gross lesions and histopathological findings

Macropathological and histopathological examinations were not reported/performed for animals at 7000 ppm sacrificed prematurely.

Non-neoplastic findings (

Table B.6.5-24)**:** Increased hematopoiesis in the bone marrow (femur, femur with joint, sternum) and extramedullary hematopoiesis in the liver was more frequently observed in females at 3500 ppm. Diffuse hyperplasia in the mammary gland and of uterine glands was noted with higher incidence in females at 3500 ppm. Likewise, endometritis occurred with higher incidence in high dose females. In the testes degeneration of the germinal epithelium, focal calcification of the seminiferous tubules and sperm stasis as well as sperm reduction in epididymides was noted with higher incidence in males at 3500 ppm. In addition, in females at 3500 ppm a higher incidence of more severe cases of chronic nephropathy were noted in the kidneys.

Neoplastic lesions:

A clearly higher incidence of mammary gland tumors was observed in females at 1000 and 3500 ppm when compared to controls (11/11/26/29) which are primarily caused by an increase in adenocarcinomas (5/2/14/14). See Table B.6.5-23.

Table B.6.5-23: Incidence of mammary tumors in female rats

Dose (ppm)	**0**	**250**	**1000**	**3500**
Findings				
Animals examined	50	50	50	50
Mammary gland - Fibroadenoma	6	9	8	10
- Adenoma	0	0	3	3
- Adenocarcinoma	5	2	14	14
- Adenocarcinoma in fibradenoma	0	0	1	2
Total mammary tumors	11	11	26	29
Mammary tumors bearing rats	9 (18 %)	11 (22 %)	23 (46 %)	26 (52 %)

Table B.6.5-24: Incidence of non-neoplastic changes

Sex		Males				Females			
Dose (ppm)		**0**	**250**	**1000**	**3500**	**0**	**250**	**1000**	**3500**
Finding	(Incidence/animals examined)								
Bone marrow (femur)	Increased hematopoiesis	16/50	12/50	15/50	13/50	21/50	18/50	24/50	39/50
Femur with joint	Increased hematopoiesis	5/49	1/11	3/13	7/50	15/50	3/11	5/10	36/50
Sternum (marrow)	Increased hematopoiesis	11/50	1/11	4/13	12/50	15/50	3/11	5/10	35/50
Mammary gland	Diffuse hyperplasia	-	-	-	-	8/50	7/50	8/50	13/50
Uterus	Diffuse glandular hyperplasia	-	-	-	-	0/50	0/24	0/27	5/50
	Endometritis	--	-	-	-	0/50	0/24	0/27	5/50
Liver	Extramedullary hematopoiesis	3/50	1/50	2/50	2/50	2/50	5/50	3/50	13/50
Testes	Degeneration germinal epith.	31/50	28/50	28/50	43/50	-	-	-	-
	Sperm stasis	13/50	7/50	4/50	20/50	-	-	-	-
	Focal calcification	14/50	17/50	19/50	30/50	-	-	-	-
Epididymides	Sperm reduction	11/49	10/50	14/50	20/50	-	-	-	-

Discussion:
Substance–related effects were seen at all dose levels. The incidence of mammary gland tumors was increased in female rats at 1000 and 3500 ppm.

Conclusion:
The NOAEL under the conditions of this study for tritosulfuron containing 2.45 % AMTT was below 250 ppm (equal to < 11.8 mg/kg bw/d in males; 16.2 mg/kg bw/d in females) based on substance-related effects at this dose level (increased water consumption, lower body weight) and on the occurrence of mammary gland tumors.

B.6.5.2.5 Fifth study

Report: Mellert W. et al., 2001
BAS 635 H – Supplementary chronic toxicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006061

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B, OECD 452, EPA/FIFRA 83-1

Deviations: This chronic toxicity study was performed with tritosulfuron containing 2.45 % AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine).

Acceptability: The study is considered to be acceptable as a supplementary study.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 20 male and 20 female Wistar rats Chbb:THOM (SPF), 42 days old at start of the administration period, 162.9-186.6 g (males), 122.7-149.3 g (females), supplied by Dr. Karl THOMAE, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0, 50 and 100 ppm for 24 months. This was equal to 2.0, and 5.0 mg/kg bw/d for males and 3.0, and 6.0 mg/kg bw/d for females.
This study was carried out as a supplementary study in order to define a NOAEL below 250 ppm (equal to 11.9 mg/kg bw/d in males; 16.4 mg/kg bw/d in females).
Food consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week.
Ophthalmological examinations were carried out prior to the start and towards the end of dosing. Urinalysis, clinico-chemical and hematological examinations were carried out at approximately 3, 6, 12, 18, and 24 months after start of the administration period. The animals were subjected to gross-pathological assessment, followed by histopathological examinations of the mammary gland and regional lymph nodes (females).

Findings:
Compared to control water consumption was significantly increased on several investigation points at 50 ppm (in males up to 36.6 % above control on day 651, in females up to 41.8 % above control on day 728) and at 100 ppm (in males up to 32.5 % above control on day 595, in females up to 18.6 % above control on day 84). Because these increases did not occur time- and dose-dependent they were not considered treatment-related.
There was no gain in mammary tumours and mammary tumour bearing female animals seen at 50 or 100 ppm when compared with control.

Table B.6.5-25: Neoplastic findings in the mammary gland of female rats

Finding	0 ppm	50 ppm	100 ppm
No. of female rats examined	20	20	20
Fibroadenoma	4	3	4
Adenoma	1	0	2
Adenocarcinoma	1	2	0
Total no. mammary gland tumors	6	5	6

Conclusion:
The NOAEL in this 24-month chronic study in rats for tritosulfuron containing 2.45 % AMTT was 100 ppm (equal to 5 mg/kg bw/d in males; 6 mg/kg bw/d in females).

B.6.5.2.6 Sixth study

Report: Mellert W. et al., 2001
BAS 635 H – Supplementary carcinogenicity study in Wistar rats. Administration in the diet for 24 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006065

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 451, EPA/FIFRA 83-2, EEC 87/302 B

Deviations: This carcinogenicity study was performed with tritosulfuron containing 2.45 % AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine).

Acceptability: The study is considered to be acceptable as a supplementary study.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 50 male and 50 female Wistar rats Chbb:THOM (SPF), 42 ± 1 days old at start of the administration period, 147.9-182.1 g (males), 129.4-154.2 g (females), supplied by Dr. Karl THOMAE, Biberach/Riss, FRG.
The rats received the test material by dietary administration at concentrations of 0, 50 and 100 ppm for 24 months. This was equal to 2.0 and 5.0 mg/kg bw/d for males and 3.0 and 6.0 mg/kg bw/d for females.
This study was carried out as a supplementary study in order to define a NOAEL below 250 ppm (equal to 11.8 mg/kg bw/d in males; 16.2 mg/kg bw/d in females).
Food consumption, water consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. The animals were examined for signs of toxicity or mortality at least once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week. Differential blood counts were determined for all surviving animals at the end of the study and also from all animals killed *in extremis* during the study. After about 24 months, the animals were subjected to gross-pathological assessment, followed by histopathological examinations of the mammary gland and regional lymph nodes (females).

Findings:
Compared to control water consumption was significantly increased on several investigation points at 50 ppm (in males up to 12.5 % above control on day 203, in females up to 14.4 % above control on day 707) and at 100 ppm (in males up to 11.6 % above control on day 539, in females up to 13.1 % above control on day 49). Because these increases did not occur time- and dose-dependent they were not considered treatment-related.
There was no gain in mammary tumors and mammary tumor bearing female animals seen at 50 or 100 ppm when compared with control.

Table B.6.5-26: Neoplastic findings in the mammary gland of female rats

Finding	0 ppm	50 ppm	100 ppm
No. of female rats examined	50	50	50
Fibroadenoma	10	10	9
Adenoma	1	1	0
Adenocarcinoma	4	2	5
Total no. mammary gland tumors	15	13	14
Mammary gl. tumor bearing animals	14 (28 %)	12 (24 %)	13 (26 %)

Conclusion:
The NOAEL in this 24-month chronic study in rats for tritosulfuron containing 2.45 % AMTT was 100 ppm (equal to 5 mg/kg bw/d in males; 6 mg/kg bw/d in females).

B.6.5.3 Carcinogenicity study in mice

Report: Mellert W. et al., 2001
BAS 635 H - Carcinogenicity study in B6C3F1/CrlBR mice.
Administration in the diet for 18 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006084

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 451; EEC 87/302; EPA/FIFRA § 83-2

Deviations: This carcinogenicity study was performed with tritosulfuron containing 2.45 % AMTT (2-amino-4-trifluoromethyl-6-methoxy-1,3,5-triazine).
Control analyses of the first and second sampling showed lower than expected values at 250 mg/kg feed. A modified extraction procedure was applied where complete recovery could be obtained.
The 7500 ppm group was discontinued after approximately 16 months of treatment.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 50 male and 50 female B6C3F1/CrlBR mice, 7 weeks old at start of the administration period, 21.6-27.4 g (males), 15.3-21.8 g (females), supplied by Charles River Lab., USA.
The mice received the test material by dietary administration at concentrations of 0, 250, 1000, 3750 and 7500 ppm for 18 months. This was equal to 36.0, 144.0 554.0 and 1199.0 mg/kg bw/d for males and 44.0, 177.0, 677.0 and 1584.0 mg/kg bw/d for females.
The 7500 ppm dose level was discontinued after approximately 16 months of treatment; the animals were killed and subjected to gross-pathological assessment without further examinations.
Food consumption, water consumption and body weight were determined once a week during the first 13 weeks, thereafter at 4-week intervals. At least once a day, the animals were examined for evident signs of toxicity or mortality. Once a week, they were subjected to an additional comprehensive clinical examination (including palpation). Blood smears were prepared after 12 months, 16 months (for 7500 ppm group only) and 18 months, and from one animal killed *in extremis*. The blood smears of the control groups and of the 3750 ppm groups were evaluated and reported. After 18 months of treatment, the animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:

Analysis of the dietary mixtures

The stability of the test substance was proven by reanalysis. The homogeneity, stability and correct concentration of the test substance in the diet were confirmed.

Two 250 ppm samples at the start of the study showed concentrations of 85.6 % or 86.4 %, respectively. These deviations were due to incomplete extraction of the test material out of the diet and not due to incorrect mixing.

Table B.6.5-27: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
250	36	44
1000	144	177
3750	554	677
7500	1199	1584

Mortality and clinical signs

Animals at 7500 ppm were prematurely sacrificed after 16 month (study days 498-499). The mortality rate was not increased shortly before when compared to mice of other groups. On day 562 the mortality rate for the remaining groups was inconspicuous. There were no clinical signs, which could be attributed to the treatment with tritosulfuron.

Table B.6.5-28: Mortality rates

Test group	% Mortality males	% Mortality females
0 ppm	2	8
250 ppm	10	6
1000 ppm	2	8
3750 ppm	0	2
7500 ppm	4 (day 499)	4 (day 481)

Food and water consumption, body weight

A tendency to slightly lower food consumption was noted in animals of all treatment groups mainly towards the end of treatment when compared to controls. At 7500 and 3750 ppm, water consumption was increased with statistical significance at most of the investigations. The increase was up to 49.8 % / 56.4 % (males/females) above controls at 7500 ppm and up to 23.2 % / 25.3 % above controls at 3750 ppm. Water consumption in mice at 250 and 1000 ppm was similar to control values.

A dose-related decrease of body weight gain was noted in all dose groups when compared to controls. As body weights were decreased in the 7500 ppm treatment groups from day 14 (males) or day 7 (females) onwards, the animals were killed prematurely after approximately 16 months of administration.

Table B.6.5-29: Body weight change in comparison with controls (day 546)

Dietary dose level	Decrease of body weight (%)		Body weight change (%)	
(ppm)	Males	Females	Males	Females
250	- 6.3	- 7	- 12.7	- 10.1
1000	- 9.9	- 12.5	- 21.1	- 21.2
3750	- 12.9	- 22.9	- 28.2	- 40.1
7500	- 19.3 (day 483)	- 28.3 (day 455)	- 44.2 (day 483)	- 52.3 (day 455)

Differential blood cell count
No treatment-related changes in white and red blood cells were seen at 3750 ppm. Therefore, the other groups were not examined.
Terminal body and organ weights
Terminal body weight was reduced in animals of all treatment groups when compared to controls, at 250 ppm reaching statistical significance in males only. All absolute and/or relative organ weight changes were considered a consequence of reduced terminal body weight and do not represent a treatment-related effect.

Table B.6.5-30: Terminal body and organ weights

Sex	Male				Female			
Dose (ppm)	**0**	**250**	**1000**	**3750**	**0**	**250**	**1000**	**3750**
Terminal body weight (g)	39.286	37.036**	35.36**	34.606**	39.154	36.313	33.087**	29.284**
Kidneys absolute (g)	0.714	0.708	0.671**	0.634**	0.471	0.45*	0.441**	0.412**
relative (%)	1.824	1.922**	1.914*	1.843	1.229	1.264	1.359**	1.424**
Liver absolute (g)	1.51	1.339**	1.379**	1.329**	1.325	1.251	1.172**	1.131**
relative (%)	3.857	3.628	3.923	3.866**	3.432	3.502	3.587*	3.892**
Ovary absolute (mg)	-	-	-	-	49.63	24.234**	25.609*	35.667*
relative (%)					0.128	0.068*	0.076	0.129
Testes absolute (g)	0.224	0.229	0.228	0.226	-	-	-	-
relative (%)	0.574	0.626**	0.652**	0.658**				
Brain absolute (g)	0.498	0.505	0.5	0.499	0.505	0.5	0.506	0.502
relative (%)	1.276	1.381**	1.432**	1.456**	1.331	1.416	1.578**	1.743**
Adr.gl.absolute (mg)	5.388	5.467	5.449	4.8**	8.565	7.064**	7.087**	6.735**
relative (%)	0.014	0.015	0.016	0.014	0.023	0.02	0.022	0.023

* P < 0.05, ** P < 0.01 (Kruskal-Wallis-H- + Wilcoxon-Test)

Pathology
Nor non-neoplastic neither neoplastic changes were noted upon histopathological examination, which could be attributed to the treatment with tritosulfuron.
The number of animals with neoplasms, with benign, malignant and systemic neoplasms as well as the number of primary, benign, malignant and systemic neoplasms was comparable between control and top dose groups for males, and even decreased in females.

Discussion:
No agreement was reached with the notifier that body weight development and reduced terminal body weight of animals at 250 ppm is not treatment-related. At the beginning of the administration period (day 0) mean body weights were similar in males and females of all groups (male mice, in g, groups 1-4: 24.3; 24.2; 24.0; 24.1; 23.8 / female mice, in g, groups 1-4: 18.7; 18.6; 18.4; 18.4; 18.5). The body weight development during the course of the study follows a clear-cut dose-response relationship. Also food consumption was found to be lower in all treatment groups.

Conclusion:
The NOAEL in this 18-month carcinogenicity toxicity study in mice was below 250 ppm (equal to < 36 mg/kg bw/d in males; < 44 mg/kg bw/d in females) based on reduced body weight gain at this dose level.
Tritosulfuron is not carcinogenic in mice.

B.6.6 Reproductive toxicity (Annex IIA 5.6)

The reproduction toxicity of tritosulfuron was investigated in a 2-generation reproduction study containing low quantities of AMTT (batch. no. N34) as well as in prenatal toxicity studies in rats (batch no. N12) and rabbits (batch no. N14). Two multigeneration studies on rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24).
In the 2-generation study in rats, tritosulfuron containing low quantities of AMTT had no adverse effects on reproductive performance or fertility of the F_0 and F_1 parental animals of all substance treated groups. Oestrus cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between the treated rats and the corresponding controls. Slight signs of general toxicity occurred in both parental generations (F_0 and F_1) at 3600 ppm evidenced by an increased incidence of urine smeared fur. In the presence of slight maternal toxicity, $F_{1a/}$ F_{1b} and F_2 pups had minimally lower body weight gain and an increased incidence of dilated renal pelves at necropsy. No substance-related clinical, gross or histopathological findings were noted at 600 and 100 ppm. The NOAEL for parental and reproductive toxicity was found to be 600 ppm (equivalent to 40 mg/kg bw/d).

Two studies were carried out with tritosulfuron containing high levels of AMTT (batch no. N24) in rats. In these studies multiple effects on reproduction were seen, the most striking being the increased pup mortality also in the absence of maternal toxicity. Fertility was not affected at any dose level.
In summary, the main findings were: Reproductive performance was impaired in the mid and high dose group F_0 parental females and in the F_1 parental females of all treatment groups substantiated by an increased pup mortality of the F_{1a}/F_{1b} pups at 700 and 3500/2100 ppm, and of the F_2 pups at all dose levels, especially during early postnatal life. The number of stillborn pups was also increased at the high dose level. As a consequence, the viability index and the lactation index were reduced. The high pup mortality led to total litter losses in several dams. General toxicity occurred in both parental generations at 700 ppm and 3500/2100 ppm (increased number of animals with fur smeared with urine, reduced food consumption, reduced body weight and body weight gain, increased water consumption). Hematology showed mild adverse effects on the red blood cells of females at 3500 ppm (decreased red blood cell count and hematocrit). Concerning pathology, none of the altered organ weights could be correlated with a histopathological finding in these organs. A NOAEL for reproductive toxicity was not achieved. The NOAEL for parental toxicity was set at 100 ppm (equal to 10 mg/kg bw/d).
A supplementary study investigating dose levels of 25 and 50 ppm was performed. In this study F_2 pup mortality was increased at 50 ppm in the absence of parental toxicity. The NOAEL for parental toxicity was 50 ppm (eqivalent to 4.8 mg/kg bw/d), the NOAEL for reproductive toxicity was 25 ppm (equivalent to 2.4 mg/kg bw/d).

In the prenatal toxicity studies, different batches of tritosulfuron were administered to rats (batch. no. N12) and rabbits (batch no. N14). In the rat fetuses a slightly higher incidence of hydrourethers in combination with renal pelvis dilatations were noted at 360 mg/kg bw/d. Maternal toxicity was substantiated by decreases in body weight gain. The NOAEL for maternal and developmental toxicity was 120 mg/kg bw/d. Tritosulfuron was not teratogenic in rats.
In the prenatal toxicity study in Himalayan rabbits signs of developmental toxicity were observed at the highest dose level only (450 mg/kg bw/d) in the form of a slightly increased occurrence of one skeletal variation (accessory 13^{th} rib). At this dose level there was overt

maternal toxicity (reduced food consumption, decreases in body weight gain, discoloured urine/hematuria). The NOAEL for maternal and developmental toxicity was found to be 150 mg/kg bw/d. Tritosulfuron was not teratogenic in rabbits.
The summary of reproduction toxicity studies with tritosulfuron are shown in Table 6.6-1.

Table 6.6-1: Summary of reproduction toxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
2-generation study Wistar rat (Chbb:THOM) 0, 100, 600, 3600 ppm N34	Parental and reproductive toxicity: 600 ppm [40]	3600 ppm: Parental toxicity: Clinical signs (urine smeared fur). Reproductive toxicity: Decreased bw gain, increased incidence of dilated renal pelves
2-generation study Wistar rats (Chbb: THOM) 0; 100; 700; 3500/2100 ppm N24	Parental toxicity: 100 ppm [10] Reproductive toxicity: < 100 ppm [< 10]	100 ppm: Increased pup mortality (F2 pups) 700 + 3500/2100 ppm: Parental toxicity: Abnormal clinical signs, increased water consumption, decreased bw, changes of hematological and clinico-chemical parameters. Reproductive toxicity: Increased number of stillborn pups and pup mortalities, decreased bw, delayed physical development
2-generation study Wistar rats (Chbb: THOM) 0; 25; 50 ppm N24	Parental toxicity: 50 ppm [4.8] Reproductive toxicity: 25 ppm [2.4]	50 ppm: Parental toxicity: None Reproductive toxicity: Increased F_2 pup mortality
Developmental toxicity Wistar rat (Chbb:THOM 0, 40, 120, 360 mg/kg bw/d days 6-15 N12	Maternal toxicity: [120] Developmental toxicity: [120]	360 mg/kg bw/d: Maternal toxicity: Decreased bw gain. Developmental toxicity: Hydrourethers/renal pelves dilatation. Tritosulfuron is not teratogenic
Developmental toxicity Himalayan rabbit 0, 50, 150, 450 mg/kg bw/d days 7-19 N14	Maternal toxicity: [150] Developmental toxicity: [150]	450 mg/kg bw/d: Maternal toxicity: Decreased food intake (days 7-13 p.i.), decreased bw gain, discoloured urine/hematuria. Developmental toxicity: Slightly increased incidence of accessory $13t^h$ rib(s) Tritosulfuron is not teratogenic

m: male; f: female; bw: body weight; p.p. post partum

B.6.6.1 Multigeneration studies in rats

B.6.6.1.1 First study

Report: Schilling K. et al., 2001
BAS 635 H - Two-generation reproduction toxicity study in Wistar rats continuous dietary administration
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006066

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 416, EPA/OPPTS 870.3800

Deviations: None, which can be considered to have an impact on the integrity or validity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch no.: N34, Purity: 99.1 %, AMTT content: 0.024 %
Test animals: Four groups of 25 male and 25 female healthy young Wistar rats (Chbb:THOM (SPF), 43 ± 1 day days old at the beginning of treatment, 121.1-148.6 (males) and 94.6-122.8 g (females) of weight, supplied by Boehringer Ingelheim, Pharma KG, Biberach/Riss, FRG.
The rats (F_0 parental generation) received the test material by dietary administration at concentrations of 0 ppm; 100 ppm; 600 ppm or 3600 ppm until or up to about 16 hours before they were sacrificed. This was equal to 9.7, 59.1 and 352.1 mg/kg bw/d for males and 10.9, 65.3 and 388.1 mg/kg bw/d for females (during premating period).
At least 74 days after the beginning of treatment, F_0 animals were mated to produce a first litter (F_{1a}). The females were allowed to litter and to rear their pups until day 4 (standardisation) or 21 days after parturition. At least 10 days after the last weaning of the F_{1a} generation pups, the F_0 generation parental animals were mated again and produced a second litter (F_{1b}). Mating pairs were from the same dose group and F_1 animals selected for breeding were continued in the same dosing group as their parents. Groups of 25 males and 25 females selected from F_{1a} pups as F_1 parental generation were offered diets containing 0 ppm; 100 ppm; 600 ppm or 3600 ppm of the test substance post weaning, and the breeding program was repeated to produce F_2 litter. The study was terminated with the terminal sacrifice of the F_2 weanlings and F_1 adult animals. Test diets containing tritosulfuron were offered continuously throughout the study.
The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances.
Food consumption of the F_0 and F_1 parents was determined regularly during premating (once weekly over a period of 7 days each), and weekly during gestation (days 0, 7, 14, 20) and lactation periods (days 1, 4, 7, 14).
Water consumption of F_0 and F_1 animals was determined weekly during the same premating weeks as for food consumption.
In general, body weights of F_0 and F_1 parents were determined once weekly. However, during gestation and lactation F_0/ F_1 females were weighed on days 0, 7, 14 and 20 of gestation and on days 1, 4, 7, 14 and 21 after birth.
Oestrus cycle data were evaluated for F_0 and F_1 generation females over a three-week period prior to mating until evidence of mating occurred. Moreover, the oestrus stage of each female was determined on the day of scheduled sacrifice.
Sperm parameters were assessed either in all F_0 and F_1 generation males (motility) or in F_0 and F_1 generation males of the control and high dose group (sperm head count, morphology) at scheduled sacrifice or shortly thereafter.
The F_{1a}, F_{1b} and F_2 pups were sexed and weighed on the day after birth and on days 4, 7, 14 and 21 post partum. Their viability was recorded. All pups were examined macroscopically at

necropsy (including weight determinations of brain, spleen and thymus in one pup/sex/litter). Sexual maturation (day of preputial separation/vaginal opening) of all F_{1a} pups selected to become F_1 parental generation animals was determined.
All F_0 and F_1 parental animals were assessed by gross pathology (including weight determinations of several organs) and subjected to an extensive histopathological examination, special attention being paid to the organs of the reproductive system. A quantitative assessment of primordial follicles, growing follicle and antral follicles in the ovaries was performed for all control and high dose F_0 and F_1 parental females.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The homogeneity of the dietary test substance preparation was proven. The correctness of the concentrations was analytically demonstrated.

Table B.6.6-1: Mean test substance intake (mg/kg bw/d) for F_0 parental generation

Dietary dose level (ppm)	F_0 Males	F_0 Females	F_0 females (F_{1a} litter)		F_0 females (F_{1b} litter)	
		Premating	Gestation	Lactation	Gestation	Lactation
100	9.7	10.9	8.9	15.3	8.1	14.3
600	59.1	65.3	51.8	85.7	47.9	82.6
3600	352.1	388.1	321.1	511.8	289.6	497.5

F_0 Generation
Mortality and clinical signs
No substance-related mortality was observed in any of the male and female F_0 parental animals. Animals at 3600 ppm showed urine smeared fur during the whole treatment period (premating, mating, gestation, lactation).
Food and water consumption, body weight
Food consumption was not affected during the whole administration period (premating, gestation, and lactation of $F_{1a/b}$ litter). Water consumption was minimally higher in animals at 600 and 3600 ppm on several investigation points but overall no clear treatment-related effect could be observed during the premating period. Mean body weight and body weight gain was not influenced during the whole treatment period.
Oestrus cycle data
All F_0 parental females showed regular oestrus cycles over the determination period lasting three weeks prior to mating, the mean days from oestrus to oestrus were similar.
Male reproduction data
For F_0 parental males, which were placed with females to generate F_{1a} pups, the male mating index was 100 % in control, 600 ppm and 3600 ppm groups. One low dose male (100 ppm) did not generate F_{1a}, but was successful in generating F_{1b} pups with another female. On the other hand, one male at 100 ppm, one male at 600 ppm and two males at 3600 ppm, which generated F1a pups, did not generate F_{1b} pups when mated with another female.

Table B.6.6-2: Male fertility indices for F0 males (in %)

	0 ppm	**100 ppm**	**600 ppm**	**3600 ppm**
concerning F_{1a} litter	100	96	100	100
concerning F_{1b} litter	100	96	96	92

Sperm parameters
No treatment-related effect was noted concerning the various sperm parameters examined (motility, sperm head count, and morphology).
Female reproduction and delivery data
For F_0 parental females, which were placed with males to generate F_{1a} pups, the female mating index was 100 % in control, 600 ppm and 3600 ppm groups. One female of the low dose group (no. 136 mated with male 36; see above) did not become pregnant.
One female at 100 ppm (no. 143), one female at 600 ppm (no. 159) and two females at 3600 ppm (nos. 188, 191) did not generate F_{1b} pups when mated with another female.
The mean duration of gestation (F_{1a} + F_{1b}) was similar in all groups, lasting from 21.7 days to 22.1 days. The gestation index varied between 96 % and 100 %, indicating that nearly all pregnant females delivered live F_{1a} and/or F_{1b} pups. Implantation was not affected by treatment since the mean number of implantation sites and postimplantation losses were comparable between all groups. All other parameters (total/mean number of delivered pups/dam, total number of liveborn pups, stillborn pups, calculated live birth indices of the F_{1a} and F_{1b} litter) did not show biologically relevant differences.

Table B.6.6-3: Female reproduction and delivery data (F_0 generation)

F_0 -> F_{1a} / F_{1b}	0 ppm	100 ppm	600 ppm	3600 ppm
Females on study (No.)	25	25	25	25
Female Mating Index (%)	100/100	100/100	100/100	100/100
Female Fertility Index (%)	100/100	96/96	100/96	100/92
Mean Duration of Gestation (d)	21.9/21.7	21.9/21.9	22.0/21.8	22.1/21.7
Females with Liveborn Pups (N)	25/25	24/24	25/23	25/23
Females with Stillborn Pups (N)	9/4	8/7	7/7	6/5
Females with all Stillborn (N)	0/0	0/1	0/0	0/0
Total No. Liveborn Pups	333/342	332/342	303/344*	301/322
Live Birth Index (%)	95/98	97/96	94/96*	97/98
Stillborn (N)	18/6	10/13	18/16*	10/6

* $P < 0.05$ (Fisher's exact test)

Terminal body and organ weights, pathology
Terminal body weights were similar between all treated groups. Mid and high dose females had even slightly higher terminal body weights than control and low dose females. There were no treatment-related differences in organ weights and no histopathologically changes were found which were considered related to the treatment with tritosulfuron.

F1 Generation (pups/litters)
Pup number and status at delivery
The mean number of delivered F_{1a}/F_{1b} pups and the rate of liveborn and stillborn pups were not affected by the administration of tritosulfuron. The slight differences in the number of liveborn pups in the second litter (F_{1b}) of the mid dose dams resulting in a lower live birth index and an increased number of stillborn pups are considered to be incidental in nature (see Table B.6.6-3).
Pup viability mortality
Viability indices as indicators for pup mortality between days 0-4 p.p. were considered unaffected by the treatment. Lactation indices as indicators for pup mortality between days 4-21 p.p. were unaffected as well.
Sex ratio
The sex distribution and sex ratios of live F_{1a} and F_{1b} pups on the day of birth and on day 21 p.p. did not show any substantial differences between controls and treated groups.

Table B.6.6-4: Summary of litter data and body weight gain

F_{1a} / F_{1b}	0 ppm	100 ppm	600 ppm	3600 ppm
Total number of pups delivered	351/348	342/355	321/360	311/328
Mean No. of pups delivered	14.0/13.9	14.3/14.8	12.8/15.7	12.4/14.3
Total number of litter	25/25	24/24	25/23	25/23
Pups dead day 0	1/0	1/1	1/1	0/1
Pups dead days 1-4	6/7	11/16	16/13	7/3
Viability Index % (days 0-4)	98/98	96/95	94/96	98/99
Lactation Index % (days 4-21)	99/99	100/99	100/98	97/98
Sex ratio, day 21				
live males %	49.7/51.9	50.3/49.7	50.5/51.1	51.1/50.3
live females %	50.3/48.1	49.7/50.3	49.5/48.9	48.9/49.7
Body weight gain (Grams, m + f)				
day 4 to 7	6.2/5.8	5.9/5.9	5.9/5.9	5.6*/5.6
day 7-14	18.0/17.5	17.7/17.5	17.7/17.6	16.7/17.2
day 14 to 21	21.5/20.0	21.3/20.5	21.3/20.5	20.3/19.4*

*: $p < 0.05$ (Dunnett-test)

Clinical signs

The F_{1a} and F_{1b} pups did not show any clinical signs up to weaning which could be attribute to treatment.

Body weight (see Table B.6.6-4)

Mean body weight an body weight gain was minimally lower in F_{1a} and F_{1b} pups at 3600 ppm, reaching statistical significance at single investigation points (days 4 to 7 (F_{1a} pups) and days 14 to 21 (F_{1b} pups)).

Sexual maturation data (Vaginal opening/Preputial separation)

There were no biologically relevant data or statistically significant differences between treated animals and concurrent control groups in either sex.

Organ weights and necropsy

Pup organ weights revealed no changes, which could have been attributed to the treatment with tritosulfuron. At necropsy of F_{1b} pups a higher incidence of dilated renal pelves was noted at 3600 ppm when compared to control and lower dose groups.

Table B.6.6-5: Incidence of dilated renal pelves of F_{1a} and F_{1b} pups

F_{1a} -pups	**0 ppm**	**100 ppm**	**600 ppm**	**3600 ppm**
Litters evaluated	25	24	25	24
Pups evaluated	300	290	266	258
Live	282	280	248	248
Stillborn	18	10	18	10
Pup incidence of dilated renal pelves (N)	1	1	3	2
Litter incidence of dilated renal pelves (N)	1	1	2	2
Affected pups / Litter	0.2	0.3	1.1	0.9
F_{1b} -pups	**0 ppm**	**100 ppm**	**600 ppm**	**3600 ppm**
Litters evaluated	25	24	23	23
Pups evaluated	346	348	354	328
Live	340	335	338	322
Stillborn	6	13	16*	6
Pup incidence of dilated renal pelves (N)	4	19	2	30
Litter incidence of dilated renal pelves (N)	3	9*	1	14**
Affected pups / Litter	0.9	5.2*	0.5	8.5**

* $P < 0.05$, ** $P < 0.01$ (Fisher's exact test or Wilcoxon-test)

F1 generation parental animals

Test substance intake

Table B.6.6-6: Test substance intake (mg/kg bw/d) for F_1 parental generation

Dietary dose level (ppm)	F_1 Males	F_1 Females (premating)	F_1 Females (F_2 litter)	
			Gestation	Lactation
100	10.7	11.3	8.7	14.3
600	65.8	67.9	52.2	87.6
3600	394.5	413.7	325.3	527.5

Mortality and clinical signs

No substance-related mortality was observed in any of the male and female F_1 parental animals. Urine smeared fur was noted in three F_1 females at 3600 ppm in week 17 after delivery of F_2 litter and in four females of this dose group during nearly the whole lactation period.

Food and water consumption, body weight

Food consumption was not affected during the whole administration period (premating, gestation, and lactation of F_2 litter). Likewise, water consumption was not affected during the premating period. Mean body weight and body weight gain was not influenced during the whole treatment period.

Oestrus cycle data

All F_1 parental females showed regular oestrus cycles over the determination period lasting three weeks prior to mating, the mean days from oestrus to oestrus were similar.

Male reproduction data

For F_1 parental males, which were placed with females to generate F_2 pups, the male mating index was 100 % in control, 96 % at 100 ppm, 100 % at 600 ppm and 100 % at 3600 ppm groups. One low dose female (100 ppm) did not become sperm positive, which was considered incidental in nature. Since a dose-response was missing, the male fertility index was considered not be affected by the treatment.

Table B.6.6-7: Male fertility indices for F_1 males (in %)

	0 ppm	**100 ppm**	**600 ppm**	**3600 ppm**
concerning F_2 litter	88	84	92	96

Sperm parameters

No treatment-related effect was noted concerning the various sperm parameters examined (motility, sperm head count, and morphology).

Female reproduction and delivery data

For F_1 parental females, which were placed with males to generate F_2 pups, the female mating index was 100 % in control, 96 % at 100 ppm, 100 % at 600 ppm and 100 % at 3600 ppm groups. One female of the low dose group (no. 342 mated with male 232) did not become pregnant. Since a dose-response was missing, the female fertility index was considered not be affected by the treatment. The mean duration of gestation (F_2) was similar in all groups, lasting from 21.8 to 22.0 days. The gestation index varied between 95 % / 100 % / 100 % / 96 %, indicating no influence of the test substance.

Implantation was not affected by treatment since the mean number of implantation sites and postimplantation losses were comparable between all groups. All other parameters (total/mean

number of delivered pups/dam, total number of liveborn pups, stillborn pups, calculated live birth indices of the F_2 litter) did not show biologically relevant differences.

Table B.6.6-8: Female reproduction and delivery data (F_2 generation)

F_1 -> F_2	0 ppm	100 ppm	600 ppm	3600 ppm
Females on study (No.)	25	25	25	25
Female Mating Index (%)	100	96	100	100
Female Fertility Index (%)	88	88	92	96
Mean Duration of Gestation (d)	22.0	21.8	21.8	22.0
Females with Liveborn Pups (N)	21	21	23	23
Females with Stillborn Pups (N)	5	3	5	6
Females with all Stillborn (N)	0	0	0	0
Total No. Liveborn Pups	259	283	314	315
Live Birth Index (%)	98	98	98	98
Stillborn (N)	5	5	5	6

No statistical significance (Fisher's exact test)

Terminal body and organ weights, pathology

Terminal body weights were similar between all treated groups. There were no treatment-related differences in organ weights and no histopathologically changes were found which were considered related to the treatment with tritosulfuron.

F_2 Generation (pups/litters)

Pup number and status at delivery

The mean number of delivered F_2 pups and the rate of liveborn and stillborn pups were not affected by the administration of tritosulfuron.

Pup viability

Some more pups died in the first four days after birth in the high dose group (3.1 % / 3.5 % / 3.5 % / 6.35 % from control to high dose, respectively) also the viability index, as indicator for pup mortality between days 0-4 p.p., was similar to the low dose group. The lactation indices were unaffected as well.

Sex ratio

The sex distribution and sex ratios of live F_2 pups on the day of birth and on day 21 p.p. did not show any substantial differences between controls and treated groups.

Table B.6.6-9: Summary of F_2 litter data

F_2	0 ppm	100 ppm	600 ppm	3600 ppm
Total number of pups delivered	259	283	314	315
Mean No. of Pups delivered	12.3	13.5	13.7	13.7
Total number of litter	21	21	23	23
Pups dead day 0	0	9	0	1
Pups dead days 1-4	8	10	11	20
Viability Index % (days 0-4)	97	93	96	93
Lactation Index % (days 4-21)	100	100	99	99
Sex ratio, day 21				
live males %	49.1	51.9	52.2	50.0
live females %	50.9	48.1	47.8	50.0
Body weight gain (Grams, m + f)				
day 4 to 7	6.0	5.4	5.3	5.1*
day 7-14	17.1	16.4	16.6	16.0
day 14 to 21	20.3	20.3	19.5	18.1

*: $p < 0.05$ (Dunnett-test)

Clinical signs
The F_2 pups did not show any clinical signs up to weaning.
Body weight
Mean body weight and body weight gain was minimally lower in F_2 at 3600 ppm reaching statistical significance on several investigations.
Sexual maturation data (Vaginal opening/Preputial separation)
Not determined.
Organ weights and necropsy
Pup organ weights revealed no changes, which could have been attributed to the treatment with tritosulfuron. At necropsy of F_2 pups a higher incidence of dilated renal pelves was noted at 3600 ppm when compared to control and lower dose groups. With the exception of one low dose pup, this finding was only observed in pups that were culled or died until day 4 p.p..

Table B.6.6-10: Incidence of dilated renal pelves of F_2 pups

F_2 -pups	0 ppm	100 ppm	600 ppm	3600 ppm
Litters evaluated	21	21	23	23
Pups evaluated	256	275	311	311
Live	251	270	306	305
Stillborn	5	5	5	6
Pup incidence of dilated renal pelves (N)	2	3	4	14
Litter incidence of dilated renal pelves (N)	1	3	2	8*
Affected pups / Litter	0.6	1.3	1.2	3.9*

* $P < 0.05$ (Fisher's exact test or Wilcoxon-test)

Discussion:
Tritosulfuron had no adverse effects on reproductive performance or fertility of the F_0 and F_1 parental animals of all substance treated groups. Oestrus cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between the treated rats and the corresponding controls.
Slight signs of general toxicity occurred in both parental generations (F_0 and F_1) at 3600 ppm evidenced by an increased incidence of urine smeared fur. In the presence of slight maternal toxicity, $F_{1a/}$ F_{1b} and F_2 pups had minimally lower body weight gain and an increased incidence of dilated renal pelvis at necropsy. Since slight signs of general toxicity were observed at 3600 ppm, the parental NOAEL should not be differentiated in F_0 and F_1 generation. No substance-related clinical, gross or histopathological findings were noted at 600 and 100 ppm.

Conclusion:
Under the conditions of this study the NOAEL for the F_0 and F_1 parental animals as well as the reproductive NOAEL was found to be 600 ppm (equal to 40 mg/kg bw/d).
The parental NOAEL is based on slight clinical signs noted at 3600 ppm (equal to 388 mg/kg bw/d). The reproductive NOAEL is based on minimally lower body weight gain of the F_1 and F_2 progeny as well as increased incidences of dilated renal pelves of the F_1 and F_2 pups at 3600 ppm (equal to 388 mg/kg bw/d).

B.6.6.1.2 Second study

Report: Schilling K. et al., 2001
BAS 635 H - Two-generation reproduction toxicity study in Wistar

rats. Continuous dietary administration
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006077

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 416, EPA/FIFRA 83-4

Deviations: This 2-generation reproduction toxicity study was performed with tritosulfuron containing 2.45 % AMTT.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Four groups of 25 male and 25 female healthy young and sexually immature Wistar rats (Chbb:THOM (SPF), 28 ± 1 days old at the beginning of treatment, 117.6-149.2 (males) and 101.3-131.2 g (females) of weight, supplied by Karl THOMAE, Biberach/Riss, FRG.
The rats (F_0 parental generation) received the test material by dietary administration at concentrations of 0, 100, 700 or 3500 / 2100 ppm. The originally selected high concentration of 3500 ppm was only administered to the first parental and the first pup generation, but had to be reduced later to 2100 ppm due to excessive pup mortality. This was equal to 9.9, 70.8 and 359.5 mg/kg bw/d for males and 10.6, 75.7 and 378.0 mg/kg bw/d for females (during premating period).
At least 70 days after the beginning of treatment, F_0 animals were mated to produce a first litter (F_{1a}) and subsequently remated to produce a second litter (F_{1b}). Because of the high mortality of F_{1a} pups at 3500 ppm up to day 21 p.p., not enough F_{1a} pups from different litters survived in this dose for subsequent rearing. Therefore, the started rearing of the weaned F_{1a} pups (originally selected as F_1 parental animals, but renamed and raised without mating as so-called FX animals) was terminated by sacrifice 3 or 5 weeks after they had been weaned. In order to get a complete F_1 parental generation to generate F_2 litters, the F_1 parental animals were derived from F_{1b} litters.
Mating pairs were from the same dose group and F_1 animals selected for breeding were continued in the same dosing group as their parents. Groups of 25 males and 25 females selected from F_{1b} pups as F_1 parental generation were offered diets containing 0; 100; 700 or 2100 ppm of the test substance post weaning, and the breeding program was repeated to produce F_2 litter. The study was terminated with the terminal sacrifice of the F_2 weanlings and F_1 adult animals. Test diets containing tritosulfuron were offered continuously throughout the study.
The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances. Pups were sexed and monitored with respect to their developmental stages and their behaviour was assessed. Their viability was recorded. All pups were examined macroscopically at necropsy; if necessary, certain pups were additionally inspected for any organ/skeletal findings. Food consumption of the F_0 and F_1 parents was determined regularly during premating (once weekly over a period of 7 days each), and weekly during gestation (days 0, 7, 14, 20) and lactation periods (days 1, 4, 7, 14).

Water consumption of F_0 and F_1 animals was determined weekly during the same premating weeks as for food consumption. In general, body weights of F_0 / F_1 / FX animals were determined once weekly. However, during gestation and lactation F_0 / F_1 females were weighed on days 0, 7, 14 and 20 of gestation, and on days 1, 4, 7, 14 and 21 after birth. The F_{1a}, F_{1b} and F_2 pups were weighed on the day after birth and on days 4, 7, 14 and 21 post partum. Blood and urine samples were taken from the first 12 surviving males and females of each test group from F_0 and F_1 parental generations towards the end of the study period for clinical pathology examinations. Furthermore, it deemed necessary to take urine and blood samples a second time after weaning of the F_{1b} pups, because of the high mortality of the 3500 ppm F_{1a} pups. All F_0 and F_1 and FX animals were assessed by gross pathology (including weight determinations of several organs) and subjected to an extensive histopathological examination, special attention being paid to the organs of the reproductive system.

Findings:

Analysis of the dietary mixtures

The stability of the test substance was proven for a period of 10 and 34 days at room temperature. The homogeneity of the dietary test substance preparation was proven. The correctness of the concentrations was analytically demonstrated.

Table B.6.6-11: Test substance intake (mg/kg bw/d) for F_0 and F_1 parental generation

Dietary dose level (ppm)	F_0 Males	F_0 Females (premating)	F_0 Females (F_{1a} Litter)		F_0 Females (F_{1b} litter)	
			Gestation	Lactation	Gestation	Lactation
100	9.9	10	8.8	15.2	8.0	14.9
700	70.8	75	64.8	108.2	58.7	99.9
3500 / 2100	359.5	378	337.8	340.1	182.2	366.6

Dietary dose level (ppm)	F_1 Males	F_1 Females (premating)	F_1 females (F_2 litter)	
			Gestation	Lactation
100	8.4	9.5	8.2	12.5
700	60.4	68.7	59.0	75.7
2100	195.3	216.7	193.5	199.8

F_0 Generation

Mortality and clinical signs

No substance-related mortality was observed in any of the male and female F_0 parental animals. Some dams at 3500 ppm showed urine smeared fur.

Food and water consumption, body weight

Food consumption was decreased in males at the beginning of the premating phase and in F_0 females during some weeks of premating and during the whole lactation period of F_{1a} litters (about 38 % less than the corresponding control group) and F_{1b} litters (about 28 % less than the control animals) at 3500 ppm.

Water consumption was increased in F_0 males and females during the whole premating period at 700 and 3500 ppm.

Table B.6.6-12: Mean parental water consumption during premating (gram/animal/d)

	Males				Females			
Dose level (ppm)	0	100	700	3500	0	100	700	3500
Week 0-1	24.7	25.8	25.7	27.6**	20.7	21.3	23.1**	24.1**
Week 1-2	27.2	27.4	29.0	33.4**	19.7	21.2	21.7	25.1**
Week 2-3	28.1	28.4	30.3	33.2**	19.9	20.3	22.6	25.4**
Week 4-5	27.3	28.9	30.0	35.0**	21.9	23.1	24.8*	26.7**
Week 6-7	24.8	26.4	28.3*	32.9**	21.1	21.2	23.5	26.5**
Week 8-9	25.7	26.4	28.8*	32.2**	22.9	23.1	26.1*	27.5**
Week 0-10	26.5	27.5	29.0	32.8	21.4	21.7	24.0	26.4

*: $p < 0.05$; ** $p < 0.01$ (Dunnett-test)

Mean body weight and body weight gain was decreased during the whole study period in the F_0 animals during premating weeks 4 –10, during gestation and lactation of F_{1a} at 3500 ppm, in females during lactation days 1 and 4 p.p. as well as in the parental animals for F_{1b} litter at 2100 ppm. Body weight gain was also reduced in males during premating (more pronounced at the beginning of the administration) and females during some weeks of the premating phase and during single weeks in males and females at 700 ppm.

Oestrus cycle data

Not reported.

Blood chemistry and hematology: Decrease in triglycerides, glucose (males), total protein (males), albumin (males), red blood cells (females), hemoglobin (females), hematocrit (females) at 3500 ppm.

Male reproduction data

For F_0 parental males, which were placed with females to generate F_{1a} or F_{1b} pups, the male mating index was 100 %. The fertility indices are shown in the table below.

Table B.6.6-13: F0 male fertility indices (in %)

	0 ppm	**100 ppm**	**700 ppm**	**3500 ppm**
concerning F_{1a} litter (m)	88	96	100	100

Sperm parameters

Not reported.

Female reproduction and delivery data

For F_0 parental females, which were placed with males to generate F_{1a} pups, the female mating index was 100 %. The mean duration of gestation (F_{1a} + F_{1b}) was similar in all groups, lasting from 21.5 days to 22.0 days. The gestation index varied between 95 % and 100 %.

Table B.6.6-14: Female reproduction and delivery data (F_0 generation)

F_0 -> F_{1a} / F_{1b}	**0 ppm**	**100 ppm**	**700 ppm**	**3500 ppm**
Females on study (no.)	25/25	25/24	25/25	25/24
Mating index (%)	100/100	100/100	100/100	100/100
Fertility index (%)	88/88	96/92	100/100	100/100
Gestation index (%)	100/100	96/95	100/100	100/100
Duration of gestation (d)	21.9/21.7	22.0/21.8	22.0/21.7	21.5**/21.5
Females with stillborn pups (N)	5/6	5/6	8/9	15*/9
Females with all stillborn (N)	0/0	0/0	0/0	0/0

* $p < 0.05$; ** $p < 0.01$ (Fisher's exact test)

F1 Generation (pups/litters)

Pup number and status at delivery

The number of stillborn F_{1a} pups was increased at 700 and 3500 ppm.

The increased F_{1a} and F_{1b} pup mortality resulted in reduced viability and lactation indices (e. g. total litter loss of 13 dams during rearing of F_{1a}) at 700 and 3500/2100 ppm (e.g. total litter loss in 5 dams during rearing of F_{1b}).

The sex distribution and sex ratios of live F_{1a} and F_{1b} pups on the day of birth and on day 21 p.p. did not show any substantial differences between controls and treated groups.

Body weight was reduced in F_{1a} (about 41 % of the control value at day 21 p.p.) at 3500 ppm and F_{1b} pups (about 29 % lower than control value at day 21 p.p.) at 2100 ppm until weaning; reduced in F_{1a} and F_{1b} pups (about 9 % / 11 % below controls on day 21 p.p.) at 700 ppm.

Body weight gain was decreased in F_{1a} pups (about 40 % less weight gain from day 4-21 p.p. than controls) at 3500 ppm and in F_{1b} pups (about 27 % less weight gain from day 4-21 p.p. than controls) at 2100 ppm; decreased in F_{1a} and F_{1b} pups between days 1-21 p.p. (about 6 % for F_{1a} / 9 % for F_{1b} less weight gain from day 4-21 p.p. than controls) at 700 ppm.

Table B.6.6-15: Summary of litter data and body weight gain

F_{1a} / F_{1b}	**0 ppm**	**100 ppm**	**700 ppm**	**3500/2100 ppm**
Total no. of pups delivered	265/306	310/301	344/394	368/329
Total no. of litter	22/22	23/21	25/25	25/24
Pups liveborn (N)	259/296	302/291	330/375	333*/313
Pups stillborn (N)	6/10	8/10	14/19	35**/16
Live birth index (%)	98/97	97/97	96/95	90/95
Pups dead day 0	0/2	5/0	0/1	3/2
Pups dead days 1-4	5/12	11/9	17/44	181/120
Viability Index % (days 0-4)	98/95	95/97	95/88	42**/61**
Lactation Index % (days 4-21)	95/99	99/99	99/97	56**/78**
Sex ratio, day 21				
live males %	48.8/46.8	50.0/48.5	52.6/53.2	51.6/50.5
live females %	51.3/53.2	50.0/51.5	47.4/46.8	48.4/49.5
Body weight gain (Grams, m + f)				
day 4 to 7	5.7/5.5	5.8/5.4	4.8*/4.4**	1.5**/2.0**
day 7-14	16.8/15.9	17.9/16.8	17.1/15.1	10.9**/11.8**
day 14 to 21	19.9/18.5	20.7/19.3	18.5/17.0*	13.5**/15.2**

*: $p < 0.05$ (Dunnett-test + Fisher's exact test)

Physical development:

Physical Development of F_{1a} and F_{1b} pups was delayed at 700 and 3500/2100 ppm. There was a lower number of pups with pinna unfolding, auditory canal/eye opening and positive grip reflex on time at 3500/2100 ppm and a lower number of F_{1a} and F_{1b} pups with pinna unfolding and auditory canal opening on time at 700 ppm.

Necropsy observations

Post mortem autolysis occurred with higher incidence in F_{1a} and F_{1b} pups. Cleft palate, uterine horns filled with watery fluid and bloody intestinal content were noted in single pups. All high dose pups had no or less milk in the stomach.

Table B.6.6-16: Necropsy observation of F_{1a} and F_{1b} pups

F_{1a} / F_{1b}	0 ppm	100 ppm	700 ppm	3500/2100 ppm
Total no. of pups evaluated	211/247	255/248	292/333	291/236
Post mortem autolysis	4/0	0/2	1/8	18/7
Cleft palate	0/0	0/0	0/	2/1
Uterine horns filled with watery fluid	0/0	0/0	0/0	0/4
Bloody intestinal content	0/0	0/0	0/0	4/0

Fisher's exact test and Wilcoxon test (no statistical significance)

F_1 parental animals

Mortality and clinical signs

No mortality was observed in any of the male and female F_1 parental animals. There were no particular clinical observation during the whole treatment period which might have been attributed to the administration of the test substance.

Food and water consumption, body weight

Food consumption was decreased in males and females during premating and in the F_1 dams during lactation at 2100 ppm. At 700 ppm food consumption was also slightly lower, with statistical significance during the lactational phase (days 4 to 7).

Water consumption was increased in females (about 18 % higher than control) during most weeks of the premating period at 700 and 2100 ppm.

Body weight and body weight gain was reduced during the whole study period in F_1 males and for females also during gestation and lactation of F_2 at 700 and 2100 ppm

Blood chemistry and hematology:

Increase in sodium, chloride, urea (males) at 2100 ppm. Decrease in glucose (males), triglycerides, hemoglobin (females) at 2100 ppm.

Male reproduction data

For F_1 parental males, which were placed with females to generate F_2 pups, the male mating index was 96 % / 100 % / 100 % / 96 % from control to high dose group, respectively. The fertility indices are shown in the table below.

Table B.6.6-17: F1 male fertility indices (in %)

	0 ppm	100 ppm	700 ppm	2100 ppm
concerning F_2 litter (m)	96	88	100	92

Female reproduction and delivery data

For F_1 parental females, which were placed with males to generate F_2 pups, the female mating index was 96 % / 100 % / 100 % / 96 % from control to high dose group, respectively. The mean duration of gestation was similar in all groups, lasting from 21.7 days to 22.0 days. The gestation index varied between 96 % and 100 %.

Table B.6.6-18: Female reproduction and delivery data (F_2 generation)

F_1 -> F_2	0 ppm	100 ppm	700 ppm	2100 ppm
Females on study (no.)	25	25	25	25
Mating index (%)	96	100	100	96
Fertility index (%)	100	88	100	96
Gestation index (%)	100	100	96	100
Duration of gestation (d)	22.0	22.0	22.0	21.7**
Females with stillborn pups (N)	4	6	7	5
Females with all stillborn (N)	0/0	0/0	0/0	0/0

** $p < 0.01$ (Fisher's exact test)

F_2 pups

Pup number and status at delivery

The increased pup mortality resulted in reduced viability and lactation indices (e.g. total litter loss in 12 dams during rearing of F_2) at 100, 700 and 2100 ppm. At 2100 ppm the sex distribution and sex ratios of live F_2 pups on day 21 p.p. was slightly in favour of male sex.
Body weight and body weight gain was reduced about 14 % below controls on day 21 p.p. at 2100 ppm and about 10 % below controls on day 21 p.p. at 700 ppm.

Table B.6.6-19: Summary of litter data and body weight gain

F_2	0 ppm	100 ppm	700 ppm	2100 ppm
Total no. of pups delivered	283	291	272	277
Total no. of litter	24	22	24	23
Pups liveborn (N)	278	283	256**	269
Pups stillborn (N)	5	8	16**	8
Live birth index (%)	98	97	94	97
Pups dead day 0	1	0	4	5
Pups dead days 1-4	12	44	88	152
Viability Index % (days 0-4)	95	84**	64**	42**
Lactation Index % (days 4-21)	98	90**	93*	63**
Sex ratio, day 21				
live males %	50.6	52.0	51.7	56.7
live females %	49.4	48.0	48.3	43.3
Body weight gain (Grams, m + f)				
day 4 to 7	5.3	5.5	4.1*	3.2**
day 7-14	1668	16.5	15.3	13.9*
day 14 to 21	13.5	13.7	13.3	14.1

* $p < 0.05$, ** $p < 0.01$ (Dunnett-test + Fisher's exact test)

Physical development:

Physical Development of F_2 pups was delayed at 700 and 2100 ppm. There was a lower number of pups with pinna unfolding and auditory canal opening on time.

Necropsy observations

Post mortem autolysis occurred with higher incidence in all dose groups.
Two pups of the high dose group had agenesia of the kidney. No or less milk in the stomach was noted in pups of all dose groups.

Table B.6.6-20: Necropsy observation of F_2 pups

F_2	0 ppm	100 ppm	700 ppm	2100 ppm
Total no. of pups evaluated	279	279	265	247
Post mortem autolysis	2	9	14	21
Agenesia of kidney (s)	0	0	0	2

Fisher's exact test and Wilcoxon test (no statistical significance)

FX animals (originally selected as F_1 parental animals, but renamed and raised without mating).
Lower food consumption at 3500 ppm.
Lower body weight/body weight gain at 3500 ppm and 700 ppm.

Summary:
Fertility was not affected at any dose level. Reproductive performance was impaired in the mid and high dose group F_0 parental females and in the F_1 parental females of all treatment groups substantiated by an increased pup mortality of the F_{1a} pups at 3500 ppm, of the F_{1b} pups at 700 ppm and 2100 ppm and of the F_2 pups at all dose levels, especially during early postnatal life. As a consequence, the viability index and the lactation index were reduced. General toxicity occurred in both parental generations at 700 ppm and 3500/2100 ppm (increased number of animals with fur smeared with urine, reduced food consumption, reduced body weight and body weight gain, increased water consumption). Hematology showed mild adverse effects on the red blood cells of females at 3500 ppm (decreased red blood cell count and hematocrit). Findings such as decrease in glucose, total protein, albumin and triglycerides, increased sodium and chloride concentrations are probably due to the reduced nutritional state of the affected animals.
Developmental toxicity was observed in progeny of the F_0 at 700 ppm and 3500 ppm and in the progeny of the F_1 parents at all dose levels. The most striking effect was the adverse effect on pup survival in the absence of maternal toxicity. The high pup mortality led to total litter losses in several dams.

Conclusion:
The NOAEL for parental toxicity is 100 ppm (10 mg/kg bw/d) based on increased water consumption and decreased body weight gain at 700 ppm (equal to 75 mg/kg bw/d).
The NOAEL for reproductive toxicity is below 100 ppm (below 10 mg/kg bw/d) based on increased pup mortality at this dose level.

B.6.6.1.3 Third study

Report: Schilling K. et al., 2001
BAS 635 H - Supplementary two-generation reproduction toxicity study in Wistar rats. Continuous dietary administration
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006067

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 416, EPA/FIFRA 83-4

Deviations: This 2-generation reproduction toxicity study was performed with tritosulfuron containing 2.45 % AMTT.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Three groups of 25 male and 25 female healthy young and sexually immature Wistar rats (Chbb:THOM (SPF), 37 ± 1 days old at the beginning of treatment, 149.9-150.6 (males) and 124.8-125.3 g (females) of weight, supplied by Boehringer Ingelheim, Pharma KG, Biberach/Riss, FRG.
The rats (F_0 parental generation) received the test material by dietary administration at concentrations of 0, 25 or 50 ppm. This was equal to 2.4 and 4.8 mg/kg bw/d for males and 2.7 and 5.3 mg/kg bw/d for females (during premating period).
At least 74 days after the beginning of treatment, F_0 animals were mated to produce a first litter (F_{1a}) and subsequently remated to produce a second litter (F_{1b}). Mating pairs were from the same dose group and F_1 animals selected for breeding were continued in the same dosing group as their parents. Groups of 25 males and 25 females selected from F_{1a} pups as F_1 parental generation were offered diets containing 0 ppm; 25 ppm or 50 ppm of the test substance post weaning, and the breeding program was repeated to produce F_2 litter. The study was terminated with the terminal sacrifice of the F_2 weanlings and F_1 adult animals. Test diets containing tritosulfuron were offered continuously throughout the study.
The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances. Food consumption of the F_0 and F_1 parents was determined regularly during premating (once weekly over a period of 7 days each), and weekly during gestation (days 0, 7, 14, 20) and lactation periods (days 1, 4, 7, 14). Water consumption of F_0 and F_1 animals was determined weekly during the same premating weeks as for food consumption. In general, body weights of F_0 and F_1 parents were determined once weekly. However, during gestation and lactation F_0 / F_1 females were weighed on days 0, 7, 14 and 20 of gestation, and on days 1, 4, 7, 14 and 21 after birth. Pups were sexed and monitored with respect to their developmental stages and their behaviour was assessed. Their viability was recorded. All pups were examined macroscopically at necropsy; if necessary, certain pups were additionally inspected for any organ/skeletal findings. All F_0 and F_1 parental animals were assessed by gross pathology (including weight determinations of several organs), special attention being paid to the organs of the reproductive system.

Findings:
Test substance intake

Table B.6.6-21: Test substance intake (mg/kg bw/d) for F_0 and F_1 parental generation

Dietary dose level (ppm)	F_0 Males	F_0 Females (premating)	F_0 females (F_{1a} litter)		F_0 females (F_{1b} litter)	
			Gestation	Lactation	Gestation	Lactation
25	2.4	2.7	2.2	3.5	2.0	3.1
50	4.8	5.3	4.4	7.1	4.1	6.3

Dietary dose level (ppm)	F_1 Males	F_1 Females (premating)	F_1 females (F_2 litter)	
			Gestation	Lactation
25	2.5	2.7	2.2	3.4
50	5.0	5.4	4.2	6.3

F_0 Generation
No substance-related signs of general toxicity were noted in the parental F_0 generation.
There were no indications that tritosulfuron caused adverse effects on fertility of the F_0 parental animals of substance treated groups.
Female reproduction and delivery data
For F_0 parental females, which were placed with males to generate F_{1a} pups, the female mating index was 100 %. The mean duration of gestation (F_{1a} + F_{1b}) was similar in all groups, lasting from 21.6 days to 21.9 days. The gestation index was 100 %.

Table B.6.6-22: Female reproduction and delivery data (F_0 generation)

F_0 -> F_{1a} / F_{1b}	**0 ppm**	**25 ppm**	**50 ppm**
Females on study (no.)	25/25	25/24	25/25
Mating index (%)	100/100	100/100	100/100
Fertility index (%)	92/100	100/92	96/92
Gestation index (%)	100/100	100/95	100/100
Duration of gestation (d)	21.9/21.9	21.7/21.6**	21.8./21.8
Females with stillborn pups (N)	5/6	1/7	6/5
Females with all stillborn (N)	0/0	0/0	0/0

** $p < 0.01$ (Fisher's exact test)

F1 Generation (pups/litters)
Pup number and status at delivery
No effect of treatment could be observed in either dose group. The statistically significant increased pup mortality at the 25 ppm level was not considered treatment-related (see Discussion).

Table B.6.6-23: Summary of litter data and body weight gain

F_{1a} / F_{1b}	**0 ppm**	**25 ppm**	**50 ppm**
Total no. of pups delivered	278/327	337/307	329/332
Total no. of litter	23/25	25/23	24/23
Pups liveborn (N)	273/321	336/295	321/327
Pups stillborn (N)	5/6	1/12	8/5
Live birth index (%)	98/98	100/96	98/98
Pups dead day 0	1/0	2/3	2/2
Pups dead days 1-4	12/12	21/22	11/13
Viability Index % (days 0-4)	95/96	93/92*	96/95
Lactation Index % (days 4-21)	97/98	94/93*	100/98
Sex ratio, day 21			
live males %	47.6	53.9	48.9
live females %	52.4	46.1	51.1

*: $p < 0.05$ (Dunnett-test + Fisher's exact test)

F_1 parental animals

Water consumption was not affected in either dose group. The increased water consumption recorded on several occasions during the premating period in F_1 males and females at 25 and 50 ppm occurred without dose-relation and was considered to be without toxicological relevance (see Discussion).

Table B.6.6-24: Mean F_1 parental water consumption (gram/animal/d) during premating

	Males			Females		
Dose level (ppm)	0	25	50	0	25	50
Week 0-1	16.3	17.5	16.7	15.2	15.7	16.5
Week 1-2	22.2	22.7	21.9	18.6	20.6*	20.8*
Week 2-3	25.6	26.8	26.3	21.3	22.4	22.0
Week 4-5	28.6	31.8**	29.8	22.1	26.3*	26.1*
Week 6-7	28.8	31.9*	30.1	24.4	28.5*	28.5*
Week 8-9	28.7	31.0	29.1	23.4	27.4*	27.3*
Week 0-14	26.7	29.0	27.9	22.7	25.7	26.1

*: $p < 0.05$; ** $p < 0.01$ (Dunnett-test)

Female reproduction and delivery data

For F_1 parental females, which were placed with males to generate F_2 pups, the female mating index was 96 % / 100 % / 100 % for control and dose groups, respectively. The mean duration of gestation was similar in all groups, lasting from 22.0 days to 22.1 days. The gestation index was 100 %.

Table B.6.6-25: Female reproduction and delivery data (F_2 generation)

F_1 -> F_2	**0 ppm**	**25 ppm**	**50 ppm**
Females on study (no.)	25	25	25
Mating index (%)	96	100	100
Fertility index (%)	96	80	96
Gestation index (%)	100	100	100
Duration of gestation (d)	22.1	22.1	22.0
Females with stillborn pups (N)	5	4	4
Females with all stillborn (N)	0/0	0/0	0/0

No statistical significance (Fisher's exact test)

F_2 pups

Pup number and status at delivery

Reproductive performance was impaired in F_1 parental females at 50 ppm substantiated by an increased pup mortality of F_2 during early postnatal life. As a consequence, the viability index was reduced (see Discussion).

Table B.6.6-26: Summary of litter data and body weight gain

F_2	**0 ppm**	**25 ppm**	**50 ppm**
Total no. of pups delivered	264	246	273
Total no. of litter	23	20	24
Pups liveborn (N)	257	242	268
Pups stillborn (N)	7	4	5
Live birth index (%)	97	98	98
Pups dead day 0	1	1	1
Pups dead days 1-4	7	8	20
Viability Index % (days 0-4)	97	96	92*
Lactation Index % (days 4-21)	99	99	98
Sex ratio, day 21			
live males %	50.6	47.1	54.4
live females %	49.4	52.9	45.6

Physical development

The number of F2 pups with pinna unfolding examined on day 4 p.p. was reduced at 50 ppm.

Discussion

F_{1a} / F_{1b} pups at 25 ppm had a statistically lower survival rate during the early postnatal phase when compared to F_{1a} / F_{1b} pups at 50 ppm. Since there was no dose-response relationship and the viability as well as the lactation index were still within the range of historical control data for this strain of rat, these effects were not considered treatment-related. Furthermore, pup mortality was not increased at 25 ppm in the second (F_2) generation showing that the finding at the low dose level was not aggravating which is supporting its fortuitousness. In contrast, the increased F_2 pup mortality at 50 ppm was considered treatment-related although absolute values are quite similar to F_{1a} / F_{1b} pups at 25 ppm and still within the range of historical control data. Since from other multi-generation studies it is known that effects are more pronounced in the F2 generation they were considered related to treatment.

Table B.6.6-27: Overview on the viability and lactation indices in F_{1a} / F_{1b} and F_2 pups

F_{1a} / F_{1b} pups dead days 1-4	12/12	21/22	11/13
Viability Index % (days 0-4)	95/96	93/92*	96/95
Lactation Index % (days 4-21)	97/98	94/93*	100/98
F_2 pups dead days 1-4	7	8	20
Viability Index % (days 0-4)	97	96	92*
Lactation Index % (days 4-21)	99	99	98

The increase in water consumption of F_1 parental animals were not considered treatment-related because they occurred without dose-relation on single investigation points. From other repeat-dose studies it is known that the increase in water consumption is occurring strictly dose-related. Furthermore, in comparison to the 2-generation study conducted in rats with batch no. N24 a clear NOAEL was seen at 100 ppm with regard to water consumption.

Conclusion:
The NOAEL for parental toxicity is 50 ppm (equivalent to 4.8 mg/kg/bw/d).
The NOAEL for reproductive toxicity is 25 ppm (equivalent to 2.4 mg/kg/bw/d) based on increased F_2 pup mortality at 50 ppm.

B.6.6.2 Developmental toxicity

B.6.6.2.1 Rat

Report:	Hellwig J., Hildebrand B. 1996 Reg.-No. 271 272 - Prenatal Toxicity in Wistar Rats After Oral Administration (Gavage) BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep. unpublished BASF RegDoc# 1996/10210
GLP:	Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)
Guideline:	EEC 87/302, OECD 414, EPA/FIFRA § 83-3, JMAFF
Deviations:	None, which are considered to have an impact on the integrity of the study.
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N 12: 95.6 %.
Test animals: Four groups of 25 pregnant female Wistar rats (Chbb:THOM (SPF)), 82-85 days old at the beginning of treatment, 235 g of weight (mean), supplied by Dr. K. THOMAE, Biberach/Riss, FRG.
The rats received the test material as an aqueous suspension by stomach tube at doses of 0; 40; 120 and 360 mg/kg bw on day 6 through day 15 post coitum (p.c.). A standard dose volume of 10 ml/kg bw was used for each group. The control group was dosed with the vehicle only (0.5 % aqueous Tylose CB 30.000 solution).
Food consumption and body weights of the animals were recorded regularly throughout the study period. The state of health of the animals was checked each day.
On day 20 p.c., all females were sacrificed and assessed by gross pathology (including weight determinations of the unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) was determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external findings. Thereafter, approximately one half of the fetuses of each litter was examined for soft tissue findings and the remaining fetuses for skeletal (incl. cartilage) findings.

Findings:

Analytical determinations

Analysis of the test substance preparations was carried out for a similar batch (N14). The stability of the test substance was proven by reanalysis. The stability and homogeneity of the test substance preparation was demonstrated. The correctness of the concentrations was analytically demonstrated.

Examination of the dams

Mortality and clinical signs

There were no mortalities in any of the groups and no abnormal clinical findings in any dam of any group.

Food consumption, body weight

Food consumption was not affected in any of the treated groups and was similar to the concurrent control group. The mean body weight gains of females at 360 mg/kg bw/d were reduced up to 20 % at the beginning of the treatment period (days 6-8 p.c.), between days 6-15 p.c. the high dose dams gained about 11 % less weight than the concurrent control group. Changes were not statistically significant.

Table B.6.6-28: Mean body weight gain of the dams (gram)

	Females			
Dose level (mg/kg bw/d)	0	40	120	360
Days 0-6	26.0	25.0	25.8	26.5
Days 6-15	46.6	46.8	46.8	41.4
Days 15-20	73.5	72.4	72.6	69.0
Days 0-20	146.1	144.2	145.2	137.0

Uterus weight

The uterus weights were not influenced by the administration of the test substance in any of the treated groups.

Necropsy findings

No substance-related changes were noted upon necropsy in any of the treated groups.

Reproduction data

In the control group 1/25 females and in the high dose group (360 mg/kg bw/d) 2/25 females did not become pregnant (conception rates: 96 % / 100 % / 100 % / 92 %).

Preimplantation losses were higher in females at 360 mg/kg bw/d, although without statistical significance. Since the values are well within the historical control data for this strain of rat this change was not considered treatment-related.

There were no further substance-related and/or biologically relevant differences between the groups with regard to conception rate, the mean number of corpora lutea, and implantation sites or in the values calculated for the postimplantation losses, the number of resorptions and viable fetuses. None of the females had aborted or gave premature birth.

Table B.6.6-29: Summary of reproduction data

	Dose level (mg/kg bw/d)			
	0	**40**	**120**	**360**
Females mated (N)	25	25	25	25
Conception rate (%)	96	100	100	92
Corpora lutea (mean)	15.8	16.1	16.0	15.6
Implantation sites (mean)	14.3	15.0	15.0	13.7
Preimplantation loss (mean %)	9.1	6.1	6.0	13.4
Postimplantation loss (mean %)	4.4	8.6	10.1	6.0
Resorptions (early/late; mean %)	3.8 / 0.6	5.3 / 3.3	8.0 / 2.1	5.5 / 0.6
Live fetuses (mean)	13.6	13.8	13.4	12.8
Sex ratio (%; m/f)	45.3 / 54.7	49.0 / 51.0	48.2 / 51.8	44.7 / 55.3

No statistical significance (Fisher's exact test or Wilcoxon-test)

Examination of the fetuses

Sex ratio, placental and fetal weight

The sex ratio was comparable within all dose groups (see Table B.6.6-29). Likewise, placental and fetal weights did not reveal any treatment-related deviation when compared to the control group.

External examination of the fetuses

The only external malformation that occurred was recorded for one control fetus, which presented with a generalised edema (anasarca). There were no external variations in any group.

Visceral examination of fetuses (see Table B.6.6-30)

Visceral changes classified as malformations were found at low incidences and the differences between the groups were without statistical significance. They consisted in dilatations of aortic arch/aorta descendent, both ventricles, left ventricle, hernia diaphragmatica and dextrocardia.

Fetal soft tissue variations, i.e. dilated renal pelvis and hydrourether occurred at higher incidences in all treated groups, the latter reaching statistical significance at 360 mg/kg bw/d.

The incidences of dilated renal pelvis were within range of historical control data for this strain of rats, while the incidence of hydrourether exceeded the upper limit of historical control data in the high dose group.

A fused placenta (unclassified observation) was noted for 2 control litter mates. These changes were considered incidental in nature and without relation to the treatment with tritosulfuron.

Table B.6.6-30: Summary of visceral observations in rat fetuses

Dose level (mg/kg bw/d)		0	40	120	360
Litters evaluated		24	25	25	22
Live fetuses evaluated		156	166	162	140
Total malformations (N)		1	0	0	4
Dilatation aortic arch/aorta desc.	(N)	1	0	0	1
Dilatation both ventricles	(N)	1	0	0	2
Dilatation left ventricle	(N)	0	0	0	1
Dextrocardia	(N)	0	0	0	1
Hernia diaphragmatica	(N)	0	0	0	1
Total variations (N)		19	29	33	31
Dilated renal pelvis	fetal incidence (%)	12.2	17.5	20.4	21.4
	litter incidence (%)	54	52	64	64
	affected fetuses/litter (%)	14.5	16.6	20.4	24.0
Hydrourether	fetal incidence (%)	1.3	3.0	4.3	5.7
	litter incidence (%)	8.3	16	24	32
	affected fetuses/litter (%)	1.7	2.8	4.1	5.4*

Skeletal examinations of fetuses

All skeletal changes classified as malformations or variations were found in comparable numbers between all dose groups and the differences between the groups were without statistical significance.

Table B.6.6-31: Incidence of skeletal observations

Dose level (mg/kg bw/d)	0	40	120	360
Litters evaluated	24	25	25	23
Live fetuses evaluated	171	179	174	155
Total malformations (N)	7	8	5	7
Total variations (N)	69	61	83	63
Total retardations (N)	76	81	79	86

Conclusion:

The NOAEL for maternal toxicity is 120 mg/kg bw/d based on lower body weight gain at 360 mg/kg bw/d. The NOAEL for developmental toxicity is 120 mg/kg bw/d based on the slightly higher occurrence of hydrourethers in combination with renal pelvis dilatations at 360 mg/kg bw/d. Tritosulfuron is not teratogenic in rats.

B.6.6.2.2 Rabbit

Report: Hellwig J., Hildebrand B., 1998
BAS 635 H - Prenatal toxicity in Himalayan rabbits after oral administration (gavage)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10227

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B, OECD 414, EPA/FIFRA 83-3, JMAFF

Deviations: None, which are considered to have an impact on the integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N14: 96.4 %.
Test animals: Four groups of 15 inseminated female Himalayan rabbits (Chbb:HM (outbred strain)), between 24 and 30 weeks old at the beginning of the study, 2528 g of weight (mean), supplied by Dr. K. THOMAE, Biberach/Riss, FRG.
The does received the test material as an aqueous suspension by stomach tube at doses of 0; 50; 150 and 450 mg/kg bw/d on day 7 through day 19 post insemination (p.i.). A standard dose volume of 10 ml/kg bw was used. The control group was dosed with the vehicle only (0.5 % Tylose CB 30.000 in doubly distilled water).
Food consumption and body weights were recorded regularly throughout the study period. The state of health of the animals was checked each day. On day 29 post insemination, all surviving females were sacrificed and assessed by gross pathology (including weight determination of the unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) was determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external, soft tissue and skeletal findings.

Findings:
Analytical determinations
The stability of the test substance was proven by analysis. The stability of the test substance preparation over a period of at least 4 hours at room temperature was proven. The homogeneity of the test substance preparation was demonstrated. The correctness of the concentrations was analytically confirmed.
Mortality and clinical signs
One low dose dam was sacrificed in a moribund condition due to an incidental luxation of the right hindlimb. No substance-related mortalities occurred in any group.
Does of the high dose group (450 mg/kg bw/d) showed discoloured urine from day 17 onwards. The test result for occult hemoglobin was positive, thus the finding hematuria was used accordingly.
Food consumption, body weight
Food consumption was dose-related decreased in dams of all treatment groups during the first half of the treatment period (days 7-13 p.i.) when compared to control. Thereafter, especially during the posttreatment period, a dose-related increase of food consumption was noted and all values exceeded those of the concurrent control group. At days 7 to 9 of gestation body weight loss reached statistical significance in high dose dams (- 22.9 g). There were no statistically significant differences in comparison to the control group concerning the weight gains of low and intermediate dose rabbits.

Examination of the dams
Uterus weights
The mean gravid uterus weights were not influenced by the administration of the test substance in any group.

Necropsy findings

There were no necropsy findings, which might have been associated with the administration of tritosulfuron.

Reproduction data

The conception rate was 100 % in all test groups. There were no substance-related differences between the groups with regard to the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and postimplantation losses, the number of resorptions and viable fetuses. No dam has aborted and no premature births occurred. One fetus of the mid dose (150 mg/kg bw/d) was already dead when the uterus of the doe was opened.

Table B.6.6-32: Summary of reproduction data

	Dose level (mg/kg bw/d)			
	0	**50**	**150**	**450**
Females mated (N)	15	15	15	15
Conception rate (%)	100	100	100	100
Corpora lutea (mean)	8.9	8.4	9.2	8.4
Implantation sites (mean)	6.6	7.4	8.1	6.9
Preimplantation loss (mean %)	25.6	10.8	11.3	19.8
Postimplantation loss (mean %)	5.2	11.9	12.4	4.2
Resorptions (early/late; mean %)	5.2 / 0.0	11.1 / 0.8	10.0 / 1.7	4.2 / 0.0
Live fetuses (mean)	6.4	6.5	7.1	6.5
Sex ratio (%; m/f)	42.7 / 57.3	52.7 / 47.3	48.6 / 51.4	46.9 / 53.1

* $P < 0.05$ (Fisher's exact test or Wilcoxon-test)

Examination of the fetuses

Sex ratio, placental and fetal weight

The sex ratio was comparable within all dose groups (see Table B.6.6-32). Likewise, placental and fetal weights did not reveal any treatment-related deviation when compared to the control group.

External examination of the fetuses

The only external malformation, which occurred, was recorded for one mid dose fetus (150 mg/kg bw/d) which was found dead when the uterus of the doe was opened. This fetus presented with "open eye". "Pseudoankylosis" of the forelimb/s was noted in 4/108 fetuses of the mid dose (150 mg/kg bw/d) and in 2/98 fetuses of the high dose (450 mg/kg bw/d). Since no dose-response relationship could be established and due to the low incidence of these findings, they were considered to be spontaneous in nature.

Visceral examination of fetuses

The incidence of visceral malformations was statistically significant increased in fetuses at 50 and 150 mg/kg bw/d. They mainly consisted of malformations of the heart (septal defects) and great vessels (dilatation of aortic arch and aorta descendens, truncus arteriosus communis). Since these changes did not occur in a dose-related manner and are well within the historical control data for this strain of rabbit they were considered not treatment-related.

Skeletal examination of fetuses

A slightly increased rate of fetuses with sternebrae of irregular shape was seen at 450 mg/kg bw/d. Accessory 13^{th} rib(s) were noted with higher incidences in all dose groups when compared to concurrent control. The incidences of both changes in all treatment groups are within the historical control data for this strain of rabbit, except for the occurrence of an accessory 13^{th} rib at 450 mg/kg bw/d. This finding is therefore considered treatment-related.

Table B.6.6-33: Summary of skeletal variations

	Dose level (mg/kg bw/d)			
	0	**50**	**150**	**450**
Litters evaluated	15	14	15	15
Live fetuses evaluated	96	91	107	98
Sternebra(e) of irregular shape				
fetal incidence (N)	4	2	3	10
litter incidence (N)	4	2	3	9
affected fetuses per litter (mean %)	5.9	1.9	2.9	9.5*
Accessory 13th rib(s)				
fetal incidence (N)	0	5	6	8
litter incidence (N)	0	2	4*	5*
affected fetuses per litter (mean %)	0	5.4	5.0*	7.3**

* P < 0.05; ** P < 0.01 (Fisher's exact test or Wilcoxon-test)

Table B.6.6-34: Incidence of external, soft tissue and skeletal observations

Dose level (mg/kg bw/d)	**0**	**50**	**150**	**450**
Litters evaluated	15	14	15	15
Fetuses evaluated	96	91	108	98
External observations				
Total malformations (N)	0	0	0	0
Total variations (N)	0	0	4	2
Visceral observations				
Total malformations (N)	0	8**	3*	0
Total variations (N)	15	26	30	33
Skeletal observations				
Total malformations (N)	0	0	1	0
Total variations (N)	11	16	18	23
Total retardations (N)	60	52	56	43

* P < 0.05; ** P < 0.01 (Fisher's exact test or Wilcoxon-test)

Discussion:

The oral administration of tritosulfuron did not induce external, soft tissue or skeletal malformations. Based on the provided historical control data and on the absence of a clear dose-response relationship, it can be concluded that the majority of observed external and soft tissue variations occurred spontaneously in nature, with one exception. At 450 mg/kg bw/d, the skeletal variation "accessory 13th rib(s)" occurred at a slightly but statistically significantly increased incidence. This might be a borderline sign of developmental toxicity of the test substance because the data are above the corresponding historical control ranges. At this dose level maternal toxicity was noted, i.e. decreased body weight gain, indications of an impaired kidney function evidenced by discoloured urine and hematuria.

Conclusion:

The NOAEL for maternal toxicity is 150 mg/kg bw/d, based on decreased food consumption, decreased body weight gain as well as indications of an impaired kidney function evidenced by discoloured urine and hematuria at 450 mg/kg bw/d.

The NOAEL for developmental toxicity is 150 mg/kg bw/d, based on the occurrence of accessory 13th rib(s) at slightly higher incidences at 450 mg/kg bw/d.

Tritosulfuron is not teratogenic in rabbits.

B.6.7 Delayed neurotoxicity (Annex IIA 5.7)

The acute and subchronic neurotoxicity studies in rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24). The developmental neurotoxicity study in rats was conducted with tritosulfuron containing low quantities of AMTT (batch. no. N59).
In the acute neurotoxicity study, the only clinical sign of toxicity (urine-smeared anogenital region) was seen at the high dose level (2000 mg/kg bw). There were no other test substance related effects at any dose level. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 1000 mg/kg bw. The NOAEL for neurotoxicity was 2000 mg/kg bw.
In the 90-day neurotoxicity study in rats, increased water consumption at 3500 ppm and 500 ppm, reduced food consumption at 3500 ppm and a smeared anogenital region at 3500 ppm were the only test substance related findings. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 100 ppm (equal to 7 mg/kg bw/d). The NOAEL for neurotoxicity was 3500 ppm (equal to 243 mg/kg bw/d).
In a developmental neurotoxicity study the only effects that were observed were an urine-smeared anogenital region, body weight loss during first day of treatment, reduced body weight during gestation period and reduced food consumption during gestation in the dams as well as slightly reduced mean body weight changes during the last week of lactation in the offspring at 8000 ppm. No signs of developmental neurotoxicity were noted up to the highest concentration. The NOAEL for maternal/neonatal toxicity was found to be 1000 ppm (equal to 65 mg/kg bw/d). The NOAEL for developmental neurotoxicity was 8000 ppm (equal to 509 mg/kg bw/d).
In conclusion, tritosulfuron is not neurotoxic to adult animals (batch no. N24) as well as to the developing animal (batch no. 59).

Table B.6.7-1: Summary of neurotoxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
Acute oral neurotoxicity study Wistar rat (Chbb:THOM) 0, 500, 1000, 2000 mg/kg bw single dose, gavage N24	Neurotoxicity: [2000] General toxicity: [1000]	2000 mg/kg bw: Clinical signs (urine smeared anogenital region). Neurotoxicity: None Tritosulfuron is not neurotoxic.
90-day subchronic neurotoxicity Wistar rat (Chbb:THOM) 0, 100, 500, 3500 ppm N24	Neurotoxicity: 3500 ppm [243] General toxicity: 100 ppm [7]	500 ppm: Increased water consumption 3500 ppm: reduced food consumption and bw, increased water consumption, urine smeared anogenital region Neurotoxicity: None Tritosulfuron is not neurotoxic.
Developmental neurotoxicity Wistar rats (Crl:CD(SD)IGS BR) 0, 200, 1000, 8000 ppm day 6 (p.c.)-21 (p.p.) N59	Developmental neurotoxicity: 8000 ppm [509] Maternal/neonatal toxicity: 1000 ppm [65]	Developmental neurotoxicity: None 8000 ppm - Maternal/neonatal toxicity: Clinical signs (urine smeared anogenital region), decreased bw gain Tritosulfuron is not neurotoxic to adult rats as well as to the developing rat

m: male; f: female; bw: body weight; p.c.: post coitum; p.p.: post partum

B.6.7.1 Acute neurotoxicity

Report: Mellert W. et al., 1998
BAS 635 H - Acute oral neurotoxicity study in Wistar rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11438

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EPA/FIFRA 81-8, EEC 92/32

Deviations: This study was performed with tritosulfuron containing 2.45 % AMTT.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 10 male and 10 female Wistar rats Chbb:THOM (SPF), 49 days old at start of the administration period, 223-263 g (males), 150-186 g (females), supplied by Dr. Karl Thomae GmbH, Biberach/Riss, FRG.
The rats received the test material as a single oral administration by gavage at dose levels of 0; 500; 1000 and 2000 mg/kg bw. The vehicle was a 0.1 % aqueous solution of carboxymethyl-cellulose, and the administration volume was 10 ml/kg bw.
The animals were observed up to 2 weeks after dosing. The general state of health of the rats was examined daily. Body weight was determined on day -7 (prior to dosing), day 0 (test substance administration), day 7 and day 14. Functional observational batteries (FOB) and motor activity measurements were carried out in all animals on day -7, on day 0 (within few hours after dosing), as well as on days 7 and 14. Five animals per sex and dose were fixed by in situ perfusion and subjected to neuropathological examinations. The remaining animals were sacrificed under CO_2-anesthesia without any further examinations.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was confirmed. The stability and homogeneity of the test substance preparation was verified. The correctness of the concentrations was analytically demonstrated.
Mortality and clinical signs
There were no mortalities in the course of the study. The only substance-related abnormal clinical finding was urine-smeared anogenital region in 1 high and 2 mid dose females during FOB on day 0, and 4 high dose females during general clinical observation on days 1-5. These signs of general toxicity were reversible at least by day 6 post exposure.
Food consumption, body weight
Food consumption and body weight development was not affected by the administration of the test substance.

Functional observation battery
With regard to *Home cage/Open field observations, Sensorimotor tests/Reflexes, Quantitative observations* as well as *Motor activity measurements* no changes, which might have been related to the treatment with the test substance, were noted.
Neuropathological examinations
Comprehensive neuropathological examinations of the central and peripheral nervous system did not reveal any substance-related effects.

Conclusion:
The NOAEL for neurotoxicity was 2000 mg/kg bw in both sexes.
The NOAEL for general toxicity was 1000 mg/kg bw based on the occurrence of clinical signs at 2000 mg/kg bw.

B.6.7.2 Subchronic neurotoxicity

Report: Mellert W. et al., 1998
BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats - Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10678
and
Mellert W., 2001
Amendment No. 1 to the report: BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats. Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006068

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EPA/FIFRA 82-7, EEC 92/32

Deviations: In amendment no. 1 the stability of the test substance was given which was proven by reanalysis after the in-life phase and was not given on page 19 of the report. In this amendment a purity of 95.4 % was given which is in contradiction to the value mentioned under “Purity: 96.8 %”.
This study was performed with tritosulfuron containing 2.45 % AMTT.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N24: 96.8 %.
Test animals: Groups of 10 male and 10 female Wistar rats Chbb:THOM (SPF), 49 days old at start of the administration period, 200-245 g (males), 147-180 g (females), supplied by Dr. Karl Thomae GmbH, Biberach/Riss, FRG.
The rats received the test material at dietary concentrations of 0 ppm; 100 ppm; 500 ppm and 3500 ppm for 3 months. This was equal to 7.0, 34.0 and 243.0 mg/kg bw/d for males and 8.0, 39.0 and 290.0 mg/kg bw/d for females
Food and water consumption was determined once a week. Body weight was determined once a week and on the days when functional observational batteries were performed. A check of the general state of health was made at least daily. Furthermore, the animals were thoroughly examined and palpated once a week. Functional observational batteries and motor activity measurements were carried out in all animals on day –7 (prior to the start of the administration) as well as on days 22, 50 and 85. Five animals per sex and dose were fixed by in situ perfusion and subjected to neuropathological examinations. The remaining animals were subjected to gross-pathological assessment, and liver and kidney weights were determined.

Findings:
Analysis of the dietary mixtures
The stability of the test substance was proven by reanalysis. The stability and homogeneity of the dietary test substance preparation was verified. The correctness of the concentrations was demonstrated.

Table B.6.7-2: Test substance intake (mg/kg bw/d)

Dietary dose level (ppm)	Males	Females
100	7	8
500	34	39
3500	243	290

Mortality and clinical signs
No mortalities occurred in course of the study. A smeared anogenital region was observed in 3 females at 3500 ppm; urine staining of the anogenital region was observed in 4 females on day 50 and 2 females on day 85 at 3500 ppm.
Food and water consumption, body weight
Food consumption was reduced in males at 3500 ppm on day 7; thereafter it was comparable between all groups. Water consumption was increased at 500 and 3500 ppm. Body weight was minimally lower in males at 3500 ppm, although without attaining statistical significance. Since in female rats body weight data were comparable among all groups, the finding in male rats were considered incidental in nature.
Functional observation battery
With regard to *Home cage/Open field observations, Sensorimotor tests/Reflexes, Quantitative observations* as well as *Motor activity measurements* no changes, which might have been related to the treatment with the test substance, were noted.
Organ weights and neuropathological examinations
Organ weights (brain, liver, kidneys) did not reveal statistically significant changes. Comprehensive neuropathological examinations of the central and peripheral nervous system did not reveal any substance-related effects.

Conclusion:
The NOAEL for neurotoxicity was 3500 ppm (243 mg/kg bw/d in males, 290 mg/kg bw/d in females).
The NOAEL for general toxicity 100 ppm (7 mg/kg bw/d in males, 8 mg/kg bw/d in females) based on an increase of water consumption at 500 ppm.

B.6.7.3 Delayed neurotoxicity in hens

No signs of neurotoxicity were reported in course of the toxicity studies with tritosulfuron. Moreover, tritosulfuron has no structural relationship to organophosphates and/or carbamates. Therefore, studies on delayed neurotoxicity in laying hens were not necessary and were not performed.

B.6.7.4 Developmental neurotoxicity

Report: Nemec M. D., 2001
Dietary development neurotoxicity study of BAS 635 H in rats
WIL Research Laboratories Inc., Ashland, OH 44805-9281, United States of America
unpublished
BASF RegDoc# 2001/1006071

GLP: Yes
(Laboratory certified by Environmental Protection Agency (EPA), Office of Enforcement and Compliance Assurance, Washington, D.C. 20460, USA)

Guideline: EPA/OPPTS 870.6300

Deviations: None, which can be considered to have an impact on the integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Tritosulfuron, batch/purity: N59: 98.19 %, AMTT content: 0.006 %
Test animals: Four groups of 30 mated female Wistar rats (Crl:CD(SD)IGS BR), approximately 89 days old when paired for breeding, 215-300 g on day 0 of gestation, supplied by Charles River Laboratories, Raleigh, North Carolina, USA.
The rats received the test material continuously as a homogeneous addition to the food at concentrations of 0 ppm, 200 ppm, 1000 ppm and 8000 ppm from day 6 post coitum (p.c.) to day 21 post partum (p.p.). This was equal to 13, 65 and 509 mg/kg bw/d for the entire treatment gestation period.
In this developmental neurotoxicity study, tritosulfuron was tested for its effect on the embryonic, fetal and postnatal development of the nervous system in Wistar rats. The dams were allowed to litter and rear their offspring until day 4 (standardisation of litters) or 21 after parturition. After the offspring were weaned (day 21 p.p.), the dams were sacrificed and subjected to a gross pathology examination.

The animals were observed twice daily for morbidity and mortality. Maternal body weights and food consumption were recorded on gestation days 0 (body weights only) and 6-20 (daily) as well as on lactation days 1-21 (daily). Clinical observations were performed on all dams daily during the treatment period. A detailed clinical examination outside the cage (open field observations; OFO) was performed in selected dams on days 6 and 13 p.c. and on days 3, 10 and 21 p.p.. The offspring were sexed on the day of birth and on days 4, 11 and 21. They were weighted on the day after birth and on day 4, 7, 11, 13, 17 and 21 p.p. and after weaning once a week in weekly intervals. Their viability was recorded. All pups were examined daily for morbidity and mortality from the day of parturition through weaning. Following culling individual clinical observations regarding general appearance, behaviour, and all signs of overt toxicity were recorded on days 4, 11, 21 and 28 and at weekly intervals thereafter. Sexual maturation (day of preputial separation/vaginal opening) of all selected offspring and the corresponding body weights were determined. A detailed clinical examination outside the cage (open field observations, OFO) was performed in selected offspring. All offspring, which were not required for any examinations, all offspring standardised on day 4 p.p. and all animals of subsets III – VI (on completion of the tests) were sacrificed and subjected to gross pathology examinations.

Table B.6.7-3: Scope of investigation (subsets)

Subsets	Number of pups selected	Test procedure
I	10/sex/group	Day 11 p.p.: Perfusion fixation, brain weights and neuropathology
II	10/sex/group	Day 72 p.p.: Perfusion fixation, brain weights and neuropathology
III	10/sex/group	Days 13, 17, 21 and 61 p.p.: Motor activity (MA)
IV	10/sex/group	Days 20 and 60 p.p.: Acoustic startle response
V	10/sex/group	Day 22 p.p.: Learning and memory test
VI	10/sex/group	Day 62 p.p.: Learning and memory test

Findings:

Analysis of the dietary mixtures

The stability of the test substance was guaranteed. The stability of the test substance in the diet was proven. The correctness of the concentrations and homogeneity were determined analytically.

Table B.6.7-4: Test substance intake (mg/kg bw/d)

Dose level (ppm)	Test substance intake		
	Gestation	Lactation	Overall
200	13	32	22.5
1000	65	159	112
8000	509	1350	929

F0 maternal generation

Mortality and clinical signs

No substance-related mortalities occurred in course of the study. A smeared anogenital region and dried yellow material at the hindlimbs was observed in females at 8000 ppm.

Modified functional observation battery

No substance-related differences were noted in any of the groups.

Food consumption, body weight

During gestation, food consumption and body weight gains were reduced in females at 8000 ppm. These reductions were mainly due to a body weight loss during first day of treatment.

Female reproduction and delivery data

The mean lengths of gestation in the treated groups were unaffected by test substance administration. The pregnancy rates were 100 % in the control and all treated groups. There were no treatment-related gross changes seen in any dose group. The mean numbers of implantation sites, the calculated differences between the number of pups born and the number of implantation sites counted (unaccounted sites) were similar in all treated groups when compared to control.

Table B.6.7-5: Female reproduction and delivery data (F_0 generation)

F_0 -> F_1	0 ppm	200 ppm	1000 ppm	8000 ppm
Females on study (No.)	30	30	30	30
Female Fertility Index (%)	100	100	100	100
Mean Duration of Gestation (d)	21.9	21.9	21.8	21.8
Implantation sites (mean)	15.8	15.6	16.1	15.1
Number of pups born (mean)	15.1	14.9	15.2	14.4
Unaccounted sites	0.8	0.8	0.9	0.7
Sex ratio (% m/f)	53.8/46.2	54.3/45.7	50.8/49.2	46.6/53.4

None significantly different from control group (Kruskal-Wallis or Dunnett's test)

F1 Generation (pups/litters)

Pups/Litter data

The mean number of pups born, live litter size and sex ratio was considered unaffected by treatment (see Table B.6.7-5).

Mortalities and general physical condition

Postnatal survival (relative to number born) up until day 72 was unaffected in any treated group. At 1000 and 8000 ppm survival was even higher on day 0 when compared to control and low dose group. The general physical condition was considered unaffected by maternal treatment. Mean body weight gain was slightly reduced during the last week of lactation on postnatal days (PND) 13-17 and 17–21.

Table B.6.7-6: Summary of litter data and body weight gain

F_1 pups	0 ppm	200 ppm	1000 ppm	8000 ppm
Number of pups born (mean)	15.1	14.9	15.2	14.4
Total number of litter	29	30	30	30
Postnatal survival (mean) day 0	98.2	98.4	99.6*	99.7*
days 1 to 4	100	98.9	99.4	99.2
days 14 to 21	100	100	100	100
Body weight gain (g, m/f)				
PND 13 to 17	10.0/9.8	10.6/10.3	10.5/10.0	9.3/8.5**
PND 17-21	12.8/12.3	12.8/12.6	12.2/11.9	11.2*/11.3
Balanopreputial separation (day)	45.5	44.8	44.9	44.5
Body weight (g)	243.2	236.7	240.5	227.3
Vaginal opening (day)	34.4	33.8	33.0	33.2
Body weight (g)	118.1	116.4	111.7	112.5

* : $p < 0.05$; **: $p < 0.01$ (Dunnett-test)

Modified functional observation battery
No remarkable differences were apparent between the control and treated groups when detailed clinical observation data were evaluated on PND 4, 11, 21, 35, 45 and 60.
Developmental landmarks, sensory function and neurobehavioural testing (see Table B.6.7-6)
All male pups were observed to have balanopreputial separation on or before day 56. Likewise, onset of vaginal opening was similar between all groups. The mean body weights of the treated groups were similar to the control group values at the time of acquisitions.
No treatment-related trends were apparent at any dose level on responses to acoustic startle test, locomotor activities and learning/memory tests.
Neuropathology
Qualitative microscopic examination of all major brain regions and of components of the spinal cord and peripheral nervous system did not reveal any treatment-related differences between control and high dose group animals of either sex.
Morphometry on the brains (PND 11) showed a slight increase in the thickness of the right, but not the left parietal cortex in treated males but not in females. On PND 72, brain morphometry revealed an increase of mean thickness of the left frontal cortex in high dose group females. Due to the occurrence only in one hemisphere and in only one sex, respectively, these findings were considered to be incidental in nature and not treatment-related.
There were no signs of developmental neurotoxicity at any dose level.

Conclusion:
The NOAEL for maternal reproductive toxicity and developmental neurotoxicity was 8000 ppm (509 mg/kg bw/d).
The NOAEL for maternal and neonatal toxicity was 1000 ppm (65 mg/kg bw/d) based on clinical signs and reductions in body weight gain at 8000 ppm.

B.6.8 Further toxicological studies (Annex IIA 5.8)

B.6.8.1 Toxicity studies of metabolites

B.6.8.1.1 635M02

635M02 (Reg. No. 292 564; BH 635-2; TBSA) is a soil metabolite and was detected in the rat metabolism study. It was tested in three mutagenicity assays as well as in acute oral tests. The metabolite was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. Two acute oral studies were conducted. The latter resulted in an oral LD_{50} of 1000 mg/kg bw, the first one in an oral LD_{50} of > 2000 mg/kg bw.

Table B.6.8-1: Summary of toxicity studies of metabolite 635M02

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in rats Wistar rats (Chbb:THOM (SPF))	Batch No. 00831-201, purity: 98.2 % Test substance preparation in 0.5 % Tylose CB 30.000 in aqua bidest	LD_{50}: 1000 mg/kg bw
Acute oral toxicity of TBSA in rats Wistar rats (Chbb:THOM (SPF))	Batch no. 26778/99; 26778/101, purity: > 98.5 % Test substance preparation in olive oil DAB 10	LD_{50}:> 2000 mg/kg bw
Salmonella typhimurium/ Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 00831-201, purity: 98.2 %	Not mutagenic
Gene mutation assay in Chinese hamster ovary (CHO) V79 cells *in vitro* (V79 / HPRT)	Batch No. 00831-201, purity: 98.2 %	Not mutagenic
In vitro chromosome aberration assay in V79 cells	Batch No. 00831-201, purity: 98.2 %	Not mutagenic

B.6.8.1.1.1 First mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1999
Report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with Reg.-No. 292 564; BH 635-2
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11412

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 92/69 B 13, EEC 92/69 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M02 (Reg.-No. 292 564; BH 635-2); batch no. 00831-201, purity: 98.2%.
Test system: Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA

635M02 was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in DMSO. The study consisted of a standard plate test (with doses ranging from 20 to 5,000 µg/plate) and preincubation test

(with doses ranging from 20 to 5,000 µg/plate) both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls (2-aminoanthracene - with S9 mix; N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and 4-nitroquinoline-N-oxide - all without S9 mix) were tested.
A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate with or without S-9 mix,
- there is a dose-response relationship, and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of 635M02 in the vehicle DMSO and in water over a period of 4 hours has been determined analytically. No test substance precipitation was observed. A weak bacteriotoxic effect was noticed only in the preincubation test from about 500 µg – 2,500 µg/plate. The mean number of revertant colonies was not increased in any strain either with or without S-9 activation. Expected increases in revertant colonies were obtained with the positive controls.

Conclusion:
According to the results of the study, 635M02 is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay.

B.6.8.1.1.2 Second mutagenicity study

Report: Wollny H.-E. et al., 1999
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT) with Reg.-No. 292 564; BH 635-2
RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11691

GLP: Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)

Guideline: EEC 87/302, OECD 476

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M02 (Reg.-No. 292 564; BH 635-2); batch no. 00831-201, purity: 98.2 %.
Test system: Chinese hamster ovary (CHO) cells
635M02 was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, using two parallel cultures each either with or

without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation). In an initial range-finding test, precipitation of the test substance occurred at doses > 300 µg/ml. Concentrations above 1,200 µg/ml led to non applicable inhomogenous suspensions. No changes in osmolarity and pH-values were observed.
The test substance was evaluated at the following doses in the 1st experiment (4 hours exposure): Without and with S-9 mix 0; 75.0; 150.0; 300.0; 600.0; and 1200.0 µg/ml.
A 2nd experiment for confirmation was performed using the following doses (4 hours exposure): Without and with S-9 mix: 0; 75.0; 150.0; 300.0; 600.0; and 1200.0 µg/ml.
After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation and an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were stained with 10 % methylene blue in 0.01 % KOH solution and counted. For control purposes and to demonstrate the sensitivity of the test system, negative controls and two appropriate positive control chemicals 7,12-dimethylbenz(a)anthracene (with S9 mix) and Ethylmethane sulfonate (without S9 mix) were tested.
The criteria for a positive response are:

- Increases of the mutation frequencies, that are three times above the spontaneous mutation frequency at least at one of the concentrations in the experiment.
- Evidence of reproducibility of any increase in mutant frequencies.
- Evidence of a dose-response relationship, even if a threefold increase of the mutant frequency is not observed.

Findings:
The stability of 635M02 in the vehicle DMSO and in water has been analytically confirmed. No cytotoxicity occurred up to the maximal concentration of 1200 µg/ml. The negative controls (untreated and vehicle controls) gave mutant frequencies within the range expected for the CHO cell line. Appropriate positive control chemicals led to the expected increase in the frequencies of forward mutations.
The test substance did not cause a relevant increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other. Two isolated increases exceeding the threshold of three times the corresponding solvent control were observed in experiment II, culture I at 75.0 µg/ml (without S-9 mix) and at 1200 µg/ml (with S-9 mix). These increases were judged as biologically irrelevant since they are based upon statistical fluctuations at such low absolute numbers. The corresponding solvent control is close to the lower border of historical solvent controls. Furthermore the effect was not reproduced in the parallel culture under identical conditions and the absolute values of colonies remained well within the range of our historical negative controls.
Thus it can be stated that in this mutagenity assay and under the experimental conditions reported the test substance did not induce gene mutations at the HPRT locus in V 79 cells.

Conclusion:
Under the experimental conditions of this assay, 635M02 is considered to be non-mutagenic *in vitro* in the CHO/HPRT mutation assay.

B.6.8.1.1.3 Third mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1999
Report: *In vitro* chromosome aberration assay with Reg.-No. 292 564; BH 635-2 in V79 cells
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11684

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 473, EEC 92/69 B 10

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M02 (Reg.-No. 292 564; BH 635-2; batch no. 00831-201, purity: 98.2 %.
Test system: V79 cells

635M02 (BH 635-2; Reg.-No. 292 564) was assessed for its potential to induce structural chromosomal aberrations in V79 cells *in vitro* both in the presence and in the absence of a metabolising system (S-9 mix of Aroclor 1254-induced Sprague-Dawley rat liver). According to an initial range-finding cytotoxicity test the following doses were evaluated.
1st experiment:
- 4 hours exposure, 18 hours harvest time, with and without S-9 mix:
  0; 575; 1,150; and 2,300 µg/ml,

2nd experiment:
- 18 hours exposure, 18 hours harvest time, without S-9 mix:
  0; 287.5; 575; and 1150 µg/ml
- 18 hours exposure, 28 hours harvest time, without S-9 mix:
  0; 2300 µg/ml
- 4 hours exposure, 28 hours harvest time, with S-9 mix:
  0; 575; 1150; and 2300 µg/ml.

The cell cycle of the untreated V79 cells is about 13 - 14 hours under the selected culture conditions. Thus, the selected 1st sampling time of 18 hours was within the 1 - 1.5 x the normal cell cycle time, as recommended by the OECD Guideline No. 473. The later sampling time of 28 hours was chosen to cover a possible cell cycle delay. About 2 - 3 hours prior to harvesting the cells, colcemid was added to arrest cells in a metaphase-like stage of mitosis (c-metaphases). After preparation of the chromosomes and staining with Giemsa, 100 metaphases for each culture in the case of the test substance and vehicle controls, or 50 or 100 cells for each culture in the case of the concurrent positive controls, were analysed for chromosomal aberrations. The criteria for a positive response are:
- A dose-related and reproducible significant increase in the number of structural chromosomal aberrations.

- The proportion of aberrations exceeded both the concurrent negative control range and the negative historical control range.

A test substance is generally considered non clastogenic in this test system if:

- There was no significant increase in the number of chromosomally damaged cells at any dose above concurrent control frequencies.
- The aberration frequencies were within the historical control range.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. Homogeneity of the test substance was achieved by mixing. The stability of 635M02 in the vehicle DMSO and in water each over a period of 4 hours has been determined analytically. Test substance precipitation occurred at concentrations of 575 µg/ml and higher. According to the results of the determination of the mitotic index, no suppression of the mitotic activity was observed under any of the experimental conditions. Cell count indicated a slight growth inhibition at 1150 µg/ml (18 hours exposure, 18 hours harvest) and 2300 µg/ml (4 hours exposure, 18 hours harvest and 18 hours exposure, 28 hours harvest) both without metabolic activation. Cell attachment was occasionally slightly reduced. Osmolarity and pH values were not influenced by test substance treatment. The negative controls (vehicle controls) gave frequencies of aberrations within the range expected for the V79 cell line. Both of the positive control chemicals, EMS (ethyl methane sulfonate) and cyclophosphamide, led to the expected increase in the number of cells containing structural chromosomal aberrations.
On the basis from the results of the present study, the test substance did not cause any biologically relevant and dose-dependent increase in the number of structurally aberrant metaphases incl. and excl. gaps at both sampling times either without S-9 mix or after adding a metabolising system in two experiments performed independently of each other. No increase in the frequency of cells containing numerical aberrations was demonstrated either.

Conclusion:
635M02 is not a chromosome-damaging (clastogenic) agent under *in vitro* conditions in V79 cells.

B.6.8.1.1.4 First acute oral toxicity study

Report: Kirsch P. et al., 1995
Report on the study on the acute oral toxicity of TBSA in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1995/11408

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M02; batch no. 26778/99; 26778/101, purity: > 98.5 %.
Test animals: Wistar rats
Single administration of a test substance preparation in olive oil DAB 10 by gavage to three male and three female fasted Wistar rats at dose levels of 200 and 2000 mg/kg bw, using an application volume of 5 ml/kg bw. The observation period lasted for up to 14 days.

Findings:
The stability of the test substance was verified by reanalysis. The stability of the test substance in the vehicle olive oil DAB 10 over a period of 4 hours was confirmed by analysis. The correctness of the concentration of the test substance preparation and its homogeneity were analytically proven. There was no mortality in either males or females. Signs of toxicity noted in the 2000 mg/kg bw dose group comprised impaired or poor general state, dyspnoea, apathy, staggering, exsiccosis, red discoloured urine, and smeared fur in the anogenital area. These symptoms were considered to be unspecific. Animals appeared normal after 6, 7 or 12 days after application. In the 200 mg/kg bw dose group no signs of toxicity were observed. Body weight development appeared to be normal. There were no macroscopic pathological findings in animals sacrificed at the end of the observation period.

Conclusion:
The oral LD_{50} was found to be > 2000 mg/kg bw for male and female rats.

B.6.8.1.1.5 Second acute oral toxicity study

Report: Wiemann C., Hellwig J., 1999
Report: Reg.-No. 292 564; BH 635-2: Acute oral toxicity in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/10099
and
Wiemann C., 1999
Amendment No. 1: Reg.-No. 292 564; BH 635-2 - Acute oral toxicity in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed.Rep.
unpublished
BASF RegDoc# 1999/10381

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 92/69, OECD 401

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M02 (Reg.-No. 292 564; BH 635-2); batch no. 00831-201, purity: 98.2 %.
Test animals: Wistar rats (Chbb:THOM (SPF))

Single administration of a test substance preparation in 0.5 % Tylose CB 30.000 in aqua bidest. Was given by gavage to five male and five female fasted Wistar rats at dose levels of 500, 2000 and 5000 mg/kg bw, using an application volume of 20 ml/kg bw. The observation period lasted for up to 14 days.

Findings:
The stability of the test substance over the study period was verified by reanalysis. The stability of the test substance in the vehicle over a period of 4 hours was confirmed by analysis. The correctness of the concentration of the test substance preparation and its homogeneity were analytically proven.
All animals of the 5000 mg/kg bw dose group died within 4 days after application. 9 animals (4 males and 5 females) of the 2000 mg/kg bw dose group died within 3 days after application. A delayed mortality (6 days after application) was observed in 1 female rat of the 500 mg/kg bw dose group. Signs of toxicity noted in all dose groups comprised impaired or poor general state, dyspnea, apathy, excitation, abdominal and lateral position, staggering, ataxia, atonia, paresis, narcotic-like state, pain and corneal reflex absent, tremor, spastic gait, erythema, exsiccosis, salivation, lacrimation, discoloured urine, squatting posture and red clammy snout and eyelid. The surviving animals appeared normal within 9 days after treatment. Body weight development appeared to be normal, except for one male rat of the 2000 mg/kg bw dose group, which showed weight reduction on day 7. Necropsy findings of the animals that died included liquid, bloody or discolored contents, or dilatation of the urinary bladder, erosion/ulcer in the glandular stomach, discoloration of contents or bloody contents of the stomach and/or small intestine, discoloration of the pancreas and kidneys, discoloration or edema in all lobes of the lung, discoloration or prominent lobular pattern of the liver and discharge of the nose. Histological examination revealed fatty infiltration of hepatocytes in the liver, vacuolation of tubular cells, tubular calcification in the medulla area, and degeneration of single tubules of the kidneys, dilatation, mucosal edema and ulceration with dystrophic calcification of the urinary bladder.

Conclusion:
The oral LD_{50} was found to be 1000 mg/kg bw for male and female rats.

B.6.8.1.2 635M03

635M03 (Reg.-No. 335 182; BH 635-3) is a soil metabolite. It was detected in the rat metabolism study as a transient metabolite. It was tested in three mutagenicity assays as well as in an acute oral test and a 90-day feeding study. Reg.-No. 335 182 was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw. The no observed adverse effect level in a 90-day dietary rat study was 15000 ppm (equal to 1187 mg/kg bw).

Table B.6.8-2: Summary of toxicity studies of metabolite 635M03

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in rats Wistar rats (Chbb:THOM (SPF))	Batch No. 00831-274, purity: 98.7 %; batch 01185-044, purity 99.4 %	$LD_{50:}$ > 5000 mg/kg bw
Subchronic toxicity study in Wistar rats. Administration in the diet for 3 months CRL:WI(GLX/BRL/HAN)IGS BR]	Batch No. 01185-269, purity: 99.2 %	No substance related effects. NOAEL: 15000 ppm (1187 mg/kg bw/d)
Salmonella typhimurium/Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch No. 00831-274, purity: 98.7 %	Not mutagenic
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT)	Batch No. 01185-085, purity: 99.8 %.	Not mutagenic
In vitro chromosome aberration assay in Chinese hamster V79 cells	Batch No. 01185-085, purity: 99.8 %.	Not mutagenic

B.6.8.1.2.1 First mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1998
Report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10810
and
Engelhardt G., 1999
Amendment No. 1 to the report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11629
and
Engelhardt G., 2000
Amendment No. 2 to the report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1019291
and
Engelhardt G., 2001
Amendment No. 3 to the report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1007726

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 92/69 B 13, EEC 92/69 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M03 (Reg.-No. 335 182; BH 635-3; batch no. 00831-274, purity: 98.7 %).
Test system: Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA
BH 635-3 (Reg.-No. 335 182) was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in DMSO. The study consisted of a standard plate test (with doses ranging from 20 to 5000 µg/plate) and preincubation test (with doses ranging from 20 to 5000 µg/plate) both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls (2-aminoanthracene - with S9 mix; N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and 4-nitroquinolineN-oxide - all without S9 mix) were tested.

A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate with or without S-9 mix,
- there is a dose-response relationship, and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of BH 635-3 in the vehicle DMSO over a period of 4 hours and in water over a period of 4 and 96 hours have been determined analytically. No test substance precipitation was observed. No bacteriotoxic effect was noticed. The mean number of revertant colonies was not increased in any strain either with or without S-9 activation. Expected increases in revertant colonies were obtained with the positive controls.

Conclusion:
According to the results of the study, BH 635-3 (Reg.-No. 335 182) is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay.

B.6.8.1.2.2 Second mutagenicity study

Report: Wollny H.-E., 1999
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT) with Reg.-No. 335 182; BH 635-3

RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/12026

GLP: Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)

Guideline: OECD 476, EEC 87/302

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M03 (Reg.-No. 335 182; BH 635-3; batch no. 01185-085, purity: 99.8 %.
Test system: Chinese hamster ovary (CHO) cells
635M03 (BH 635-3, Reg.-No. 335 182) was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, using two parallel cultures each either with or without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation). In an initial range-finding test the solubility of the test substance was reduced at doses > 300 µg/ml. No changes in osmolarity and pH-values were observed.
Therefore the test substance was evaluated at the following doses in the 1st experiment (4 hours exposure): Without and with S-9 mix 0: 18.8; 37.5; 75.0; 150.0; and 300.0 µg/ml.
A 2nd experiment for confirmation was performed using the following doses (4 hours exposure): Without and with S-9 mix: 0; 18.8; 37.5; 75.0; 150.0; and 300.0 µg/ml.
After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation, an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were stained with 10 % methylene blue in 0.01 % KOH solution and counted. For control purposes and to demonstrate the sensitivity of the test system, negative controls and two appropiate positive control chemicals 7,12-dimethylbenz(a)anthracene (with S9 mix) and Ethylmethane sulfonate (without S9 mix) were tested.
The criteria for a positive response are:
- Increases of the mutation frequencies, that are three times above the spontaneous mutation frequency at least at one of the concentrations in the experiment.
- Evidence of reproducibility of any increase in mutant frequencies.
- Evidence of a dose-response relationship, even if a threefold increase of the mutant frequency is not observed.

Findings:
The stability of 635M03 (BH 635-3; Reg.-No. 335 182) in the vehicle DMSO and in water has been confirmed by analysis. Moderate cytotoxicity was observed by reduced cloning efficiency at doses > 150 µg/ml and > 300 µg/ml (without metabolic activation) in the 1st experiment in culture I. The negative controls (untreated and vehicle controls) gave mutant frequencies within the range expected for the CHO cell line, except the negative and solvent control in culture I of the first experiment. This deviation was considered to be not of biological relevance since the effect was not observed in the parallel culture and the positive

control and the test substance gave results within the expected range. Appropriate positive control chemicals led to the expected increase in the frequencies of forward mutations. The test substance did not cause an increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other.

Conclusion:
Under the experimental conditions of this assay, 635M03 (BH 635-3; Reg.-No. 335 182) is considered to be non-mutagenic *in vitro* in the CHO/HPRT mutation assay.

B.6.8.1.2.3 Third mutagenicity study

Report: Czich A. et al., 1999
In vitro chromosome aberration assay in Chinese hamster V79 cells with Reg.-Nr. 335 182 (BH 635-3)
RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11504

GLP: Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)

Guideline: OECD 473, EEC 92/69, B 10

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M03 (Reg.-No. 335 182; BH 635-3; batch no. 01185-085, purity: 99.8 %.
Test system: V79 cells
635M03 (BH 635-3; Reg.-No. 335 182) was assessed for its potential to induce structural chromosomal aberrations in V79 cells of the Chinese hamster *in vitro* both in the presence and in the absence of a metabolising system (S-9 mix of Aroclor 1254-induced Sprague-Dawley rat liver).
Test substance precipitation in the pretest occurred at concentrations of ≥ 625 µg/ml with and without S-9 mix. According to the initial range-finding cytotoxicity test and the solubility properties of the test substance the following doses were evaluated.
1st experiment:
- 4 hours exposure, 14 hours recovery time, and 18 hours preparation interval; with and without S-9 mix: 0; 312.5; 625.0 and 1250.0 µg/ml,

2nd experiment:
- 18 hours exposure, 18 hours preparation interval, without S-9 mix: 0; 156.3; 312.5; and 625.0 µg/ml
- 18 hours exposure, 10 hours recovery time, and 28 hours preparation interval, without S-9 mix: 0; 1250.0 µg/ml
- 4 hours exposure, 24 hours recovery time, and 28 hours preparation interval, with S-9 mix: 0; 312.5; 625.0 and 1250.0 µg/ml

The cell cycle of the untreated V79 cells is about 13 - 14 hours under the selected culture conditions. Thus, the selected 1st sampling time of 18 hours was within the 1 - 1.5 x the normal cell cycle time, as recommended by the OECD Guideline No. 473. The later sampling time of 28 hours was chosen to cover a possible cell cycle delay. About 2 - 3 hours prior to harvesting the cells, colcemid was added to arrest cells in a metaphase-like stage of mitosis (c-metaphases). After preparation of the chromosomes and staining with Giemsa, 100 metaphases for each culture were analysed for chromosomal aberrations. For each experiment two cultures were used.
The criteria for a positive response are:

- The number of induced structural chromosomal aberrations are not in the range of the historical control data.
- Either a concentration-related or a significant increase of the number of structural chromosome aberrations are observed.

  A test substance is generally considered non clastogenic in this test system if:
- There was no significant increase in the number of chromosomally damaged cells at any dose above concurrent control frequencies.
- The aberration frequencies were within the historical control range.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of 635M03 (BH 635-3; Reg.-No. 335 182) in the vehicle DMSO and in water over a period of 4 hours was determined analytically. Test substance precipitation occurred at concentrations of 1250 µg/ml. In the 1st experiment no signs of toxicity were noticed up to the highest evaluated concentrations. Reduced mitotic indices were observed in the 2nd experiment after 18 hours of treatment without S-9 mix at the highest evaluated concentrations. Osmolarity and pH values were not influenced by test substance treatment. Both of the positive control chemicals, EMS (ethylmethane sulfonate) and cyclophosphamide, led to a significant increase ($p < 0,05$) in the number of cells with structural chromosomal aberrations. The test substance did not cause any biologically relevant or statistically significant increase in the number of cells carrying structural chromosomal aberrations in both independent experiments. No increase in the frequencies of polyploid metaphases was found after treatment with the test substance as compared to the frequencies of the control.

Conclusion:
635M03 (BH 635-3; Reg.-No. 335 182) is not a chromosome-damaging (clastogenic) agent under *in vitro* conditions in V79 cells.

B.6.8.1.2.4 Acute oral toxicity study

Report: Wiemann C., Hellwig J., 1998
Report: Reg.-No. 335 182 (BH 635-3): Acute oral toxicity in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10843
and
Wiemann C., 1999
Amendment No. 1: Reg.-No. 335 182 (BH 635-3) - Acute oral toxicity in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.

unpublished
BASF RegDoc# 1999/11221

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 92/69, OECD 401

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M03 (Reg.-No. 335 182; BH 635-3); batch no. 00831-274, purity: 98.7 %; batch no. 01185-044, purity 99.4 %.
Test animals: Wistar rats (Chbb:THOM (SPF))
Single administration of the test substance preparation in 0.5 % aqueous Tylose CB 30.000 by gavage to five male and five female fasted Wistar rats at dose levels of 2000 and 5000 mg/kg bw, using an application volume of 20 ml/kg bw. The observation period lasted for up to 14 days.

Findings:
The stability of the test substance was guaranteed. The stability of the test substance in the vehicle for a period of 4 hours was confirmed by analysis. The correctness of the concentration and its homogeneity were analytically confirmed. There was no mortality in either males or females. No signs of toxicity were noticed. Body weight development was normal. There were no macroscopic pathological findings in animals sacrificed at the end of the observation period.

Conclusion:
The oral LD_{50} was found to be > 5000 mg/kg bw for male and female rats.

B.6.8.1.2.5 Subchronic toxicity study

Report: Mellert W. et al., 2001
Report: Reg.-No. 335 182 (BH 635-3) – Subchronic toxicity study in Wistar rats. Administration in the diet for 3 months
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006072

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 408, EPA/OPPTS 870.3100

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M03 (Reg.-No. 335 182; BH 635-3); batch no. 01185-269, purity: 99.2 %.
Test animals: Wistar rats CRL:WI(GLX/BRL/HAN)IGS BR]
635M03 (BH 635-3) was administered to groups of 10 male and 10 female Wistar rats at dietary concentrations of 0; 1000; 5000; and 15000 ppm for 3 months. Food consumption, water consumption (from day 49 onward) and body weights were determined each week. The animals were examined for signs of toxicity or mortality at least once a day. Detailed clinical examinations in an open field were conducted prior to the administration period and weekly during the administration period. A functional observational battery (FOB) and motor activity measurement (MA) was carried out at the end of dosing. Ophthalmological examinations were carried out prior to the start and towards the end of dosing. Urinalysis, clinico-chemical and hematological examinations were carried out at the end of the administration period. All animals were subjected to gross-pathological assessment, followed by histopathological examinations.

Findings:
The stability of the test substance during the study period was demonstrated. The stability and homogeneous distribution of the test substance in the diet were confirmed by analysis. The correctness of the concentrations were analytically proven.

Table B.6.8-3: Test substance intake (mg/kg bw)

Dietary dose level (ppm)	Males	Females
1000	79	83
5000	392	478
15000	1187	1440

There were no mortalities or clinical signs of toxicity in any of the dose groups. Findings during FOB were assessed not to be test substance related and during MA there were no substance related effects noticed. There were no effects on body weight gain or food consumption in any of the dose groups. Clinical-chemical and hematological examinations did not show any treatment related changes in the parameters measured at any dose level either in males or females.
Urinalysis revealed increased numbers of crystals of unknown origin in 4 of 10 male and 8 of 10 females of the highest test group. In the mid dose group 9 of 10 female rats showed also an increased number of crystals. This were the only test substance related findings. They are considered to be of no pathological relevance, since the formation of crystals occurs when chemicals constituents become saturated and undergo altered solubilities when urine is stored at cooler temperatures. Therefore the formation of crystals is regarded as an artifact of the system of collection.
There were no test substance related effects seen in ophthalmoscopy. Organ weight determination did not show any relation to the treatment. Neither gross macroscopical nor microscopical examinations detected any test substance related changes in the organs. In conclusion no substance related adverse effects were observed in this study.

Conclusion:
The no observed adverse effect level in this 90-day dietary rat study was 15000 ppm (equal to 1187 mg/kg bw).

B.6.8.1.3 635M01

635M01 (Reg.-No. 335 184; BH 635-4) is a soil metabolite. It was detected in the rat metabolism study. It was tested in three mutagenicity assays as well as in an acute oral test. It was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells. An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw.

Table B.6.8-4: Summary of toxicity studies of metabolite Reg. 635M01

Study/strains/species	Test material/conditions	Results
Acute oral toxicity in rats Wistar rats (Chbb:THOM (SPF))	Batch no. 01185-088, purity: 97.0 %	LD_{50}: > 5000 mg/kg bw
Salmonella typhimurium/Escherichia coli reverse mutation assay S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch no. 00831-277, purity: 97.9 %	Not mutagenic
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT) Chinese hamster ovary (CHO) cells	Batch no. 01185-088, purity: 97.0 %	Not mutagenic
In vitro chromosome aberration assay in V79 cells (cells derived Chinese hamster)	Batch no. 01185-088, purity: 97.0 %	Not mutagenic

B.6.8.1.3.1 First mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1998
Report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with Reg.-No. 335 184 (BH 635-4)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11635

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 92/69 B 13, EEC 92/69 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M01 (Reg.-No. 335 184; BH 635-4); batch no. 00831-277, purity: 97.9 %.
Test system: Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA
635M01 was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The

Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in DMSO. The study consisted of a standard plate test (with doses ranging from 20 to 5000 µg/plate) and preincubation test (with doses ranging from 20 to 5000 µg/plate) both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls (2-aminoanthracene - with S9 mix; N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine, and 4-nitroquinoline-N-oxide - all without S9 mix) were tested.
A substance is considered positive in this test if the following criteria are met:

- there is at least a doubling of the negative control mutation rate with or without S-9 mix, there is a dose-response relationship, and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of 635M01 (Reg.-No. 335 184) in the vehicle DMSO over a period of 4 hours and in water over a period of 4 and 96 hours has been determined analytically. Test substance precipitation was observed at 5000 µg/plate. A slight bacteriotoxic effect was noticed at about 5000 µg/plate. The mean number of revertant colonies was not increased in any strain either with or without S-9 activation. Expected increases in revertant colonies were obtained with the positive controls.

Conclusion:
According to the results of the study, 635M01 (Reg.-No. 335 184) is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay.

B.6.8.1.3.2 Second mutagenicity study

Report:	Wollny H.-E. et al., 1999 Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79 / HPRT) with Reg.-No. 335 184; BH 635-4 RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep. unpublished BASF RegDoc# 1999/12016
GLP:	Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)
Guideline:	OECD 476, EEC 87/302
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: 635M01 (Reg.-No. 335 184; BH 635-4); batch no. 01185-088, purity: 97.0 %.
Test system: Chinese hamster ovary (CHO) cells

635M01 was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, using two parallel cultures each either with or without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation). In an initial range-finding solubility of the test substance was reduced at doses > 300 µg/ml. No changes in osmolarity and pH-values were observed. Due to the solubility of the test substance in DMSO the following doses were evaluated in the 1st experiment (4 hours exposure): Without and with S-9 mix: 0; 56.3; 112.5; 225.0; 450.0 and 900.0 µg/ml. A 2nd experiment for confirmation was performed using the following doses (4 hours exposure): Without and with S-9 mix: 0; 56.3; 112.5; 225.0; 450.0 and 900.0 µg/ml.
After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation, an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were stained with 10 % methylene blue in 0.01 % KOH solution and counted. For control purposes and to demonstrate the sensitivity of the test system, negative controls and two appropiate positive control chemicals 7,12-dimethylbenz(a)anthracene (with S9 mix) and Ethylmethane sulfonate (without S9 mix) were tested.
The criteria for a positive response are:

- Increases of the mutation frequencies, that are three times above the spontaneous mutation frequency at least at one of the concentrations in the experiment.
- Evidence of reproducibility of any increase in mutant frequencies.
- Evidence of a dose-response relationship, even if a threefold increase of the mutant frequency is not observed.

Findings:
The stability of 635M01 in the vehicle DMSO and in water was analytically confirmed. No cytotoxicity was observed at the maximum concentration of 900 µg/ml. Test substance precipitation occurred at > 450 µg/ml (1st experiment) and > 225 µg/ml (2nd experiment) in the absence and at > 900 µg/ml in the presence of metabolic activation throughout the experiments. The negative controls (untreated and vehicle controls) gave mutant frequencies within the range expected for the CHO cell line. Appropriate positive control chemicals led to the expected increase in the frequencies of forward mutations. The test substance did not cause an increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other.

Conclusion:
Under the experimental conditions of this assay, 635M01 is considered to be non-mutagenic *in vitro* in the CHO/HPRT mutation assay.

B.6.8.1.3.3 Third mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1999
Report: *In vitro* chromosome aberration assay with Reg.-Nr. 335 184 (BH 635-4) in V79 cells
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/11685

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 473, EEC 92/69 B 10

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M01 (Reg.-No. 335 184; BH 635-4); batch no. 01185-088, purity: 97.0 %.
Test system: V79 cells (Chinese hamster derived)

635M01 was assessed for its potential to induce structural chromosomal aberrations in V79 cells *in vitro* both in the presence and in the absence of a metabolising system (S-9 mix of Aroclor 1254-induced Sprague-Dawley rat liver). According to an initial range-finding cytotoxicity test and the solubility of the test substance the following doses were evaluated.
1st experiment:
- 4 hours exposure, 18 hours harvest time, with and without S-9 mix:
  0; 500; 1000; and 2000 µg/ml,

2nd experiment:
- 18 hours exposure, 18 hours harvest time, without S-9 mix:
  0; 500; 1000; and 2000 µg/ml,
- 18 hours exposure, 28 hours harvest time, without S-9 mix:
  0; 2000 µg/ml
- 4 hours exposure, 28 hours harvest time, with S-9 mix:
  0; 500; 1000; and 2000 µg/ml.

The cell cycle of the untreated V79 cells is about 13 - 14 hours under the selected culture conditions. Thus, the selected 1st sampling time of 18 hours was within the 1 - 1.5 x the normal cell cycle time, as recommended by the OECD Guideline No. 473. The later sampling time of 28 hours was chosen to cover a possible cell cycle delay. About 2 - 3 hours prior to harvesting the cells, colcemid was added to arrest cells in a metaphase-like stage of mitosis (c-metaphases). After preparation of the chromosomes and staining with Giemsa, 100 metaphases for each culture in the case of the test substance and vehicle controls, or 50 cells for each culture in the case of the concurrent positive controls, were analysed for chromosomal aberrations.

The criteria for a positive response are:
- A dose-related and reproducible significant increase in the number of structural chromosomal aberrations.
- The proportion of aberrations exceeded both the concurrent negative control range and the negative historical control range.

A test substance is generally considered non clastogenic in this test system if:
- There was no significant increase in the number of chromosomally damaged cells at any dose above concurrent control frequencies.
- The aberration frequencies were within the historical control range.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. Homogeneity of the test substance was achieved by mixing and was verified by analysis. The stability of a comparable batch in the vehicle DMSO over a period of 4 hours and in water for 96 hours has been determined analytically. Test substance precipitation occurred at concentrations of 1000 µg/ml and higher. According to the results of the determination of the mitotic index, no suppression of the mitotic activity was observed under any of the experimental conditions. No growth inhibition was noticed by cell count. Cell attachment was slightly reduced from about 1000 µg/ml. Osmolarity and pH values were not influenced by test substance treatment. The negative controls (vehicle controls) gave frequencies of aberrations within the range expected for the V79 cell line. Both of the positive control chemicals, EMS (ethyl methane sulfonate) and cyclophosphamide, led to the expected increase in the number of cells containing structural chromosomal aberrations.

On the basis from the results of the present study, the test substance did not cause any increase in the number of structurally aberrant metaphases incl. and excl. gaps at both sampling times either without S-9 mix or after adding a metabolising system in two experiments performed independently of each other. No increase in the frequency of cells containing numerical aberrations was demonstrated either.

Conclusion:
635M01 is not a chromosome-damaging (clastogenic) agent under *in vitro* conditions in V79 cells.

B.6.8.1.3.4 Acute oral toxicicty study

Report: Wiemann C., Hellwig J., 1999
Report: Reg.-No. 335 184 (BH 635-4) - Acute oral toxicity in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/10213

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 92/69, OECD 401

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M01 (Reg.-No. 335 184; BH 635-4); batch no. 01185-088, purity: 97.0 %.
Test animals: Wistar rats (Chbb:THOM (SPF))

Single administration of a aqueous test substance preparation by gavage to five male and five female fasted Wistar rats at dose levels of 5000 mg/kg bw, using an application volume of 20 ml/kg bw respectively. The observation period lasted for up to 14 days.

Findings:
The stability of the test substance was guaranteed for the duration of the study. The homogeneity of the test substance was confirmed by analysis. The stability of the test substance in aqua bidest for a time period of 96 hours was confirmed by analysis. The correctness of the concentration and the homogeneity of the test substance preparation were analytically confirmed. There was no mortality in either males or females. Signs of toxicity were not noted. Body weight development appeared to be normal. There were no macroscopic pathological findings in animals sacrificed at the end of the observation period.

Conclusion:
The oral LD_{50} was found to be > 5000 mg/kg bw for male and female rats.

B.6.8.1.4 635M17

635M17 (Reg.-No. 373 906) is a plant metabolite. It was detected in the rat metabolism study in minor quantities. It was tested in three mutagenicity assays as well as in an acute oral test. It was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) *in vivo*. There were no indications of any impairment of chromosome distribution in the course of mitosis.
An acute oral toxicity study revealed an LD_{50} of > 2000 mg/kg bw.

Table B.6.8-5: Summary of toxicity studies of metabolite 635M17

Study/strains/species	Test material/ conditions	Results
Acute oral toxicity study in Wistar rats Crl: WI(GLX/BRL/HAN)IGS BR (SPF)	Batch no. 01742-22, purity: 98.3 %	$LD_{50:}$ > 2000 mg/kg bw
Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch no. 01742-22, purity: 98.3 %.	Not mutagenic
In vitro gene mutation test in Chinese hamster ovary (CHO) cells (HPRT Locus Assay)	Batch no. 01742-22, purity: 98.3 %	Not mutagenic
Cytogenetic study *in vivo* in the mouse micronucleus test after two intraperitoneal administrations (NMRI mice)	Batch no. 01742-22, purity: 98.3 %.	Not mutagenic

B.6.8.1.4.1 First mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 2000
Report: Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test) with Reg.-No. 373 906
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006087

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 2000/32 B 13, EEC 2000/32 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M17 (Reg.-No. 373 906); batch no. 01742-22, purity: 98.3 %
Test system: Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA

635M17 (Reg.-No. 373 906) was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in acetone. The study consisted of a standard plate test (with doses ranging from 20 to 5000 µg/plate) and preincubation test (with doses ranging from 4 to 2500 µg/plate) both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.

For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls (2-aminoanthracene - with S9 mix; N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and 4-nitroquinoline-N-oxide - all without S9 mix) were tested.
A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate with or without S-9 mix,
- there is a dose-response relationship, and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of Reg.-No. 373 906 in the vehicle acetone and in water over a period of 4 hours has been determined analytically. No test substance precipitation was observed. A slight bacteriotoxic effect was noticed from about 500 – 2500 µg/plate depending on the strain and test conditions. The mean number of revertant colonies was not increased in any strain either

with or without S-9 activation. Expected increases in revertant colonies were obtained with the positive controls.

Conclusion:
According to the results of the study, 635M16 is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay.

B.6.8.1.4.2 Second mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 2000
Report: *In vitro* gene mutation test with Reg.-No. 373 906 in CHO cells (HPRT Locus Assay)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006073

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 476, EEC 2000/32 B 17

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M17 (Reg.-No. 373 906); batch no. 01742-22, purity: 98.3 %.
Test system: Chinese hamster ovary (CHO) cells

Reg.-No. 373 906 was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, using two parallel cultures each either with or without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation).

In an initial range-finding test cytotoxicity was observed by reduced cloning efficiency at doses > 1000 µg/ml (with and without metabolic activation). Precipitation of the test substance occurred at doses > 1000 µg/ml. No changes in osmolarity and pH-values were observed.
Thus, the test substance was evaluated at the following doses in the 1st experiment (4 hours exposure): Without S-9 mix: 0; 31.25; 62.5; 125; 250; 500; and 1000 µg/ml
With S-9 mix: 0; 62.5; 125; 250; 500; 1000; and 2000 µg/ml
A 2nd experiment for confirmation was performed using the following doses (4 hours exposure): Without and with S-9 mix: 0; 62.5; 125; 250; 500; 1000; and 2000 µg/ml.

After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation, an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were fixed with methanol, stained with Giemsa, and counted. For control purposes and to demonstrate the sensitivity of the test system,

negative controls and two appropiate positive control chemicals methylcholanthrene (with S9 mix) and Ethyl methane sulfonate (without S9 mix) were tested.

The criteria for a positive response are:
- Increases of the corrected mutation frequencies above the concurrent negative control values and above 15 mutants per 106 clonable cells and/or the evidence of a dose response relationship in the increase in mutant frequencies.
- Evidence of reproducibility of any increase in mutant frequencies.
- A statistically significant increase in mutant frequencies and the existence of a dose-response relationship.

Findings:
The stability of the test substance throughout the study period was determined by reanalysis. Its homogeneity was guaranteed. The stability of Reg.-No. 373 906 in the vehicle acetone and in water over a period of 4 hours was verified by analysis. Cytotoxicity was observed at > 1000 µg/ml (with and without metabolic activation). The negative controls gave mutant frequencies within the range expected for the CHO cell line. Both of the positive control chemicals led to the expected increase in the frequencies of forward mutations. The test substance did not cause any increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other.

Conclusion:
Under the experimental conditions of this assay, 635M17 (Reg.-No. 373 906) is considered to be non-mutagenic *in vitro* in the CHO/HPRT mutation assay.

B.6.8.1.4.3 Third mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 2000
Report: Cytogenetic study *in vivo* with Reg.-No. 373 906 in the mouse micronucleus test after two intraperitoneal administrations
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1018736

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 474, EEC 2000/32 B 12

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M17 (Reg.-No. 373 906); batch no. 01742-22, purity: 98.3 %.
Test animals: NMRI mice

635M17 was tested for clastogenicity and for the ability to induce spindle poison effects in NMRI mice using the micronucleus test method. For this purpose the test substance, suspended in an aqueous 0.5 % CMC (carboxymethyl cellulose) formulation, was administered twice intraperitoneally with an 24-hour interval between administration, to male animals at dose levels of 100 mg/kg, 200 mg/kg and 400 mg/kg body weight in a volume of 10 ml/kg body weight in each case.

As a negative control the vehicle, 0.5 % CMC was applicated to male mice by the same route. As a positive control, 20 mg cyclophosphamide (CPP)/kg body weight or 0.15 mg vincristine sulphate (VCR)/kg body weight, both, dissolved in purified water, were administered to male and female animals once intraperitoneally each in a volume of 10 ml/kg body weight.

The animals were sacrificed and the bone marrow of the two femora was prepared 24 hours after the second administration. After staining of the preparations, 2000 polychromatic erythrocytes were evaluated per animal and investigated for micronuclei. The normocytes with and without micronuclei occurring per 2000 polychromatic erythrocytes were also registered.

The test chemical is to be considered positive in this assay if the following criteria are met:
- A dose-related and significant increase in the number of micronucleated polychromatic erythrocytes.
- The proportion of cells containing micronuclei exceed both, the values of the concurrent negative control range and the negative historical control range.

Findings:
The stability of the test substance was verified by reanalysis. Homogeneity of the test substance was achieved by mixing. The stability of Reg.-No. 373 906 in water over a period of 4 hours was analytically confirmed. The homogeneity of the test substance in the vehicle was guaranteed by constant stirring before removal and administration and by analytical determination of 3 individual samples of each concentration. Animals which were administered the vehicle or the positive control substances cyclophosphamide or vincristine did not show any clinical signs of toxicity. The administration of the test substance led to evident signs of toxicity as there were piloerection and squatting posture in all dose groups. All animals recovered within of 2 days after treatment at latest. The negative control gave frequencies of micronucleated polychromatic erythrocytes within the historical control range. Both of the positive control chemicals, cyclophosphamide for clastogenicity and vincristine for aneugenic effects, led to the expected increase in the rate of polychromatic erythrocytes containing small or large micronuclei. An inhibition of erythropoiesis determined from the ratio of polychromatic to normocromatic erythrocytes induced by the treatment of mice with Reg.-No. 373 906 was detected at a dose of 400 mg kg body weight.
According to the results of the present study, the two intraperitoneal administrations of Reg.-No. 373 906 did not lead to any increase in the number of polychromatic erythrocytes containing either small or large micronuclei. The rate of micronuclei was always in the same range as that of the concurrent negative control in all dose groups and within the range of the historical control data.

Conclusion:
The test substance 635M17 (Reg.-No. 373 906) has no chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis.

B.6.8.1.4.4 Acute oral toxicity study

Report: Gamer A. O., Hoffmann H. D., 2000
Report: Reg.-No. 373 906 – Acute oral toxicity study in Wistar rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006074

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 423, EEC 96/54

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M17 (Reg.-No. 373 906); batch no. 01742-22, purity: 98.3 %.
Test animals: Wistar rats (SPF) Crl: WI(GLX/BRL/HAN)IGS BR

Single administration of the test substance preparation in 0.5 % aqueous Tylose® by gavage to three male and three female fasted Wistar rats at dose levels of 2000 mg/kg bw, using an application volume of 10 ml/kg bw. The observation period lasted for up to 14 days.

Findings:
The stability and homogeneity of the test substance was guaranteed. The stability of the test substance in distilled water for a period of 4 hours was confirmed by analysis. The correctness of the concentration of the test substance preparation and its homogeneity were analytically confirmed. There was no mortality in either males or females. No signs of toxicity were noticed. Body weight development was normal during the study period. There were no macroscopic pathological findings in animals sacrificed at the end of the observation period.

Conclusion:
The oral LD_{50} was found to be > 2000 mg/kg bw for male and female rats.

B.6.8.2 Supplementary studies – AMTT (635M04)

AMTT was an impurity in the batch no. N24 (2.45 %). It is also a metabolite in the rat, soil and water. A separate metabolism study was conducted with AMTT, it was tested in an acute oral test, as well as in three mutagenicity tests. Furthermore, in order to prove that the effects seen in the 2-generation study using tritosulfuron batch no. N24 was due to high AMTT content, it was tested in a pre/postnatal toxicity study. In order to understand the mechanism

by which AMTT exerts its effects it was subjected to two additional studies: a subchronic toxicity study with estrus cycle determination as well as hormone analysis and determination of the binding capacity to the estrogen receptor.
AMTT does not accumulate in rats, but is effectively excreted. The major metabolite AHTT is generated by demethylation and is detected as different tautomeric structures. The oral LD_{50} was found to be > 200 < 2000 mg/kg bw. Estrus cycle determination, hormone analysis as well as PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes in a subchronic toxicity study. AMTT is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse and therefore is considered to be non-mutagenic in this micronucleus assay. The oral application of AMTT induced severe maternal and developmental toxicity at 20 mg/kg bw/day and at 50 mg/kg bw/day in a pre/postnatal screening study. Therefore, AMTT might be responsible for the effects observed in the 2-generation study with tritosulfuron containing high levels of AMTT, with respect to pup mortality. In the presence of endogenous estrogens, the bonding capacity of tritosulfuron and AMTT to the estrogen receptor is regarded as extremely low. A biological effect of the substances, the activation of the receptor-mediated gene expression, is extremely unlikely.

Table B.6.8-6: Summary of supplementary studies with AMTT (635M04) (CAS-Nr. 5311-05-07)

Study/strains/species	Test material/ conditions	Results
Study of the biokinetics and metabolism in Wistar rats (Chbb:THOM (SPF))	14C-AMTT; Batch no. 687-1008, chemical purity > 98 %, radiochemical purity: > 95 %.	Rapid exceretion, major metabolite: AHTT
Study on the acute oral toxicity of AMTT in Wistar rats (Chbb:THOM (SPF))	Batch no. 27 939/16, purity: 92.3 % - 94.2 %.	LD_{50}: > 200 < 2000 mg/kg bw
Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats (Chbb:THOM (SPF)) Administration in the diet up to 32 weeks 0, 40, 120 ppm	Batch no. 01185-097, purity: 99.9 %	LOAEL: 40 ppm (3.6 mg/kg bw/d): Estrus cycle determination, hormone analysis, PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes.
Ames Salmonella/mammalian-microsome mutagenicity test and Escherichia coli / mammalian microsome reverse mutation assay (standard plate test and preincubation test) S. typhimurium strains TA 100, TA 1535, TA 1537, TA 98 and E. coli strain WP2 uvrA	Batch no. 27 939/16, purity: 92.3 % - 94.2 %.	Not mutagenic
Gene mutation assay in Chinese hamster ovary (CHO) V79 cells *in vitro* (V79/HPRT) with AMTT	Batch no. 01185-097, purity: 99.9 %.	Not mutagenic
Micronucleus assay in bone marrow cells of the mouse (NMRI) after a single intraperitoneal administration	Batch no. 27939-141 CP031929, purity: 99.8 %.	Not mutagenic
AMTT and BisSH - Pre-/ postnatal screening toxicity study in Wistar rats (Chbb: THOM (SPF)) – Oral administration (gavage)	Batch no. CP031929, purity: 99.8 %, BisSH; batch no. CP 031930, purity: 99.7 %	Severe maternal and developmental toxicity at 20 mg/kg bw/d and at 50 mg/kg bw/d AMTT
Study of a possible bond of AMTT and tritosulfuron to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line	Endometrial RUCA-I-adenocarcinoma cell line of the rats	Extremely low bonding capacity of tritosulfuron and AMTT to the estrogen receptor in the presence of endogenous estrogens

B.6.8.2.1 Study of the biokinetics and metabolism in rats

Report: Leibold E. et al., 2001
14C-Reg.-No. 231 700 - Study of the biokinetics and metabolism in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1018485

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

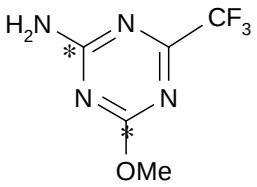
Guideline: EPA/OPPTS 870.7485

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 14C-Reg.-No. 231 700; (635M04; AMTT); batch: 687-1008, chemical purity > 98 %, radiochemical purity: > 95 %.
Test animals: Wistar rats Chbb:THOM (SPF)

14C-Labelled AMTT (2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine-2,4-14C) was fed to female Wistar rats at 0.25 mg/kg bw as one single oral dose. The test substance was solubilised in 0.5 % aqueous Tylose for administration. In the excretion experiment the dose solution was administered to five animals and urine and faeces were collected throughout seven days. In the bile experiment four female rats were dosed and only bile was collected up to 48 hours.

Figure B.6.8-1 Structure and position of the ^{14}C-label of AMTT (Reg.-No.: 231 700)



* [14C-Triazine label]

Excretion balances were determined and metabolite patterns were investigated by radio-HPLC from urine, faeces extracts and bile. The relevant transformation products of AMTT were identified.

Findings:
Absorption, Distribution and Excretion of Radioactivity
The amounts of radioactivity excreted within seven days via urine and faeces accounted for 91.9 % and 7.3 % of the dose, respectively. Via bile, 7.3 % of the dose were excreted within 48 hours. Overall, the test substance was rapidly and completely absorbed from the gastrointestinal tract. The excretion of radioactivity occurred predominantly via urine. Within the first 24 hours 53 % of the dose were excreted. Remaining radioactivity in organs and tissues was significantly below 0.5 % of the dose.

Metabolite Patterns and Metabolite Identities
For isolation of metabolites, all matrices were analysed by HPLC. The resulting metabolite pattern of urine mainly showed the demethylated metabolite AHTT (2-amino-4-hydroxy-6-(trifluoromethyl)-1,3,5-triazine) which was identified by mass spectrometry. Including the tautomeric forms of AHTT, the relative quantities accounted for 73.6 % of the dose within the first 72 hours. Remaining AMTT in urine accounted for 7.9 % of the dose. Faeces collected from 0-72 hours contained 4.3 % of the dose as AMTT and 2.3 % of the dose as AHTT and its

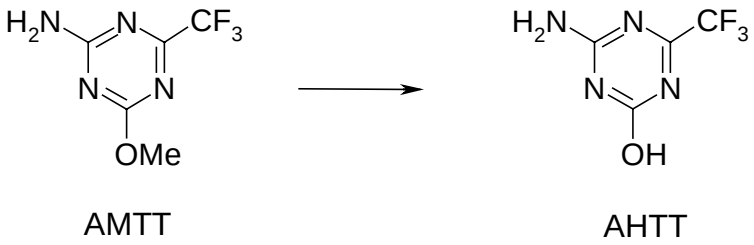
tautomers. Bile almost exclusively showed AMTT excreted at 6.9 % of the dose within 48 hours.

Table B.6.8-7: Summary of identified metabolites in urine, faeces and bile after administration of a single oral dose of [triazine-^{14}C]-AMTT at 0.25 mg/kg bw. Excretion in % of dose within specified time period.

Metabolite identity	Urine (0-72 h)	Faeces (0-72 h)	Bile (0-48 h)
	female	female	female
AMTT	7.9	4.3	6.9
AHTT	73.6	2.3	-

Metabolic Pathway
The metabolism of AMTT resulted in the predominant formation of the demethylated compound AHTT and its tautomeric structures [see Figure B.6.8-2].

Figure B.6.8-2 Metabolic pathway of ^{14}C-AMTT (635M04) in rats:



Conclusion:
AMTT does not accumulate in rats, but is effectively excreted. The major metabolite AHTT (635M11) is generated by demethylation of the parent compound and is detected as different tautomeric structures.

B.6.8.2.2 Study on the acute oral toxicity

Report:
Poelloth C., Hellwig J., 1996
Study on the acute oral toxicity of AMTT, tech. CAS-Nr. [5311-05-7] in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1996/1000678
and
Poelloth C., 1997
Amendment No. 1 to the report: Study on the acute oral toxicity of AMTT, techn. in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/1000919

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04), techn., CAS-Nr. 5311-05-07; batch no. 27 939/16, purity: 92.3 % - 94.2 %.
Test animals: Wistar rats Chbb:THOM (SPF)

Single administration of the test substance preparation in 0.5 % aqueous Tylose CB 30.000 by gavage to three male and three female fasted Wistar rats at dose level of 200 and to three female fasted Wistar rats at dose level of 2000 mg/kg bw. The application volume was 10 ml/kg bw. The observation period lasted for up to 14 days.

Findings:
The stability of the test substance over the study period was guaranteed. The stability of the test substance in water for 96 hours was confirmed by analysis. The correctness of the concentration of the test substance in the vehicle and its homogeneity were analytically confirmed.
All animals of the 2000 mg/kg bw died within one day after application. There was no mortality in the 200 mg/kg bw dose group. Signs of toxicity in both dose groups comprised impaired or poor general state, dyspnoea, apathy, abdominal or lateral position, staggering, ataxia, atonia, paresis, narcotic-like state, pain reflex absent, twitching, erythema, anemic pallor, exsiccosis, salivation, lacrimation, red clammy snout and eyelid and compulsory gnawing. Body weight development appeared to be normal. During necropsy the animals that died showed erosion/ulcer in the glandular stomach, agonal congestion, discoloration of contents of the urinary bladder, and discoloration of the small intestines and the caecum. There were no macroscopic pathological findings in animals sacrificed at the end of the observation period.

Conclusion:
The oral LD_{50} was found to be > 200 < 2000 mg/kg bw for male and female rats.

B.6.8.2.3 Subchronic toxicity study

Report: Mellert W. et al., 2001(j)
Report: AMTT - Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats. Administration in the diet up to 32 weeks
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1006078

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: No test guidelines exist for this type of study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04); batch no. 01185-097, purity: 99.9 %
Test animals: Wistar rats [Chbb:THOM (SPF)]

In order to detect a possible influence of AMTT (2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine) on estrus cycle, hormonal status and/or cell proliferation in the mammary gland, AMTT was administered to groups of 30 female Wistar rats at dietary concentrations of 0, 40 and 120 ppm up to 32 weeks. The animals were observed for abnormal clinical signs at least once a day. Food consumption, water consumption and body weight were determined. Vaginal smears for estrus cycle determination were prepared and evaluated from day 70 to day 100. After 16 weeks of treatment, blood was taken from each 10 animals per group being in diestrus, and from each 10 animals per group being in proestrus. Luteinising hormone, progesterone, prolactin and estradiol were determined. Thereafter, these animals were subjected to gross-pathological assessment, followed by histopathological examinations. Proliferating cell nuclear antigen (PCNA) was evaluated in the mammary gland.

The remaining 10 animals per group were treated up to 32 weeks. Vaginal smears for estrus cycle determination were prepared and evaluated in these animals from day 147 to day 164 and day 202 to day 224. Towards the end of treatment period, osmotic minipumps were implanted three days prior to necropsy for evaluation of cell proliferation (S-phase response) and apoptosis in the mammary gland. All animals were subjected to gross-pathological assessment without further examinations.

Findings:
The stability of the test substance was proven by reanalysis during the in-life phase of the study. The stability of the test substance in the diet over a period of up to 34 days at room temperature was verified. As the mixtures were stored no longer than this time period, the stability was guaranteed. The homogeneity of the mixtures was verified; the correctness of the concentrations was analytically confirmed.

Table B.6.8-8: AMTT - Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats - Test substance intake

Dietary dose level (ppm)	Test substance intake (mg/kg bw/d)
40	3.6
120	11.1

Clincial signs of toxicity were piloerection and increased water consumption in the high dose group, as well as reduced food consumption and body weight in both treatment groups.

In the estrus cycle determination from day 202 to day 224, the mean days from estrus to estrus were statistically significantly reduced in both dose groups. This was, however, most probably due to the high value (with a high standard deviation) in the control group rather than being a

substance-related effect. Moreover, as no effect was seen regarding the single estrus stages, a substance-related effect was not assumed.
Hormone analyses revealed no test substance-related changes in the treated animals either on diestrus or on proestrus.
After both treatment periods, the terminal body weights of dose 1 (40 ppm) and dose 2 (120 ppm) groups showed a significant, dose–dependent decrease which is regarded to be treatment–related. The slightly increased number of erosions/ulcers in the glandular stomach (0/20 in control, 3/20 in group 1, 4/20 in group 2) noted at necropsy (16–week groups only) , is most probably due to the general toxicity ("stress phenomenon"), indicated by the terminal body weight decrease.
Neither macroscopy nor histopathology of the mammary gland, the uterus and the vagina revealed a treatment – related change of structure.
PCNA or BrdU – labeling of the mammary gland did not detect any significant increase of labeling indices after 16 as well as 32 weeks of treatment. Thus, no induction of cell proliferation was detected. The slight significant decrease of the PCNA–labeling index in top dose females is interpreted as being incidental and of no biological significance. A compound–related influence on apoptosis was not found (TUNEL–stain) when the labeling indices of control and top dose female mammary glands of the 32–week treatment group were compared.
Estrogen (Eα) – and progesterone receptors could be recognized in uterus and vagina of control and top dose animals of the 16–week treatment groups. However, the density of receptors did not change, when control and top dose group animals were compared semiquantitatively, indicating no influence on these parameters under the conditions of this study.
In conclusion, the following substance-related effects were obtained (Table B.6.8-9):

Table B.6.8-10: AMTT - Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats - substance related effects

Dietary dose level (ppm)	Effects
40 ppm	Reduced food consumption, predominantly in the early phase of the study, reduced body weight (up to 10.5 %), reduced body weight change (24.2 %), slight increase of erosions/ulcers in the glandular stomach (3/20)
120 ppm	Piloerection in 6 animals, reduced food consumption in the early phase of the study, increased water consumption, reduced body weight (13.9 %), reduced body weight change (39.5 %), slight increase of erosions/ulcers in the glandular stomach (4/20).

Conclusion:
Thus, only general signs of toxicity were observed in both treatment groups. The LOAEL was 40 ppm (equal to 3.6 mg/kg bw/d). Estrus cycle determination, hormone analysis as well as PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes.

B.6.8.2.4 First mutagenicity study

Report: Engelhardt G., Hoffmann H. D., 1996
Report on the study of AMTT, techn. CAS-Nr. [5311-05-7] in the Ames Salmonella/mammalian-microsome mutagenicity test and Escherichia coli / mammalian microsome reverse mutation assay (standard plate test and preincubation test)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1996/1000679
and
Engelhardt G., 1997
Amendment No. 1 to the report on the study of AMTT, techn. CAS-Nr. [5311-05-7] in the Salmonella typhimurium/Escherichia coli reverse mutation assay (standard plate test and preincubation test)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/1000920

GLP: Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 471, OECD 472, EEC 92/69 B 13, EEC 92/69 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04), techn., CAS-Nr. 5311-05-07; batch no. 27 939/16, purity: 92.3 % - 94.2 %.
Test system: Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA
AMTT, techn. CAS-Nr. [5311-05-7] was tested for its mutagenic potential based on the ability to induce back mutations in selected loci of several bacterial strains in the Ames reverse mutation assay. The Salmonella typhimurium strains TA 100, TA 1535, TA 1537 and TA 98 and Escherichia coli strain WP2 uvrA were exposed to the test substance dissolved in DMSO. The study consisted of a standard plate test (with doses ranging from 20 to 5000 µg/plate) and preincubation test (with doses ranging from 20 to 5000 µg/plate) both with and without metabolic activation (Aroclor induced Sprague-Dawley rat liver S-9 mix). Three plates were used per dose for each strain and test condition.
For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S9 mix) and positive controls (2-aminoanthracene - with S9 mix; N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and N-ethyl-N'-nitrosoguanidin - all without S9 mix) were tested.

A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate with or without S-9 mix,
- there is a dose-response relationship, and
- the results are reproducible.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of AMTT techn. CAS-Nr. [5311-05-7] in the vehicle DMSO and in water has been determined analytically. No test substance precipitation was observed. No bacteriotoxic effect was noticed. The mean number of revertant colonies was not increased in any strain either with or without S-9 activation. Expected increases in revertant colonies were obtained with the positive controls.

Conclusion:
According to the results of the study, AMTT techn. CAS-Nr. [5311-05-7] is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay.

B.6.8.2.5 Second mutagenicity study

Report: Wollny H.-E. et al., 1999
Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79/HPRT) with AMTT
RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep.
unpublished
BASF RegDoc# 1999/10870

GLP: Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)

Guideline: EEC 87/302, OECD 476

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04); batch no. 01185-097, purity: 99.9 %.
Test system: Chinese hamster ovary (CHO) cells
AMTT, techn. CAS-Nr. [5311-05-7] was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells *in vitro*. Two independent experiments were carried out, using two parallel cultures each either with or without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation).
In an initial range-finding test, precipitation of the test substance occurred at doses > 1000 µg/ml. No changes in osmolarity and pH-values were observed. Thus, the test substance was evaluated at the following doses in the 1st experiment (4 hours exposure): 125.0; 250.0; 500.0; 1000.0; and 2000.0 µg/ml (without and with S-9 mix). A 2nd experiment for confirmation was performed using the following doses (4 hours exposure): 125.0; 250.0; 500.0; 1000.0; and 2000.0 µg/ml (without and with S-9 mix). After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation, an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were stained with 10 % methylene blue in 0.01 % KOH solution and counted. For control purposes and to demonstrate the sensitivity of the test system, negative controls

and two appropriate positive control chemicals 7,12-dimethylbenz(a)anthracene (with S9 mix) and Ethylmethane sulfonate (without S9 mix) were tested.
The criteria for a positive response are:

- Increases of the mutation frequencies, that are three times above the spontaneous mutation frequency at least at one of the concentrations in the experiment.
- Evidence of reproducibility of any increase in mutant frequencies.
- Evidence of a dose-response relationship, even if a threefold increase of the mutant frequency is not observed.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of AMTT, techn. CAS-Nr. [5311-05-7] in the vehicle DMSO and in water has been confirmed by analysis. No cytotoxicity was observed up to the maximal concentration of 2000 µg/ml. In both main experiments precipitation of the test substance occurred at the highest test concentration of 2000 µg/ml. The negative controls (untreated and vehicle controls) gave mutant frequencies within the range expected for the CHO cell line. Appropriate positive control chemicals led to the expected increase in the frequencies of forward mutations.
The test substance did not cause a relevant increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other. An isolated increase exceeding the threshold of three times of the corresponding solvent control was observed at the maximal concentration of experiment I, culture I (with S-9 mix). This increase was judged as biologically irrelevant since it is based upon statistical fluctuations at such low absolute numbers. The corresponding solvent control is close to the lower border of historical solvent controls. Compared to the corresponding negative control the threshold is not reached. Furthermore the effect was not reproduced in the parallel culture and the absolute value remained well within the range of the historical negative controls.
Thus it can be stated that in this mutagenity assay and under the experimental conditions reported the test substance did not induce gene mutations at the HPRT locus in V 79 cells.

Conclusion:
Under the experimental conditions of this assay, AMTT, techn. CAS-Nr. [5311-05-7] is considered to be non-mutagenic *in vitro* in the CHO/HPRT mutation assay.

B.6.8.2.6 Third mutagenicity study

Report: Voelkner W. et al., 1998
Micronucleus assay in bone marrow cells of the mouse after a single intraperitoneal administration of AMTT
RCC Cytotest Cell Research GmbH, Roßdorf, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/11043

GLP: Yes (Laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)

Guideline: OECD 474, EEC 92/69, B 12

Deviations: In deviation to the protocol for a short period the relative humidity was higher than 70 % (highest value 88 %). In deviation to the protocol for the test groups vehicle and test article at preparation interval 48 hours 4000 instead of 2000 PCEs were scored for micronuclei. These deviations had no influence on the integrity and validity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04); batch no. 27939-141 CP031929, purity: 99.8 %.
Test animals: NMRI mice
AMTT, techn. CAS-Nr. [5311-05-7] was tested for its potential to induce micronuclei in polychromatic erythrocytes (PCE) in the bone marrow of male mice. For this purpose the test substance was formulated in DMSO (dimethylsulfoxide) and was administered once intraperitoneally to male animals in a volume of 4 ml/kg bw. After 24 hours and 48 hours post application the bone marrow cells were collected for micronuclei analysis.
Five animals were evaluated per test group for the occurrence of micronuclei. 2000 or 4000 (test group at preparation interval 48 hours; two independent evaluations of 2000 PCEs in order to verify the results) polychromatic erythrocytes (PCEs) per animal were scored for micronuclei. To describe a cytotoxic effect due to the treatment with the test article the ration between polychromatic and normochromatic erythrocytes (NCEs) was determined in the same sample. As a negative control the vehicle, DMSO was applicated to male mice by the same route. As a positive control, 30 mg cyclophosphamide (CPP)/kg body weight dissolved in deionised water, were administered to male animals once intraperitoneally in a volume of 10 ml/kg body weight.
The following dose levels of the test substance were investigated:
- 24 hours preparation interval: 6.25; 12.5; and 25.0 mg/kg bw.
- 48 hours preparation interval: 25.5 mg/kg bw.

The highest dose was estimated by pre-experiments to be close to the maximum tolerated dose. The animals expressed toxic reactions. The test chemical is to be considered positive in this assay if the following criteria are met:
- A dose-related increase in the number of micronucleated polychromatic erythrocytes or a statistically significant positive response for at least one of the test points.

Findings:
The stability of the test substance was determined by reanalysis. The stability of AMTT, techn. CAS-Nr. [5311-05-7] in DMSO for a period of 4 hours was determined by analysis. The concentrations of the test substance in the vehicle were analytically determined. The administration of the test substance led to evident signs of toxicity. Application of the positive control chemical cyclophosphamide led to a statistically significant increase of induced micronucleus frequency. The mean number of normochromatic erythrocytes was not substantially increased after treatment with the test article as compared to the mean value of NCEs of corresponding vehicle controls indicating that AMTT had no cytotoxic properties in the bone marrow.
In comparison to the corresponding vehicle controls there was no significant or biologically relevant enhancement in the frequency of the detected micronuclei at preparation interval 24 hours after administration of the test article. A statistically enhancement of the micronucleus

frequency at preparation interval 48 hours is considered not to be of biological relevance, since the frequency was within the historical negative control range. Additionally, the micronucleus frequency was lower than the vehicle control value at preparation interval 24 hours, indicating that the statistical significance was rather caused by the low vehicle control value than by a test article induced increase of the micronucleus frequency.

Conclusion:
The test substance AMTT, techn. CAS-Nr. [5311-05-7] did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse and therefore is considered to be non-mutagenic in this micronucleus assay.

B.6.8.2.7 Pre-/postnatal screening toxicity study in Wistar rats

Report: Schilling K. et al., 2001
AMTT and BisSH - Pre-/postnatal screening toxicity study in Wistar rats - Oral administration (gavage)
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2001/1003834

GLP: No

Guideline: No test guidelines exist for this type of study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: AMTT (635M04); batch no. CP031929, purity: 99.8 %, BisSH (impurity Reg.-No. 302571); batch no. CP 031930, purity: 99.7 %.
Test animals: Wistar rats [Chbb:THOM (SPF)]
The study was conducted in order to prove that the effects observed in the 2-generation study with tritosulfuron containing 2.45 % AMTT derive from AMTT and not from tritosulfuron nor BisSH (the other major impurity). AMTT and BisSH (also an impurity of tritosulfuron) were tested for their effects on pregnant Wistar rats during gestation and lactation and consequences on pre-/postnatal development of the progeny. The test substances were administered to 8 mated female Wistar rats/group at doses of 20 and 50 mg/kg bw/d for AMTT and 5 and 30 mg/kg bw/d for BisSH from day 6 post coitum up to day 9 post partum at latest (depending on dam/pup survival). A standard dose volume of 5 ml/kg bw was used; the control group (8 females) was dosed with the vehicle only (0.5 % Tylose CB 30.000 in doubly distilled water). The dams were allowed to deliver. All AMTT treated pups from both dose groups died within 3 days after birth; therefore, the study was terminated and the surviving animals and pups were sacrificed without further examinations with the following exceptions: all surviving dams of AMTT treated dose groups and seven dams of the control group (6 while nursing, 1 after five days of withdrawal) were sacrificed by decapitation. The blood was collected and stored at – 80 °C. The exsanguinated animals were necropsied and assessed by gross pathology. Parts of the female mammary gland were fixed, processed and assessed histopathologically.

Findings:
The following test substance-related adverse findings were obtained:
AMTT; 50 mg/kg bw/d
Maternal toxicity: 4/5 dams showing distocia had to be sacrificed, the other was found dead. One dam delivered fetuses (8 in total; 6 liveborn, 2 stillborn). Severely affected impaired health status (piloerection, lateral position, unsteady gait, apathy, partial eye closure chromodacryorrhea, urine smeared fur in all or single dams). No nesting activity in 3 dams. The dam that delivered showed insufficient care of the pups and nursed insufficiently. Reduced food consumption during the whole treatment period. Impaired body weight gains during gestation days 6-20 (70 % below control). 2 dams with gastroenteritis, stomach with ulcerations and large intestine bloody feces. Moderate (grade 3) involution of the mammary gland tissue with milky fluid in dilated mid-sized milk ducts in the examined dam.
Developmental toxicity: All pups died until 1 day post partum (viability index 0 %). All liveborn pups showed clinically no or little milk in the stomach, hypothermia; necropsy revealed 3 pups with an empty stomach.
AMTT; 20 mg/kg bw/d
Maternal toxicity: Piloerection in 3/8 dams during the second third of gestation and in all dams within lactation. All dams showed insufficient care of the pups and nursed their pups insufficiently. Reduced food consumption during measured lactation days 0-7 post partum (57 % lower than control). Increased water consumption during gestation days 13-14 (53 % above control) but reduced values during measured lactation days 4-5 and 7-8 post partum (up to 57 % below control). Lower mean body weight gains during gestation days 6-20 (26 % below control) and mean body weights during lactation days 6-9 (up to 15 % below control). Morphologically a resting (inactive) mammary gland tissue was noted in all dams. Three animals showed a slight focal milk production. All pups died until day 3 post partum (viability index 0 %). Lower pup body weights on day 1 post partum.
Developmental toxicity: All pups showed clinically no or little milk in the stomach, hypothermia; necropsy revealed an empty stomach in the vast majority of pups.
BisSH treatment: No treatment-related adverse effects were observed in the both BisSH treatment groups.

Conclusion:
The oral application of AMTT induced severe maternal and developmental toxicity at 20 mg/kg bw/d and at 50 mg/kg bw/d.

B.6.8.2.8 Study of a possible bond of AMTT and Tritosulfuron to the estrogen receptor

Report: Vollmer G., 2000
Study of a possible bond of Reg.-No. 231 700 and Reg.-No. 271 272 to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line
Molecular Medicine Luebeck Medical University, Luebeck, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1019272

GLP: No

Guideline: No test guidelines exist for this type of study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 635M04 (Reg.-No. 231 700; AMTT) and Reg.-No. 271 272 (tritosulfuron)
Test system: Endometrial RUCA-I-adenocarcinoma cell line of rats
The bonding affinity of the substances tritosulfuron (Reg.-No. 271272) and AMTT (Reg.-No. 231700) to the estrogen receptor was determined in the endometrial RUCA-I-adenocarcinoma cell line of the rat.
The relative bonding affinity of the substances was measured in a competition assay as compared with a certain amount of unlabeled estradiol (50 pmol/l) as an internal control. Nonylphenol was used as the positive control in a concentration of 1 µmol/l. First, the relative bonding affinity of the two test substances was roughly estimated as compared with the internal control, estradiol; then, the relative bonding affinity was determined exactly in a concentration of 50 µM in a further four experiments with the test substances. For the determination of the total bond, (2,4,6,7-3H)- estradiol was added in different concentrations to 100 µl of cytosolic extract (control or treated with the test substances). Unlabeled estradiol was used to expel the radioactive hormone from the specific bonding site (estrogen receptor) and therefore determine the nonspecific bond.

Findings:
All four experiments carried out produced data which could be evaluated for the calculation of the bonding affinities of the test substances to the estrogen receptor. The relative bonding affinities of AMTT (Reg.-No. 231700) were about 0.000045 % with reference to estradiol and those of tritosulfuron (Reg.-No. 271272) were 0.000025 %. As compared with nonylphenol, the bonding affinities of the test substances were 2000 x weaker for AMTT and more than 4000 x weaker for tritosulfuron.

Conclusion:
In the presence of endogenous estrogens, the bonding capacity of tritosulfuron and AMTT to the estrogen receptor is regarded as extremely low. A biological effect of the substances, the activation of the receptor-mediated gene expression, is extremely unlikely.

B.6.9 Medical data and information (Annex IIA 5.9)

B.6.9.1 Medical surveillance on manufacturing plant personnel

Since industrial production has not yet commenced no data on medical surveillance of the manufacturing personnel is available. The personnel which is handling developmental compounds is surveyed by regular medical examinations. This surveillance programme is not aimed to specifically identify tritosulfuron related symptoms or diseases.

B.6.9.2 Direct observation, e.g. clinical cases and poisoning incidents

No clinical cases or poisoning incidents are known to us.

B.6.9.3 Observations on exposure of the general population and epidemiological studies if appropriate

No observations regarding health effects after exposure of the general public are known to us.

B.6.9.4 Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

Methods for determination of active substance or metabolites in biological fluids are not established. Specific signs of poisoning or clinical tests are not known.

B.6.9.5 Proposed treatment: first aid measures, antidotes, medical treatment

See safety data sheet/precautions; symptomatic and supportive treatment, no specific antidote known.

B.6.9.6 Expected effects of poisoning

Effects of poisoning are not known.

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and drinking water limit (Annex IIA 5.10)

Preamble

In the course of toxicity testing for tritosulfuron different batches containing different impurities were used. In the long-term and the 2-generation studies which were conducted with batch no. N24 severe effects were observed, including mammary gland tumors and a high pup mortality in rats, respectively. Further studies with the same batch were conducted in order to obtain a NOAEL for these effects. Upon checking differences between the batches, it was shown that batch no. N24 contained an impurity – AMTT – in higher quantities than batches nos. N34, N42, N53 and N59 (see Table B.6.10-1). Two long-term rat studies were conducted with these batches and a 2-generation study in rats was performed with batch no. N34. These new studies did not show the effects observed before, with regard to mammary gland tumors and pup mortality. Therefore, it might be considered that AMTT was responsible for these effects. In order to understand the mechanism that is behind the mode of action of AMTT, and keeping in mind that AMTT is also a metabolite in soil and water, a variety of additional studies with AMTT were conducted.

The toxicological evaluation is only supporting an Annex I inclusion of technical tritosulfuron specified with an AMTT content ≤ 0.02 % (as impurity). Anyhow, the derivation of an ADI and an ARfD for AMTT is considered necessary because of residues in soil, water and plants.

Table B.6.10-1: Overview on the content of AMTT and purity of different batches of tritosulfuron

Batch No.	Purity	Study	Content AMTT
N12	95.6 %	Acute oral/dermal/inhalation toxicity (rat), dermal/eye irritation (rabbit), Skin sensitisation (guinea pig), prenatal toxicity in Wistar Rats/gavage	0.24 %
N12	96.1 %	*Salmonella typhimurium*/*E. coli* reverse mutation assay	0.16 %
N14	96.4 %	28-day oral (rat+mouse), 90-day oral (rat + mouse), prenatal toxicity in Himalayan rabbits/gavage	0.05 %
N24	96.8 %	28-day dermal (rat), 90-day + 12-month oral (dog), Ames-Test, *in vitro* gene mutation test in CHO cells, *in vitro* chromosome aberration assay in V79 cells, *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, *in vivo* mouse micronucleus test, 24-month feeding (rat), supplementary 24-month feeding (rat), 18-month feeding (mouse), 2-gen. reproduction study (rat), supplementary 2-gen. reproduction study (rat), Acute and subchronic oral neurotoxicity study (rat)	2.45 %
N24	95.9 %	28-day dermal, rat	2.45 %
N34	99.1 %	24-month feeding (rat), supplementary 24-month feeding (rat), 2-gen. reproduction study (rat)	0.024 %
N42	98.7 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat)	0.02 %
N53	99.8 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat)	0.012 %
N59	98.2 %	12-month feeding (rat), 24-month feeding (rat), supplementary 24-month feeding (rat), Developmental neurotoxicity study (rat)	0.006 %

Table B.6.10-2: Overview on study type and batches of tritosulfuron

Study type	Batch No. / Purity
Absorption, distribution, excretion; oral/ intravenous, rat	Triazine-14C labelled tritosulfuron: 437-32: radiochemical/chemical purity > 99 % 537-01; radiochemical purity > 99 %, chemical purity > 98 %. Phenyl-14C labelled tritosulfuron: 436-23: radiochemical purity > 97 %, chemical purity > 96 % 538-01: radiochemical purity > 99 %, chemical purity > 98 %. Phenyl-13C labelled tritosulfuron: 481-05; chemical purity > 99 %. Non radiolabelled tritosulfuron: N 14; chemical purity > 96 %
Metabolism	Triazine-14C labelled tritosulfuron: 437-32: radiochemical purity 99.2 % Phenyl-14C labelled tritosulfuron: 436-23: radiochemical purity 97.0 % Phenyl-13C labelled tritosulfuron: 481-05: radiochemical purity > 99 % 691-33-1 (unlabelled): 99.8 % (chemical)
Metabolism	Triazine-14C labelled tritosulfuron: 437-1406 (triazin-2,4-14C): radiochemical purity: > 99 %, chemical purity 97 %
Acute oral toxicity, rat	N12: 95.6 %
Acute dermal toxicity, rat	N12: 95.6 %
Acute inhalation toxicity, rat	N12: 95.6 %
Dermal irritation, rabbit	N12: 95.6 %
Eye irritation, rabbit	N12: 95.6 %
Skin sensitisation, guinea pig	N12: 95.6 %
28-day oral, rat	N14: 96.4 %
28-day oral, mouse	N14: 96.4 %
28-day dermal, rat	N24: 95.9 %
90-day, rat	N14: 96.4 %
90-day, mouse	N14: 96.4 %
90-day, dog	N24: 96.8 %
12-month, dog	N24: 96.8 %
Ames Test	N24: 96.8 %
Ames test	N12: 96.1 %
CHO	N24: 96.8 %
V79, Chinese hamster	N24: 96.8 %
UDS, Rat hepatocytes	N24: 96.8 %
Micronucleus test, mouse	N24: 96.8 %
12-month, rat	N42: 98.7 %; N53: 99.8 %; N59: 98.2 %
24-month, rat	N34: 99.1 %; N42: 98.7 %; N53: 99.8 %; N59: 98.2 %
24-month, rat	N24: 96.8 %
24-month, mice	N24: 96.8 %
2-generation, rat	N34: 99.1 %
2-generation, rat	N24: 96.8 %
2-generation, rat	N24: 96.8 %
Developmental toxicity, rat	N12: 95.6 %
Developmental toxicity, rabbit	N14: 96.4 %
Acute neurotoxicity, rat	N24: 96.8 %
Subchronic neurotoxicity, rat	N24: 96.8 %
Developmental neurotoxicity, rat	N59: 98.2 %

B.6.10.1 Metabolism / Toxicokinetics

Tritosulfuron was rapidly and almost completely absorbed after oral administration to male and female rats at dose levels of 50 and 500 mg/kg bw. The radioactivity was preferably excreted via the renal route. The bioavailability was in the range of 90-100 %. The initial plasma half-life was short at both dose levels (5 - 6 hours). At the low dose level a slower terminal phase (19 - 24 hours) followed. Highest tissue concentrations were found in the gastro-intestinal tract and the excretion organs. There was no indication of accumulation of radioactivity in fat or other tissues. The test substance was metabolised to the sulfonamide 635M02 of the trifluoromethyl-phenyl ring and its sulfonic acid 635M23. After hydroxylation at the 4-position of the phenyl ring this compound was further conjugated with glucuronic acid or sulfate. No significant amounts of AMTT were produced in the rat by transformation of tritosulfuron. The metabolic pathway of tritosulfuron in rats covers the relevant metabolites identified in farm animals, plants, soil and water.

B.6.10.2 Dermal absorption

The *in vivo* dermal absorption of tritosulfuron in rats is approximately 3 % or less depending on the duration of exposure and concentration. The initial rate of absorption through rat epidermal membranes was at least 2.27 fold greater relative to human epidermal membranes. Therefore, it can be assumed that human dermal penetration is in the order of 1 %.

B.6.10.3 Acute toxicity, local irritation and skin sensitising properties

Tritosulfuron (batch no. N12) is characterised by a low acute oral (LD_{50}: 4700 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) and inhalation toxicity (LC_{50} > 5.4 mg/l). The substance is neither irritating to the skin nor to the eyes. It is a skin sensitiser in the Maximisation Test (R 43).

B.6.10.4 Short-term toxicity

The short-term toxicity of tritosulfuron was investigated in dietary 4-week studies in rats and mice, 3-month studies in rats, mice and dogs and in a 12-month study in dogs. In addition, the short-term toxicity following dermal exposure was determined in a 28-day study in rats.
The 3-month and 12-month dog studies as well as the 28-day dermal study in rats were conducted with tritosulfuron containing high amounts of AMTT (batch no. N24). The dietary 4-week and 3-month studies in rats and mice were performed with batch no. N14 (purity 96.4 %). See Table B.6.10-1 and Table B.6.10-2.

The signs of toxicity in the mouse were minor and consisted mainly of some clinical chemical changes (after 3 months: increased urea and decreased serum triglyceride levels in males), as well as decreased body weights and increased water consumption. In the 3-month toxicity study cystitis was noted in 3/10 female mice and in one male mouse as well as decreased adrenal weights in females. Both, in the 28-day study and in the 3-month study the NOAEL was found to be 3000 ppm (equal to 547 mg/kg bw/d in male mice/692 mg/kg bw/d in female mice and 770 mg/kg bw/d in male mice/938 mg/kg bw/d in female mice).
The main target organs in the rat were liver and kidney. After 28 days of tritosulfuron administration the signs of toxicity consisted of decreased body weight gain, increased water

consumption and urinary volume with decreased urinary specific gravity, altered clinical-chemical parameters, i.e. decreases in glucose, triiodthyronine and triglycerides and an increase in total bilirubin levels. Histopathological evaluation revealed papillary necrosis and nephropathies. The NOAEL was found to be 3000 ppm (equal to 296 mg/kg bw/d in males, 313 mg/kg bw/d in females).

After 3 months of administration to rats, increased liver weights, centrilobular hypertrophy in hepatocytes as well as altered clinical-chemical and hematological parameters and altered enzyme activities were noted in addition to the results obtained after the 4-week administration. At the dose level of 15000 ppm, premature deaths were noted in female rats, most likely due to the occurrence of severe nephropathies. The NOAEL was found to be 1000 ppm (equal to 75 mg/kg bw/d in males, 85 mg/kg bw/d in females).

Overall, the signs of toxicity observed in the dogs were similar to rats and mainly consisted of centrilobular hypertrophy of liver hepatocytes and single cell necrosis accompanied by increased organ weights and altered clinical-chemical parameters, i.e. higher platelet counts, shorter partial thromboplastin times, higher activities of alkaline phosphatase and alanine aminotransferase, lower levels of triglycerides, cholesterol, creatinine, potassium, calcium, lower concentrations of total proteins, mainly due to lower albumin levels and higher levels of inorganic phosphate. In the kidneys, a degeneration of renal tubular epithelium was noted after the 3-month administration period. Weights of adrenal and thyroid glands were increased. The NOAEL was found to be 500 ppm (equal to 15 mg/kg bw/d in males, 17 mg/kg bw/d in females).
Feeding of tritosulfuron to dogs for one year resulted in clinical chemical changes mainly at the high dose level of 5000 ppm. At this dose level and to a lesser extent at 1000 ppm there was decreased body weight gain at the beginning of the study. Functional and/or morphological changes of the liver consisted of decreased urea levels and increased activities of alkaline phosphatase in female dogs, increased organ weights together with necrosis of hepatocytes in two males and inflammatory reactions in the liver of females. The NOAEL in this 12-month dog study was 200 ppm (equal to 6 mg/kg bw/d).
The overall NOAEL in dogs was considered to be 500 ppm (equal to 15 mg/kg bw/d from the 90-day study) based on the LOAEL from the 12-month study.

In a 4-week dermal toxicity study in rats no substance-related systemic adverse effects were detected up to the highest dose level tested of 1000 mg/kg bw. There were no signs of local irritation in this study.
A summary of short-term toxicity studies is given in Table B.6.10-3.

Table B.6.10-3: Summary of short-term toxicity studies

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
28-day feeding Chbb:THOM Wistar rat 0, 3000, 8000, 15000 (m) / 20000 (f) ppm N14	3000 ppm [296]	8000 ppm: Increased water consumption and urinary volume, lower sodium, chloride and triglyceride values. At 15000 ppm (m): Reduced bw, bw gain and food consumption. 20000 ppm (f): Papillary necrosis, multifocal vacuolar degeneration of renal tubules in one female, altered hematological parameters.
28-day feeding B6C3F1 CrlBr mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [547]	8000 ppm: Increased water consumption
28-day dermal Chbb:THOM Wistar rat 0 50, 200, 1000 mg/kg bw/d N24	[1000]	No systemic adverse effects. No signs of local irritation.
90-day feeding study Chbb:THOM Wistar rat 0, 1000, 5000, 15000 ppm N14	1000 ppm [75]	5000 ppm: Increased water consumption, slightly lower red blood cell parameters; centrilobular hypertrophy in hepatocytes; increased liver weights, nephropathies (slight). 15000 ppm: Premature deaths (5/10 f), reduced bw and bw gain, altered clinical-chemical and hematological parameters; altered enzyme activities; papillary necrosis; nephropathies (severe)
90-day feeding study B6C3F1 CrlBR mice 0, 1000, 3000, 8000 ppm N14	3000 ppm [770]	8000 ppm: Increased water consumption, reduced bw and bw gain (m), increased urea/decreased triglyceride levels (m), increased adrenal gland weights and cystitis (f)
90-day feeding study Beagle dogs 0, 500, 3000, 9000 ppm N24	500 ppm [15]	3000 ppm: Increased platelet count (f day 41); decreased albumin concentration (f day 41); increased alkaline phosphatase activity (m day 91), increased rel. adrenal gland weights (f), centrilobular hypertrophy (m) 9000 ppm: Decreased bw and bw gain, altered clinical chemical and hematological parameters (increase in alkaline phosphatase and alanine aminotransferase activity, decreased albumin conc.), increased weights of liver, kidney, adrenal and thyroid glands, centrilobular hypertrophy and degeneration of hepatocytes; focal and multifocal lesions in kidneys; degenerative changes of tubular epithelium with reactive inflammatory response in cortical region of kidneys.
12-month feeding study Beagle dogs 0, 200, 1000, 5000 ppm N24	200 ppm [6]	1000 ppm: Initial bw loss (m), increased activity of alkaline phosphatase (f), decreased urea concentrations (f) 5000 ppm: Initial bw loss (m), retarded bw development (f), altered clinical chemical and hematological parameters, increased liver weights, centrilobular necrosis of hepatocytes (m), inflammatory reactions in livers (f), increased adrenal gland weights (m)

m: male; f: female; bw: body weight; d: day

B.6.10.5 Genotoxicity

The potential genotoxicity of tritosulfuron (batch no. N24) was investigated in a series of both *in vitro* and *in vivo* studies. Batch no. N12 was additionally tested in a bacterial mutagenicity test. All regular end points for genetic damage (point mutations, chromosome damage and DNA-damage and repair) were assessed. Tritosulfuron was evaluated for its potential

genotoxicity *in vitro* using bacterial and mammalian cell mutagenicity tests, a chromosome damage (clastogenicity) test and an unscheduled DNA synthesis test. There was no indication for genotoxic potential. *In vivo*, the test substance was assessed for the induction of micronuclei in mice. The results of this study showed that tritosulfuron (N24) has no chromosome-damaging potential. It is therefore concluded, that tritosulfuron of batches with a high content of AMTT has no mutagenic or genotoxic properties both *in vitro* and *in vivo*.

B.6.10.6 Long term toxicity and carcinogenicity

The 12-month chronic toxicity study (batches nos. N42, N53, N59) and two 24-month carcinogenicity studies in rats (batches nos. N34, N42, N53, N59) conducted with tritosulfuron containing low quantities of AMTT and the 18-month carcinogenicity study in mice which was conducted with tritosulfuron containing high quantities of AMTT (batch no. N24) did not show a carcinogenic potential.
In the 12-month chronic toxicity study in rats the administration of 7000 ppm of tritosulfuron resulted in an increase in water consumption in both sexes, a mild anemic process as well as clues to slight impairment of renal function in females which was evidenced by increases in urinary volume with decreased urinary specific gravity. Males at this dose level showed slightly increased incidence of chronic interstitial nephritis in the kidneys and slightly increased incidence of pericholangitis in the liver. Increased number of animals with ‘anogenital region smeared with urine’ and/or ‘inflammation in the anogenital region’ was seen at 7000 and 3500 ppm. These findings indicate that the kidney is the main target organ for tritosulfuron toxicity in chronic rat studies, which is in accordance with the subchronic rat toxicity studies. The NOAEL was found to be 1000 ppm (equal to 51.7 mg/kg bw/d in males and 68.4 mg/kg bw/d in females.
In a 24-month carcinogenicity study in rats conducted with tritosulfuron containing low quantities of AMTT the main findings consisted in an increase in water consumption and the clinical finding ‘anogenital region smeared with urine’ in both sexes at 3500 ppm. The NOAEL was found to be 1000 ppm (equal to 48 mg/kg bw/d in males and 64 mg/kg bw/d in females).
In supplementary 24-month carcinogenicity study in rats conducted with with doses of 0 ppm and 7000 ppm (equal to 327 mg/kg bw/day in males, 463 mg/kg bw/day in females) tritosulfuron containing low quantities of AMTT the main changes consisted in the clinical observation “anogenital region smeared with urine” and/or “inflammation in the anogenital region”, an increase in water consumption, as well as changes in certain red blood cell parameters (polychromasia, anisocytosis and microcytosis) in females. In the kidney, papillary necrosis was noted in either sex, pyelonephritis in males and angiectasis in renal papilla in females. In addition, male animals had cystitis and urothelial hyperplasia in the urinary bladder.
A carcinogenicity study in mice was conducted with tritosulfuron containing high quantities of AMTT. Animals of the high dose group (7500 ppm) were prematurely sacrificed after 16 months of treatment without further examinations. At 3750 ppm there was increased water consumption. Decreased body weight gain was seen at all dose levels. The NOAEL was found to be below 250 ppm (equal to < 36 mg/kg bw/d in males, < 44 mg/kg bw/d in females).
In 24-month carcinogenicity studies in rats conducted with a batch of tritosulfuron containing high levels of AMTT (N24: 2.45 %) neoplastic lesions were found in the mammary glands, i.e. adenocarcinomas and fibroadenomas. Non-neoplastic lesions consisted in effects on the testes (degeneration of the germinal epithelium, sperm stasis, focal calcification of seminiferous tubules), on the uterus and mammary gland (diffuse hyperplasia) and in

increased haematopoiesis in the bone marrow at 3500 ppm. Rats of the high dose groups (7000 ppm) were prematurely sacrificed after 16 months of treatment without further examinations.

The main toxicological profile of tritosulfuron could also be confirmed in these long-term studies conducted with tritosulfuron containing high levels of AMTT. Water consumption was increased and body weight gain was decreased. Changes of white cell (leukocytosis, mainly lymphocytosis, increased numbers of polymorphonuclear granulocytes) and red cell parameters (anemia, increases in reticulocytes), distinct changes in clinico-chemical parameters (increases in alanine aminotransferase, calcium, cholesterol, decreases in triglycerides, alkaline phosphatase, increases or decreases of proteins, i.e. globulins and albumin) as well as urinary parameters (polyuria with decreased specific gravity, cloudy and/or discoloured urine samples, increased numbers of epithelial cells, granular casts and macrohematuria) were recorded.

It was concluded that tritosulfuron with a high AMTT content did show a carcinogenic potential in Wistar rats.

A summary of long-term toxicity and carcinogenicity studies with tritosulfuron is shown in Table B.6.10-4.

Table B.6.10-4: Summary of long-term toxicity and carcinogenicity studies with tritosulfuron

Study type / species / dose levels /batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
12-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500; 7000 ppm N42, N53, N59	1000 ppm [51.7]	3500 ppm: Anogenital region smeared with urine and/or "inflammation in the anogenital region. 7000 ppm: Increased water consumption and urinary volume (f), decreased urinary specific gravity (f), anemia (f), chronic interstitial nephritis in the kidneys (m), pericholangitis in liver (m)
24-month feeding study Wistar rats (Chbb: THOM) 0; 100; 1000; 3500 ppm N34, N42, N53, N59	1000 ppm [48]	3500 ppm: Anogenital region smeared with urine, increased water consumption; no carcinogenic properties.
Supplementary 24-month feeding study Wistar rats (Chbb: THOM) 0; 7000 ppm N34, N42, N53, N59	1000 ppm [48]	Anogenital region smeared with urine, inflammation in the anogenital region, increased water consumption, changes in red blood cell parameters (f), papillary necrosis in the kidney, pyelonephritis (m), cystitis and urothelial hyperplasia in urinary bladder (m), angiectasis in renal papilla (f), no carcinogenic properties.
24-month feeding study Wistar rats (Chbb: THOM) 0; 250; 1000; 3500; 7000 ppm N24	< 250 ppm [< 11.8]	250 ppm: Lower body weight, increased incidence of palpable masses in the skin 1000 ppm: Additionally increased water consumption, changes of hematological and clinico-chemical parameters. 3500 ppm: Additionally, increased mortality in females, abnormal clinical signs, changes of urinary parameters, effects on testes, uterus and mammary gland 7000 ppm: Premature sacrifice after 16 months. Mammary gland tumors at all dose levels.
24-month feeding study Wistar rats (Chbb: THOM) 0; 50; 100 ppm N24	100 ppm [5]	No effects
18-month feeding study B6C3F1 CrlBR mice 0; 250; 1000; 3750; 7500 ppm N24	< 250 ppm [< 36]	250 and 1000 ppm: Decreased bw and bw gain. 3750 ppm: Additionally increased water consumption. 7500 ppm: Premature sacrifice after 16 months No carcinogenic properties.

m: male; f: female; bw: body weight; d: day

B.6.10.7 Reproduction and developmental toxicity (teratogenicity)

The reproduction toxicity of tritosulfuron was investigated in a 2-generation reproduction study containing low quantities of AMTT (batch. no. N34) as well as in prenatal toxicity studies in rats (batch no. N12) and rabbits (batch no. N14). Two multigeneration studies on rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24).
In the 2-generation study in rats, tritosulfuron containing low quantities of AMTT had no adverse effects on reproductive performance or fertility of the F_0 and F_1 parental animals of all substance treated groups. Oestrus cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between the treated rats and the

corresponding controls. Slight signs of general toxicity occurred in both parental generations (F_0 and F_1) at 3600 ppm evidenced by an increased incidence of urine smeared fur. In the presence of slight maternal toxicity, $F_{1a/}$ F_{1b} and F_2 pups had minimally lower body weight gain and an increased incidence of dilated renal pelves at necropsy. No substance-related clinical, gross or histopathological findings were noted at 600 and 100 ppm. The NOAEL for parental and reproductive toxicity was found to be 600 ppm (equivalent to 40 mg/kg bw/d).

Two studies were carried out with tritosulfuron containing high levels of AMTT (batch no. N24) in rats. In these studies multiple effects on reproduction were seen, the most striking being the increased pup mortality also in the absence of maternal toxicity. Fertility was not affected at any dose level.
In summary, the main findings were: Reproductive performance was impaired in the mid and high dose group F_0 parental females and in the F_1 parental females of all treatment groups substantiated by an increased pup mortality of the F_{1a}/F_{1b} pups at 700 and 3500/2100 ppm, and of the F_2 pups at all dose levels, especially during early postnatal life. The number of stillborn pups was also increased at the high dose level. As a consequence, the viability index and the lactation index were reduced. The high pup mortality led to total litter losses in several dams. General toxicity occurred in both parental generations at 700 ppm and 3500/2100 ppm (increased number of animals with fur smeared with urine, reduced food consumption, reduced body weight and body weight gain, increased water consumption). Hematology showed mild adverse effects on the red blood cells of females at 3500 ppm (decreased red blood cell count and hematocrit). Concerning pathology, none of the altered organ weights could be correlated with a histopathological finding in these organs. A NOAEL for reproductive toxicity was not achieved. The NOAEL for parental toxicity was set at 100 ppm (equal to 10 mg/kg bw/d).
A supplementary study investigating dose levels of 25 and 50 ppm was performed. In this study F_2 pup mortality was increased at 50 ppm in the absence of parental toxicity. The NOAEL for parental toxicity was 50 ppm (eqivalent to 4.8 mg/kg bw/d), the NOAEL for reproductive toxicity was 25 ppm (equivalent to 2.4 mg/kg bw/d).

In the prenatal toxicity studies, different batches of tritosulfuron were administered to rats (batch. no. N12) and rabbits (batch no. N14). In the rat fetuses a slightly higher incidence of hydrourethers in combination with renal pelvis dilatations were noted at 360 mg/kg bw/d. Maternal toxicity was substantiated by decreases in body weight gain. The NOAEL for maternal and developmental toxicity was 120 mg/kg bw/d. Tritosulfuron was not teratogenic in rats.
In the prenatal toxicity study in Himalayan rabbits signs of developmental toxicity were observed at the highest dose level only (450 mg/kg bw/d) in the form of a slightly increased occurrence of one skeletal variation (accessory 13^{th} rib). At this dose level there was overt maternal toxicity (reduced food consumption, decreases in body weight gain, discoloured urine/hematuria). The NOAEL for maternal and developmental toxicity was found to be 150 mg/kg bw/d. Tritosulfuron was not teratogenic in rabbits.
The summary of reproduction toxicity studies with tritosulfuron are shown in Table B.6.10-5.

Table B.6.10-5: Summary of reproduction toxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
2-generation study Wistar rat (Chbb:THOM) 0, 100, 600, 3600 ppm N34	Parental and reproductive toxicity: 600 ppm [40]	3600 ppm: Parental toxicity: Clinical signs (urine smeared fur). Reproductive toxicity: Decreased bw gain, increased incidence of dilated renal pelves
2-generation study Wistar rats (Chbb: THOM) 0, 100, 700, 3500/2100 ppm N24	Parental toxicity: 100 ppm [10] Reproductive toxicity: < 100 ppm [< 10]	100 ppm: Increased pup mortality (F2 pups) 700 + 3500/2100 ppm: Parental toxicity: Abnormal clinical signs, increased water consumption, decreased bw, changes of hematological and clinico-chemical parameters. Reproductive toxicity: Increased number of stillborn pups and pup mortalities, decreased bw, delayed physical development
2-generation study Wistar rats (Chbb: THOM) 0, 25, 50 ppm N24	Parental toxicity: 50 ppm [4.8] Reproductive toxicity: 25 ppm [2.4]	50 ppm: Parental toxicity: None Reproductive toxicity: Increased F_2 pup mortality
Developmental toxicity Wistar rat (Chbb:THOM 0, 40, 120, 360 mg/kg bw/d days 6-15 N12	Maternal toxicity: [120] Developmental toxicity: [120]	360 mg/kg bw/d: Maternal toxicity: Decreased bw gain. Developmental toxicity: Hydrourethers/renal pelves dilatation. Tritosulfuron is not teratogenic
Developmental toxicity Himalayan rabbit 0, 50, 150, 450 mg/kg bw/d days 7-19 N14	Maternal toxicity: [150] Developmental toxicity: [150]	450 mg/kg bw/d: Maternal toxicity: Decreased food intake (days 7-13 p.i.), decreased bw gain, discoloured urine/hematuria. Developmental toxicity: Slightly increased incidence of accessory $13t^h$ rib(s) Tritosulfuron is not teratogenic

m: male; f: female; bw: body weight; p.p. post partum

B.6.10.8 Neurotoxicity/Delayed neurotoxicity

The acute and subchronic neurotoxicity studies in rats were conducted with tritosulfuron containing high quantities of AMTT (batch no. N24). The developmental neurotoxicity study in rats was conducted with tritosulfuron containing low quantities of AMTT (batch. no. N59).
In the acute neurotoxicity study, the only clinical sign of toxicity (urine-smeared anogenital region) was seen at the high dose level (2000 mg/kg bw). There were no other test substance related effects at any dose level. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 1000 mg/kg bw. The NOAEL for neurotoxicity was 2000 mg/kg bw.
In the 90-day neurotoxicity study in rats, increased water consumption at 3500 ppm and 500 ppm, reduced food consumption at 3500 ppm and a smeared anogenital region at 3500 ppm were the only test substance related findings. No signs of neurotoxicity were observed. The NOAEL for general toxicity was found to be 100 ppm (equal to 7 mg/kg bw/d). The NOAEL for neurotoxicity was 3500 ppm (equal to 243 mg/kg bw/d).
In a developmental neurotoxicity study the only effects that were observed were an urine-smeared anogenital region, body weight loss during first day of treatment, reduced body weight during gestation period and reduced food consumption during gestation in the dams as

well as slightly reduced mean body weight changes during the last week of lactation in the offspring at 8000 ppm. No signs of developmental neurotoxicity were noted up to the highest concentration. The NOAEL for maternal/neonatal toxicity was found to be 1000 ppm (equal to 65 mg/kg bw/d). The NOAEL for developmental neurotoxicity was 8000 ppm (equal to 509 mg/kg bw/d). In conclusion, tritosulfuron is not neurotoxic to adult animals (batch no. N24) as well as to the developing animal (batch no. 59). A summary of the neurotoxicity studies is presented in Table B.6.10-6.

Table B.6.10-6: Summary of neurotoxicity studies with tritosulfuron

Study type / species / dose levels / batch no.	NOAEL [mg/kg bw/d]	LOAEL / Critical effects
Acute oral neurotoxicity study Wistar rat (Chbb:THOM) 0, 500, 1000, 2000 mg/kg bw single dose, gavage N24	Neurotoxicity: [2000] General toxicity: [1000]	2000 mg/kg bw: Clinical signs (urine smeared anogenital region). Neurotoxicity: None Tritosulfuron is not neurotoxic.
90-day subchronic neurotoxicity Wistar rat (Chbb:THOM) 0, 100, 500, 3500 ppm N24	Neurotoxicity: 3500 ppm [243] General toxicity: 100 ppm [7]	500 ppm: Increased water consumption 3500 ppm: reduced food consumption and bw, increased water consumption, urine smeared anogenital region Neurotoxicity: None Tritosulfuron is not neurotoxic.
Developmental neurotoxicity Wistar rats (Crl:CD(SD)IGS BR) 0, 200, 1000, 8000 ppm day 6 (p.c.)-21 (p.p.) N59	Developmental neurotoxicity: 8000 ppm [509] Maternal/neonatal toxicity: 1000 ppm [65]	Developmental neurotoxicity: None 8000 ppm - Maternal/neonatal toxicity: Clinical signs (urine smeared anogenital region), decreased bw gain Tritosulfuron is not neurotoxic to adult rats as well as to the developing rat

m: male; f: female; bw: body weight; p.c.: post coitum; p.p.: post partum

B.6.10.9 Further toxicological studies

635M02 (Reg.-No. 292 564; BH 635-2; TBSA) was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells.
Two acute oral studies were conducted: one with the intermediate TBSA (635M02; Reg.-No. 292 564) and another with the synthesized metabolite BH 635-2 (635M02). The latter resulted in an oral LD_{50} of 1000 mg/kg bw, the first one in an oral LD50 of > 2000 mg/kg bw.

635M03 (Reg.-No. 335 182; BH 635-3) was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells.
An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw. The no observed adverse effect level in a 90-day dietary rat study was 15000 ppm (1187 mg/kg bw/d in males and 1440 mg/kg bw/d in females).

635M01 (Reg.-No. 335 184; BH 635-4) was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the

CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) under *in vitro* conditions in V79 cells.
An acute oral toxicity study revealed an LD_{50} of > 5000 mg/kg bw.

635M17 (Reg.-No. 373 906) was found to be not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and not chromosome-damaging (clastogenic) *in vivo*; there were no indications of any impairment of chromosome distribution in the course of mitosis.
An acute oral toxicity study revealed an LD_{50} of > 2000 mg/kg bw.

AMTT (635M04) does not accumulate in rats, but is effectively excreted. The major metabolite AHTT is generated by demethylation of the parent compound and is detected as different tautomeric structures.
The oral LD_{50} was found to be > 200 < 2000 mg/kg bw.
Oestrus cycle determination, hormone analysis as well as PCNA resp. BrdU and TUNEL–stain analysis of mammary glands and a density calculation of estrogen (Eα)– and progesterone receptors in uterus and vagina revealed no treatment-related changes in a subchronic toxicity study.
AMTT (635M04) is not mutagenic in the Salmonella typhimurium/Escherichia coli reverse mutation assay, not mutagenic *in vitro* in the CHO/HPRT mutation assay and did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse and therefore is considered to be non-mutagenic in this micronucleus assay.
The oral application of AMTT (635M04) induced severe maternal and developmental toxicity at 20 mg/kg bw/d and at 50 mg/kg bw/d in a pre/postnatal screening study. Therefore, AMTT might be considered responsible for the effects observed in the 2-generation study with tritosulfuron containing high levels of AMTT.
In the presence of endogenous estrogens, the bonding capacity of tritosulfuron and AMTT to the estrogen receptor is regarded as extremely low. A biological effect of the substances, the activation of the receptor-mediated gene expression, is extremely unlikely.

B.6.10.10 Human experience

Since industrial production has not yet commenced no data on medical surveillance of the manufacturing personnel is available. The personnel who are handling developmental compounds are surveyed by regular medical examinations. This surveillance programme is not aimed to specifically identify tritosulfuron related symptoms or diseases. Poisoning incidents or clinical cases are not reported.

B.6.10.11 Acceptable Daily Intake (ADI)

B.6.10.11.1 ADI for tritosulfuron (AMTT max. 0.02 %)

From the studies conducted with tritosulfuron containing low concentrations of AMTT (batches nos. N34, N42, N53, N59) there is no evidence for carcinogenic, teratogenic or reproduction disturbing properties of the active substance. The overall NOAEL is approximately 50 mg/kg bw/d from the long-term and 2-generation studies in rats. The

standard assessment factor of 100 is considered appropriate. This results in a proposed **ADI of 0.5 mg/kg bw**.

B.6.10.11.2 ADI for AMTT

From the studies conducted with tritosulfuron containing high concentrations of AMTT (batch no. N24) there is evidence for carcinogenic and reproduction disturbing properties. *In vitro* and *in vivo* mutagenicity studies which were conducted with this batch were negative. With regard to carcinogenic properties the lowest NOAEL is 5 mg/kg bw/d from the 24-month feeding study in rats. Calculated for an amount of 2.45 % AMTT the NOAEL is 0.123 mg/kg bw/d.
The NOAEL for reproductive toxicity was 25 ppm (equivalent to 2.4 mg/kg bw/d) based on increased F_2 pup mortality at 50 ppm. Calculated for the amount of AMTT the overall NOAEL is 0.06 mg/kg bw/d. A safety factor of 100 is considered appropriate. This results in a proposed **ADI of 0.0006 mg/kg bw.**

B.6.10.12 Acceptable Operator Exposure Level (AOEL)

B.6.10.12.1 Systemic AOEL for tritosulfuron (AMTT max. 0.02%)

Tritosulfuron (batch no. N12) is of low acute oral, dermal and inhalation toxicity. Under the condition of following the rules of good agricultural practice the risk of an acute intoxication by tritosulfuron can be ruled out if the purity of technical tritosulfuron is > 95 % and the AMTT content maximal 0.02 %. Likewise, batches tested for chronic toxicity/carcinogenicity and reproductive toxicity in rats with a minimum purity of 98.2 % and a maximal AMTT content of 0.024 % proved to be devoid of carcinogenic and reproductive disturbing properties.
The AOEL is usually derived on the basis of so-called mid-term toxicity studies, i.e. the subacute/subchronic toxicity studies. The lowest NOAEL is 75 mg/kg bw/d from the 90-day feeding studies in rats (batch no. N14). Since the extent of absorption after oral administration is almost complete, correction from the oral AOEL to a systemic AOEL is not needed. Applying the standard assessment factor of 100 in accordance with current EU assessment practice this results in a **systemic AOEL of 0.75 mg/kg bw/d**.

Note: The NOAELs from the 90-day and 12-month studies in dogs were lower than the NOAEL from the 90-day study in rats. The overall NOAEL in dogs was considered to be 500 ppm (equal to 15 mg/kg bw/d from the 90-day study). The conservative approach would be to derive the AOEL on the basis of this NOAEL but both short-term studies in dogs were conducted with tritosulfuron containing high levels of AMTT (batch no. N24). Since the rat was proved to be more sensitive against high AMTT levels it was considered more appropriate to derive the AOEL from the lowest NOAEL in rats treated with low AMTT levels.

B.6.10.12.2 Systemic AOEL for AMTT

The derivation of an AOEL for AMTT is not necessary because the Annex I inclusion is only supported for tritosulfuron specified with an AMTT content ≤ 0.02 %.

B.6.10.13 Acute Reference Dose (ARfD)

B.6.10.13.1 ARfD for tritosulfuron (AMTT max. 0.02 %)

On the basis of its toxicological profile, tritosulfuron containing low concentrations of AMTT is unlikely to present an acute hazard for consumers. The acute oral toxicity of tritosulfuron (batch no. N12) is low and there are no acute toxicological alerts seen in repeated dose toxicity studies.

B.6.10.13.2 ARfD for AMTT

FAO/WHO (2000) stated that there is a need to establish an ARfD if developmental/reproductive effects are observed, except when these are clearly a consequence of maternal toxicity, and if hormonal or other biochemical alterations are observed in studies with repeated doses, which might conceivably be elicited also by a single dose. From the studies conducted with tritosulfuron containing high levels of AMTT there is evidence for carcinogenic as well as reproduction disturbing properties. Since the critical endpoint in the 2-generation reproduction toxicity study was pup mortality it is considered necessary to derive an ARfD especially for a sensitive sub-population (e.g. pregnant women) and the unborn offspring. It is proposed to derive an ARfD on the same basis as the ADI value applying a safety factor of 100. This results in an **ARfD of 0.0006 mg/kg bw (same as ADI).**

B.6.10.14 Drinking Water Limit

The determination of a MAC value is not necessary, because according to Directive 91/414/EC only the ADI and AOEL values have to be determined. Therefore, the establishment of a maximum admissible concentration for drinking water from an ADI value is not yet confirmed by a harmonised EU proposal. In addition to that, the maximum admissible concentration of an active substance is 0.1 µg/l, as established by the Directive 89/778/EEC.

B.6.11 Acute toxicity including irritancy and skin sensitization of preparations (Annex IIIA 7.1)

BAS 635 00 H is formulated as a water-dispersible granule containing nominal 714 g/kg of the active ingredient (a.i.) tritosulfuron. In both the acute toxicity studies with the active ingredient as well as in the acute toxicity studies with the preparation, technical tritosulfuron with a purity of about 95 % at a minimum has been used. The AMTT content of these batches is not mentioned.
As outlined by the notifier, the intended use of BAS 635 00 H is in a tank-mix with surfactants like Citowett New (BAS 152 00 S), preferably, Dash HC (BAS 904 70 S) or other

additives to which no data are given because these additives are not to assess in this monograph.
BAS 635 00 H has low acute toxicity after oral, dermal and inhalation exposure. The formulation is not irritating to the skin and eyes, and it has no skin sensitising properties in the Modified Buehler Test (Table B.6.11-1).
In accordance with Directive 78/631/EEC in combination with the latest classification and labelling guidance under Directive 67/548/EEC (i.e. in the 18th ATP published as Directive 93/21/EEC) for BAS 635 00 H no classification/labelling is required.

Table B.6.11-1: Acute toxicity of BAS 635 00 H

Study type	Results
Acute oral LD_{50} rat	3310 mg/kg bw.
Acute dermal LD_{50} rat	> 2000 mg/kg bw.
Acute inhalation LC_{50} rat	5.9 mg/l (4 h)
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitisation (Buehler test: 9 Inductions)	Not sensitising

B.6.11.1 Oral

Report: Kuehlem C., Hellwig J., 1997(d)
Study on the acute oral toxicity of BAS 635 00 H in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/10617
Date of experimental work: July-August 1996.

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: OECD 401, EEC 92/69, EPA 81-1

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 96-2; formulation: 73.45 % BAS 635 H.
Test animals: Wistar rats; CHBB:THOM (SPF)

Single administration of a test substance preparation in aqua bidest. by gavage to five male and five female fasted Wistar rats per dose level. Three dose levels were tested: 1000; 2000; and 5000 mg/kg bw, using an application volume of 10 ml/kg bw. The observation period was 14 days.

Findings:
The stability of the test substance over the study period was guaranteed. The stability of the test substance in aqua bidest. for a time period of 4 hours was confirmed by analysis. The

correctness of the concentration of the test substance preparation and its homogeneity were analytically demonstrated.
Two male and five female animals of the 5000 mg/kg dose group, one male and two female animals of the 2000 mg/kg dose group died within 2 or 3 days after the application. No mortality occurred in the 1000 mg/kg dose group.

Table B.6.11-2: Acute oral toxicity of BAS 635 00 H in rats: Mortality*

Sex	Dose level (mg/kg bw)		
	1000	2000	5000
Males	0/5	1/5	2/5
Females	0/5	2/5	5/5

* number of animals that died / number of animals exposed

Signs of toxicity noted in the 5000 and 2000 mg/kg dose group comprised impaired or poor general state, dyspnoea, apathy, abdominal or lateral position, staggering, ataxia, atonia, paresis, twitching, erythema, exiccosis, salivation, compulsary gnawing, shaking and red clammy snout and eyelid. The animals of the 1000 mg/kg dose group showed impaired or poor general state, dyspnoea, apathy and staggering. The surviving animals appeared normal within 6 days after application. Body weight development appeared to be normal in the course of the study.
Necropsy findings of the animals that died included erosion/ulcer in the glandular stomach, hemorrhage of urinary bladder and agonal congestion. No abnormalities were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The LD_{50} for male rats was about 5000 mg/kg bw and and the LD_{50} for female rats was about 2000 mg/kg bw. The oral LD_{50} for male and female animals was calculated to be 3310 mg/kg bw (confidence limits, 95 %: 2260 – 6210 mg/kg bw).

B.6.11.2 Percutaneous

Report: Kuehlem C., Hellwig J., 1997
Study on the acute dermal toxicity of BAS 635 00 H in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/10523
Date of experimental work: August 1996.

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69 B.3, OECD 402, EPA 81-2

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 96-2; formulation: 73.45 % BAS 635 H.
Test animals: Wistar rats; CHBB:THOM (SPF)

The test material was applied dermally as a suspension in aqua bidest. to five male and five female Wistar rats for 24 hours under semiocclusive dressing at a dose level of 2000 mg/kg bw. The application area was about 50 cm². The observation period was 14 days.

Findings:
The stability of the test substance in the vehicle aqua bidest. over a period of 4 hours was confirmed by analysis.

No mortality occurred. No signs of systemic toxicity or local effects were noticed. Body weight development appeared to be normal. No abnormalities were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The dermal LD_{50} was found to be > 2000 mg/kg bw for male and female rats.

B.6.11.3 Inhalation

Report:	Gamer A. O., Hoffmann H. D., 1997 BAS 635 00 H - Acute inhalation toxicity study in Wistar rats 4-hour dust exposure BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep. unpublished BASF RegDoc# 1997/10289 Date of experimental work: October 1996.
GLP:	Yes (Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)
Guideline:	EEC 92/69, OECD 403, EPA/FIFRA 81-3, EPA/TSCA 40 CFR § 798.1150
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 96-2; formulation: 73.45 % BAS 635 H.
Test animals: Wistar rats; CHBB:THOM (SPF)

Five male and five female Wistar rats per dose group were exposed to a dust aerosol of the test material for four hours in a head/nose inhalation system. The mean analytical concentrations tested were 2.1 mg/l, and the limit test dose 5.9 mg/l. The observation time was 14 days.

Findings:
The stability of the test substance was ensured over the study period, the homogeneity was confirmed by analysis. The homogenous distribution of atmospheres in this inhalation system has been proven. The particle size distribution revealed a mass median aerodynamic diameter (MMAD) of 1.5 and 2.3 µm, which are well within the respirable range.

Table B.6.11-3: Acute inhalation toxicity of BAS 635 00 H in rats: Mortality*

Sex	Concentration (mg/l)	
	2.1	**5.9**
Males	0/5	1/5
Females	0/5	3/5

* number of animals that died / number of animals exposed

No mortality occurred at 2.1 mg/l. Three of five females and one of five males died at 5.9 mg/l. Clinical examination in the low dose group comprised irregular and accelerated respiration as well as attempts to escape, piloerection and smeared fur. No abnormalities were observed from post exposure day 3 onward. In the high concentration dose group intermittent respiration, eyelid closure, nasal crust formation and salivation was observed additionally. No clinical signs were noticed from day 6 (male rats) and from day 7 (female rats) onward.
Body weight development of the animals in the low dose group was not influenced. Body weight development in the surviving animals of the high concentration group was slightly depressed in the first post exposure week, but recovered in the second.
The animals that died showed congestive hyperaemia of the lung and bloody nasal discharge during necropsy. No pathologic findings were noted at necropsy of animals sacrificed at the end of the study.

Conclusion:
The inhalation LC_{50} was found to be about 5.9 mg/l (4 h) for males and females.

B.6.11.4 Skin irritation

Report: Kuehlem C., Hellwig J., 1997
Study on the acute dermal irritation/corrosion of BAS 635 00 H in the rabbit
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1997/10490
Date of experimental work: July 1996.

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69 B.4, OECD 404, EPA 81-5

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 96-2; formulation: 73.45 % BAS 635 H.
Test animals: New Zealand White rabbits (SPF)

The unchanged test substance (0.5 g) was applied dermally to the intact skin of three male and three female New Zealand White rabbits for 4 hours on a 2.5 cm x 2.5 cm test patch under a semiocclusive dressing (test patch: Idealbinde, Pfälzische Verbandstoff-Fabrik, Kaiserslautern and Fixomull® strech: adhesive fleece, Beiersdorf AG). After the patches were removed the treated area was rinsed with Lutrol® and Lutrol®/water (1 : 1). The animals were observed for skin irritation for 72 hours after test material application. Skin readings were performed at 1, 24, 48 , 72 hours and 8 days after removal of the patch.

Findings:
The stability of the test substance for the duration of the study was guaranteed. The homogeneity of the test substance was analytically confirmed.
Skin findings are summarised in Table B.6.11-4.

Table B.6.11-4: Skin irritation scores (erythema/edema)

Animal	Time after patch removal					
Number	1 h	24 h	48 h	72 h	8 d	Mean
1	2/1	1/0	1/0	0/0	0/0	0.7/0.0
2	3/1	3/0	2/0	1/0	0/0	2.0/0.0
3	3/1	3/0	2/0	2/0	0/0	2.3/0.0
4	2/1	2/0	1/0	1/0	0/0	1.3/0.0
5	3/1	3/0	2/0	1/0	0/0	2.0/0.0
6	2/0	1/0	0/0	0/0	0/0	0.3/0.0
1-6		**x**	**x**	**x**		**1.4/0.0**

The mean score (24 to 72 hours) for all animals was calculated to be 1.4 for erythema and 0.0 for edema. Additionally mechanical skin lesions due the adhesive test substance were observed in some animals during the first 48 hours after application. All cutaneous reactions were reversible in all animals within 8 days after removal of the patch.
Under the test conditions chosen, only non persistent very slight to moderate erythema were seen.

Conclusion:
Non persistent very slight to moderate erythema (mean score 24 to 72 hours: = 1.4) were observed.
In accordance with the criteria specified in Council Directive 67/548/EEC (adapting Commission Directive 93/21/EEC), regarding the skin irritating properties BAS 635 00 H has not to be classified.

B.6.11.5 Eye irritation

Report: Kuehlem C., Hellwig J., 1997
Study on the acute eye irritation of BAS 635 00 H in the rabbit
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished

BASF RegDoc# 1997/10491
Date of experimental work: July 1996.

GLP: Yes
(Laboratory certified by Ministerium fuer Arbeit, Soziales und Gesundheit, Postfach 3180, 55021 Mainz)

Guideline: EEC 92/69 B.5, OECD 405, EPA 81-4

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 96-2; formulation: 73.45 % BAS 635 H.
Test animals: New Zealand White rabbits / HSDIF: NZW (SPF)

The test substance was applied in a single dose to the conjunctival sac of three female and three male New Zealand White rabbits. The application bulk volume was about 0.1 ml. The test substance was washed out with tap water about 24 hours after the application. Readings were carried out at 1, 24, 48 and 72 hours after application of the test substance.

Findings:
The stability of the test substance was guaranteed for the duration of the study. The homogeneity was analytically confirmed.
The mean values (readings of 24 h, 48 h and 72 h) for all animals are given in Table B.6.11-5.

Table B.6.11-5: Eye irritation; mean readings

Animal No.	Opacity	Iris	Conjunctiva	
			Redness	Swelling
1	0.0	0.0	0.3	0.0
2	0.0	0.0	0.0	0.0
3	0.0	0.0	0.7	0.0
4	0.0	0.0	1.3	0.3
5	0.0	0.0	1.0	0.0
6	0.0	0.0	0.3	0.0
Mean	**0.0**	**0.0**	**0.6**	**0.1**

The average score (24 to 72 hours) for irritation was calculated to be 0.0 for corneal opacity, 0.0 for iritis, 0.6 for conjunctival redness and 0.1 for chemosis. The findings were reversible in all animals within 72 hours after application.

Conclusion:
Under the test conditions chosen, only slight conjunctival irritation were observed. In accordance with the criteria specified in Council Directive 67/548/EEC (adapting Commission Directive 93/21/EEC), regarding the eye irritating properties BAS 635 00 H has not to be classified.

B.6.11.6 Skin sensitisation

Report: Wiemann C., Hellwig J., 2000
BAS 635 00 H - Modified Buehler test (9 inductions) in guinea pigs
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 2000/1013137
Date of experimental work: Pretest - November 1999; main test – Januar/Februar 2000.

GLP: Yes
(Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 406, EPA/OPPTS 870.2600, EEC 96/54 B 6

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 635 00 H; batch/purity: 99-1; formulation: 73.2 % BAS 635 H.
Test animals: Guinea pig; Hsd Poc: DH (SPF)

BAS 635 00 H was tested for its sensitising effect on the skin of the guinea pig in the Modified Buehler Test with nine inductions. The study was performed in 20 guinea pigs in the test group and 10 animals in each of the control groups 1 and 2. All nine inductions were performed with 60 % test substance preparations in aqua bidest. For the induction 2 x 2 cm gauze patches containing the test substance preparation were applied to the skin of the flank under an occlusive dressing. A volume of 0.5 ml of the test substance preparation was applied to each animal. The control animals were not treated.
The duration of exposure was 6 hours, the material was applied on the anterior left flank. Reading of the skin was performed at 24 h after the beginning of application.

A challenge was performed 13 days after the ninth induction. A volume of 0.5 ml of a 25 % test substance preparation in aqua bidest. was applied to each animal. The test group and control group 1 were treated with the test substance preparation (control group 2 remained untreated). The duration of exposure was 6 hours and the test substance preparation was applied on the middle of the right flank. Readings were performed at 24 and 48 h after the removal of the patch.

A positive control (reliability check) with known sensitisers is performed twice a year in the laboratory. The positive controls with 2-mercaptobenzothiazole and formaldehyde (minimum 36.5 % plus 10 % methanol) showed that the test system was able to detect sensitising compounds under the laboratory conditions chosen.

Findings:
The stability of the test substance was guaranteed for the duration of the study. The homogeneity of the test substance was confirmed by analysis. The stability of the test

substance in aqua bidest. for a time period of 4 hours was analytically demonstrated and its homogeneity was provided by stirring.
The concentration used in this study were selected based on the results of a pretest for skin irritation.
During the first, second, fourth and seventh induction some test animals showed discrete or patchy erythema (in one case in addition to swelling). The third, fifth until sixth induction did not cause any signs of skin irritation in all test group animals. Additionally during the induction phase a tearing out of hair at the edge of application area and a brownish discoloration of the skin after the challenge were observed. However, this did not impair the evaluation of erythema formation. The challange did not cause any skin reactions neither in control group 1 nor in the test group 24 and 48 hours after removal of the patches (Table B.6.11-6). Control group 2 that had been intended for a potential rechallenge was not treated and therefore not reported.

Table B.6.11-6: Skin findings after challenge

	Challenge (Test substance 25 % in aqua bidest) (number of animals with skin finding / number of animals tested)
Control group 1	0 / 10
Test group	0 / 20

Under the test conditions chosen BAS 635 00 H does not have a sensitising effect on the skin of the guinea pig in the Modified Buehler Test.

Conclusion:
BAS 635 00 H has no sensitising effect to the skin of the guinea pig in the Modified Buehler Test (9 inductions).

B.6.11.7 Supplementary studies for combinations of plant protection products

"Not applicable" as noted by the applicant.
Nevertheless, the intended use is in a tank-mix with surfactants like Citowett New (BAS 152 00 S), preferably, Dash HC (BAS 904 70 S) or other additives to which no data are given because these additives are not to assess in this monograph.

B.6.12 Dermal absorption (Annex IIIA 7.3)

The absorption, distribution and excretion of radioactivity was studied in male rats following a single dermal administration of [14C]-tritosulfuron mixed with the blank of a commercial formulation (BAS 635 01 H) and taken up in water. Nominal dose levels were 0.02, 0.2 and 2.0 mg/animal. Animals were exposed for 4 or 8 hours. About 3 % of the radioactivity applied were maximally absorbed at the low dose level of 0.002 mg/cm^3, about 0.6 – 0.7 % was absorbed at the higher doses. *In vitro* investigations on dermal absorption have been performed. The results of this study demonstrated that the rate of dermal penetration (µg/cm^2/h) through human skin was at least 2.2 fold less than through rat skin. Based on the *in vivo* results outlined above the dermal absorption of tritosulfuron in rats is determined to be 3.0 % at the most. Taking into account the difference between rat and human skin permeability, human skin penetration is 2-fold lower than rat skin penetration as demonstrated

by *in vitro* investigations. For calculation purposes a value of 1 % of the applied dose during an 8-hour exposure period will be used.

B.6.12.1 Dermal absorption in rats *in vivo*

Report: Leibold E. et al., 1998
^{14}C-BAS 635 H - Study of the dermal absorption in rats
BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep.
unpublished
BASF RegDoc# 1998/10802

GLP: Yes (Laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 417

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: 14C-tritosulfuron; Batch/radiochemical purity: 436-23 (phenyl-U-14C): > 97 %;
Tritosulfuron; Batch/purity: 691-33-1: > 98 %.
Test animals: Wistar rats (Chbb:THOM (SPF))
The absorption, distribution and excretion of radioactivity was studied in male Wistar rats following a single dermal administration of 14C-tritosulfuron mixed with the blank of a formulation (BAS 635 01 H) and taken up in water at nominal dose levels of 0.002, 0.02 and 0.2 mg/cm^2 corresponding to 0.02, 0.2 and 2 mg/animal or about 0.087, 0.87 and 8.7 mg/kg body weight. Animals were exposed for 4 or 8 hours and sacrificed 4, 8, 24 or 72 hours after beginning of exposure.
Twenty-four hours prior to dosing the back shoulders of the rats were clipped free of hair and the area (about 10 cm^2) was washed with acetone. A silicone ring was glued to the skin, the test substance preparation (about 10 µl/cm^2) was administered with a syringe which was weighed before and after application. A nylon mesh was then glued to the surface of the silicone ring and a porous bandage used to encircle the trunk of the animal.
The animals were dosed and then placed in metabolism cages in order to collect excreta up to 72 hours. For each dose level 16 animals were used. The test design for each dose level was as follows:

Table B.6.12-1: Study design *in vivo* dermal penetration

Duration of exposure [h]	4	8		
Sacrifice after [h]	4	8	24	72
number of animals	4	4	4	4

After the respective exposure period the protective cover was removed and the exposed skin was washed with a mild soap solution. At the end of the various collection periods animals were sacrificed and the following specimens/tissues were checked for remaining radioactivity:

excreta, blood cells, plasma, liver, kidneys, carcass, treated skin (application site) and non-treated areas (surrounding skin). For balance estimates the cage wash and skin wash as well as the protective cover (including the silicone ring) were also checked for radioactivity.

Findings:
The stability, homogeneity and correctness of the test substance preparation was analytically verified. Mean recoveries of radioactivity from all dose groups were in the range of 92.70 - 109.28 % of the total radioactivity administered. The main proportion of the radioactivity was recovered from the application site, skin wash, dressings and the skin surrounding the application site. Some of the radioactivity remained in the skin at the application site after end of exposure with part of it being absorbed during up to 64 hours post-exposure observation.

The total amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) increased with dose. The relative amount of radioactivity absorbed was very similar at the mid and high dose level (0.02 and 0.2 mg/cm^2). However, at the low dose level (0.002 mg/cm^2) this value was increased as compared to the other dose levels indicating saturation of penetration at the mid and high dose level under the conditions chosen.
The results are summarised in the table below:

Table B.6.12-2: Percentage of radioactivity absorbed and total amount of radioactive material absorbed

Exposure time [h]	Sacrifice time [h]	0.2 mg/cm^2		0.02 mg/cm^2		0.002 mg/cm^2	
		% abs.	mg/animal	% abs.	mg/animal	% abs.	mg/animal
4	4	0.18	0.0043	0.27	0.0007	3.33	0.0006
8	8	0.23	0.0056	0.35	0.0009	1.92	0.0004
8	24	0.32	0.0077	0.28	0.0007	2.72	0.0005
8	72	0.58	0.0138	0.71	0.0018	2.35	0.0004

About 3 % of the radioactivity applied were maximally absorbed at a dose level of 0.002 mg/cm^2, whereas at dose levels of 0.02 and 0.2 mg/cm^2 about 0.6-0.7 % of the dose applied was absorbed maximally.

The radioactivity absorbed was excreted mainly via the urine. Due to the very limited skin penetration, concentrations of radioactivity in organs and tissues analysed were very low.

Conclusion:
The *in vivo* dermal absorption of tritosulfuron in rats is approximately 3 % or less depending on the duration of exposure and concentration.

B.6.12.2 Dermal absorption *in vitro*

Report: Cotton H., 2001
(^{14}C)-BAS 635 H: Rates of penetration through rat and human skin using an *in vitro* system
Covance Laboratories (formerly Corning Hazleton), Harrogate, North Yorkshire HG3 1PY, United Kingdom

unpublished
BASF RegDoc# 2001/1006076

GLP: Yes (Laboratory certified by Department of Health of the Government of the United Kingdom, United Kingdom)

Guideline: Principles of draft OECD guideline on *in vitro* dermal penetration

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: (14C)-tritosulfuron; Batch/radiochemical purity: 538-0304: > 99 %;
Tritosulfuron; Batch/purity: N59; 98.19 %.
Test system: Rat and human epidermal membranes
The *in vitro* dermal absorption of (14C)-tritosulfuron, from a commercial formulation (BAS 635 00 H) was determined at three dose levels (20, 200 and 2000 µg active ingredient/cm^2), through rat and human epidermal membranes. The epidermal membranes were left un-occluded throughout the 24 h exposure period. To determine the integrity of the skin, prior to dose application, tritiated water was applied to the epidermal surface of the skin and penetration was measured. At termination of the membrane integrity check and prior to dose application, the receptor chamber was refilled with ethanol:water (1:1 v/v). The receptor fluid was chosen on the basis that the test substance is soluble in ethanol. The dose formulation was applied to the upper surface of the epidermal membranes using a positive displacement pipette. The amount of dose solution applied to each membrane was calculated by weight difference of the positive displacement pipette before and after dose administration.
Duplicate aliquots (0.1 ml) of receptor fluid were taken at 0 (i.e. pre-dose), 1, 2, 4, 6, 10 and 24 h after application of the formulation to the skin. An equal volume of fresh receptor fluid was added to the receptor chamber after each sampling occasion, excluding the final sample time, in order to maintain a constant volume of receptor fluid in the receptor chamber of the diffusion cell.
At 24 h post-application (after the last receptor fluid sampling) the receptor fluid was removed from the receptor chamber of all cells and retained. Any residual formulation was washed from the surface of the skin with a solution of Liquid Ivory™ soap (approximately 10 % w/v) containing no organic solvent and rinsed with deionised water. The washings were retained for analysis. The skin preparations were removed from the cells and solubilised. The glass diffusion chambers were dismantled and the glass donor and receptor portions placed into separate containers, where they were immersed with ethanol. The apparatus was removed from the container and the washings retained.
Radioactivity was determined in the receptor fluid, skin section, skin washings and apparatus washings to determine the overall mass balance of radioactivity. The percentage of the applied dose in each sample and the rate of penetration (µg equivalents/cm^2/h) was determined.

Findings:
The stability, homogeneity and correctness of the test substance preparation was analytically verified. An overall mean recovery of radioactivity of 92.42 % of the applied dose was attained for cells containing rat epidermal membranes, while 94.85 % was the recovery for human skin. The table below, summarises the key mean absorption parameters of formulated tritosulfuron in the BAS 635 00 H vehicle, through rat and human epidermal membranes.

Table B.6.12-3: Absorption of tritosulfuron *in vitro*

	Mean cumulative absorption of (14C)-tritosulfuron (µg/cm^2 skin)					
Administered dose	20 µg/cm^2		200 µg/cm^2		2000 µg/cm^2	
Time (hours)	rat skin	human skin	rat skin	human skin	rat skin	human skin
1	1.466	0.994	1.505	0.177	5.516	2.599
2	1.448	1.012	2.135	0.331	5.566	2.565
4	1.609	1.100	2.015	0.396	7.015	12.46
6	1.707	1.210	2.384	0.468	7.378	9.357
10	1.688	1.188	2.342	0.709	10.53	2.735
24	2.142	1.453	3.344	1.350	9.764	3.810
Lag Time (hours)	0.000	0.000	0.000	0.000	0.000	0.000
Mean rate of penetration (µg/cm^2/h)	0.041	0.018	0.104	0.032	0.322	0.087
Permeability coefficient (x 10-5 cm/h)	2.335	1.055	0.559	0.170	0.226	0.061

Penetration of (14C)-tritosulfuron through rat epidermal membranes

Independent of the concentration of the formulation, estimation of the lag phase by extrapolating the regression line for the initial rate of absorption, indicated almost instantaneous penetration (< 1 minute) of the radiolabel through rat epidermal membranes. Absorption of radioactivity was rapid during the early sample times of the experiment. Thereafter, the amount of radioactivity absorbed with time decreased, the rate of absorption measured between 10 and 24 hours being less than the initial rate.

Absorption of radioactivity at study termination accounted for 13 %, 1.8 % and 0.62 % at the low, medium and high dose levels respectively. The proportion of applied radioactivity recovered from the skin surface accounted for 63 %, 80 % and 94 % at the low, medium and high dose levels respectively and was unabsorbed. Radioactivity distributed within the epidermal membrane decreased with increasing formulation concentration, from 12 % to 1.8 % for the low and high dose levels respectively. For a 10 and a 100-fold increase in the concentration of the formulation applied to rat, a corresponding 2.56 and 7.94 fold increase in the initial rate of penetration was apparent. There was a 7-fold decrease in the amount of radioactivity absorbed, between the low and intermediate dose levels and at study termination (24 h), the proportion of radioactivity absorbed for the intermediate and high dose levels had decreased three-fold.

Penetration of (14C)-tritosulfuron through human epidermal membranes

Radioactivity was absorbed through human epidermal membranes < 1 minute after application, regardless of the concentration of (14C)-tritosulfuron in the formulation. As with the rat, there was evidence to suggest an initial high rate of absorption within the first six hours for some human epidermal membranes. The rate of absorption increased 1.72 and 4.75 times for a 10 and 100 fold increase in the concentration of (14C)-tritosulfuron. Thereafter, there was generally a linear relationship between the absorption of radioactivity through human epidermal membranes and time at each of the dose levels, albeit at a marginally slower rate. Washing was an effective method of removing the test material from rat epidermal membranes, particularly at the high application rate.

Figure B.6.12-1: Absorption of radioactivity through rat and human epidermal membranes following a single application of (^{14}C)-tritosulfuron at a nominal dose level of 20 µg/cm^2 (2 mg/ml) – groups A and D

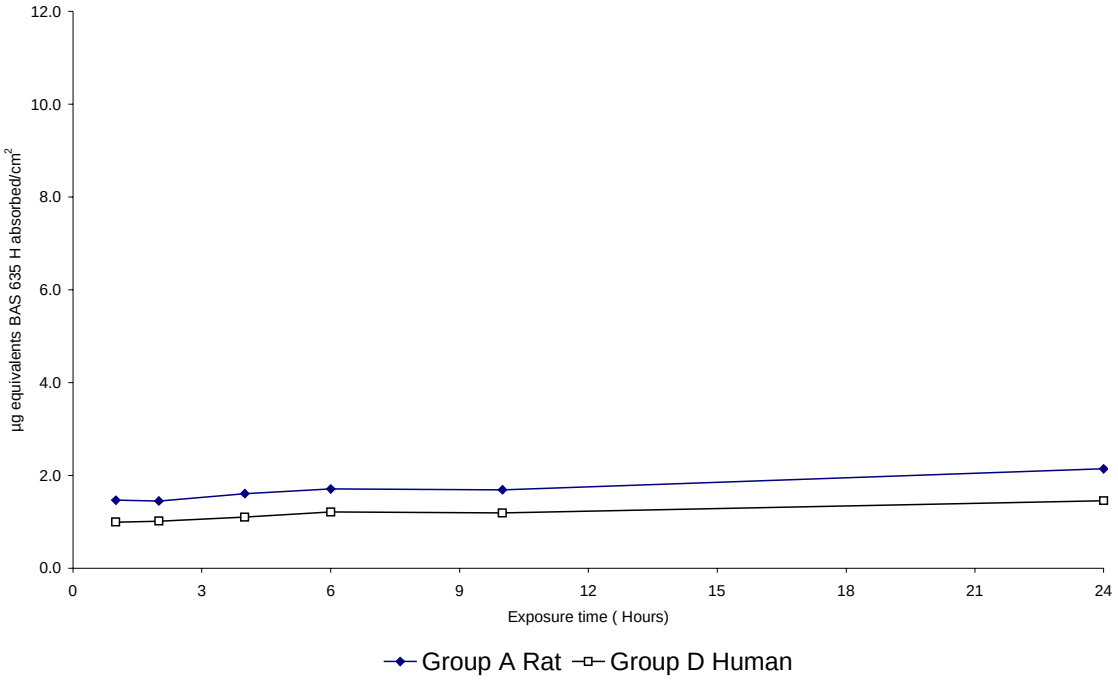


Figure B.6.12-2 Absorption of radioactivity through rat and human epidermal membranes following a single application of (^{14}C)-tritosulfuron at a nominal dose level of 200 µg/cm^2 (20 mg/ml) – groups B and E

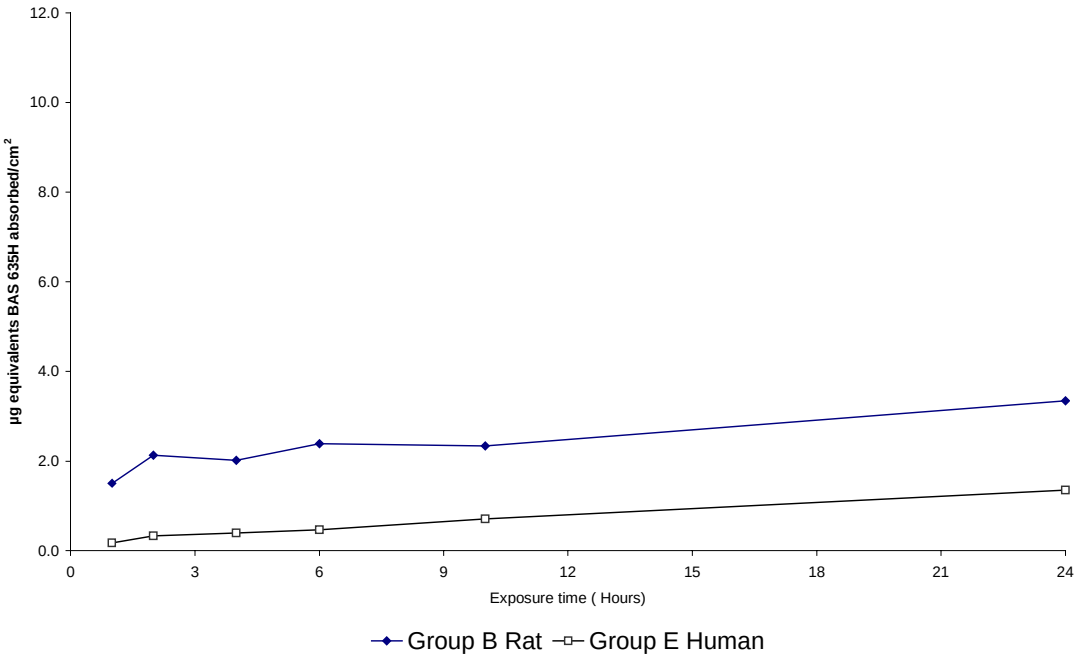
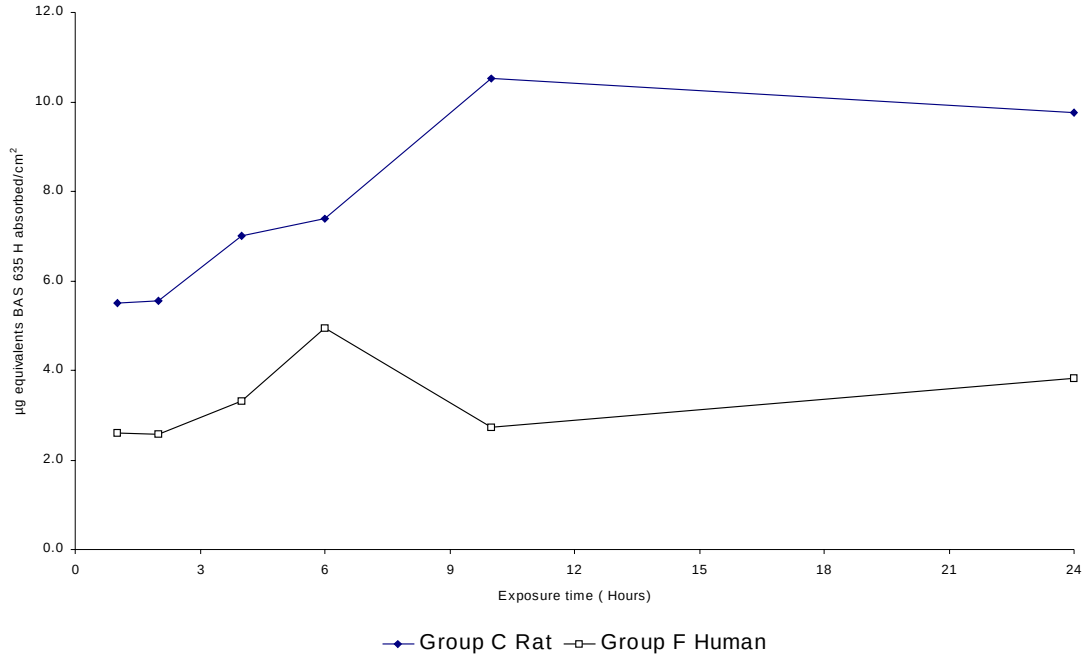


Figure B.6.12-3 Absorption of radioactivity through rat and human epidermal membranes following a single application of (^{14}C)-tritosulfuron at a nominal dose level of 2000 µg/cm^2 (200 mg/ml) – groups C and F



Difference in skin penetration through rat and human skin

The differences in the skin penetration between human and rat skin at the different dose levels (based on the rate of penetration) are shown in Table B.6.12-4:

Table B.6.12-4: Difference in skin penetration of tritosulfuron through rat and human skin

	Mean rate of penetration (µg/cm^2/h)		
Administered dose	20 µg/cm^2	200 µg/cm^2	2000 µg/cm^2
Mean rate of penetration rat epidermis	0.041	0.104	0.322
Mean rate of penetration human skin	0.018	0.032	0.087
Difference	2.27	3.25	3.70

Comparison of the initial rates of absorption between skin types showed that absorption was 2.27, 3.25 and 3.70 times faster through rat epidermal membranes than through human epidermal membranes following exposure to a formulation containing 0.02, 0.20 and 2.00 mg/cm^2, respectively. For both skin types, the increase in the amount of (^{14}C)-tritosulfuron absorbed, was less between the low and intermediate dose level, than the increase observed between the intermediate and high dose level. In addition, the permeability constants were much greater at the low dose level (2.335 x 10^{-5} cm/h for rat and 1.055 x 10^{-5} cm/h for human), than at the intermediate and high dose levels (0.559 x 10^{-5} cm/h and 0.226 x 10^{-5} cm/h for rat, and 0.170 x 10^{-5} cm/h and 0.061 x 10^{-5} cm/h for human), possibly suggesting retention of the active ingredient in the low dose formulation.

Comparison of the rat and human absorption characteristics at the high dose level revealed two anomalous results in the human skin cells (F1, 4 hours and F6, 6 hours). The inclusion of

these two figures resulted in an absorption plot which didn't follow any trend within this or other dose groups. These two results have not been included in the mean results quoted.

Conclusion:
The initial rate of absorption through rat epidermal membranes was at least 2.27 fold greater relative to human epidermal membranes.

B.6.13 Toxicological data on non active substances (Annex IIIA 7.4 and point 4 of the introduction)

The plant protection product BAS 635 00 H is formulated as a water-dispersible granule containing nominal 714 g/kg of the active ingredient tritosulfuron. As outlined by the notifier, the intended use is in a tank-mix with surfactants like Citowett New (BAS 152 00 S), preferably, Dash HC (BAS 904 70 S) or other additives to which no data are given because these additives are not to assess in this monograph.
Beside the active substance tritosulfuron, BAS 635 00 H contains antifoam and dispersing agents. Material Safety Data Sheets (MSDS) for the co-formulants which are contained are submitted and the possibly acute toxic properties are covered by the studies with the preparation.

B.6.14 Exposure data (Annex IIIA 7.2)

Information on product and use:
BAS 635 00 H is formulated as a water-dispersible granule containing nominal 714 g/kg of the active ingredient (a.i.) tritosulfuron. It is intended as a post emergence herbicide in cereals: winter and spring wheat, winter and spring barley, winter rye, oats, maize. The maximum application rate is 0.07 kg product/ha and therefore 0.050 kg a.i./ha. The intended use is in a tank-mix with surfactants like BAS 152 00 S (preferably), Dash HC (BAS 904 70 S) or other additives. Its recommended application is in the growth stage (BBCH-Code) 13 - 39 of the cereal crops. Applications of BAS 635 00 H will be carried out by using vehicle-mounted or drawn boom sprayers with hydraulic nozzles. Water will be the diluent/carrier in all situations. The spray volume will be in the range of 150 - 400 liters per hectar.

B.6.14.1 Operator exposure

B.6.14.1.1 Estimation of operator exposure; risk assessment

On the basis of the data submitted by the notifier, the operator exposure estimates are calculated using both the German model and the UK-POEM:

- Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, n° 277, 1992;

- Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) (UK MAFF) 1992.

To assess the estimated exposures, a comparison with tolerable exposure values has to be done. In the German model, the different parts of estimated exposures should be compared with the route specific AOELs (dermal or inhalation) to see whether there are problems and if so take specific PPEs into consideration in order to reduce the risk for the critical route of exposure. In the UK-POEM, the total estimated systemic exposures are to be compared with the systemic AOEL. In cases where no route specific AOELs can be derived, the estimated exposures of both models are to be assessed via the absorption rates on the basis of the systemic AOEL derived for the active ingredient.

Determination of the acceptable operator exposure level (systemic AOEL)
For setting the AOEL the most relevant study was considered to be the 90-day study in rats (NOAEL 75 mg/kg bw/d). Since the absorption was > 90 % of the administered dose by the oral route, no adjustment for systemic toxicity is needed (B.6.10.2). Applying a standard assessment factor of 100 a systemic AOEL of 0.75 mg/kg bw/d results.

$$\text{systemic AOEL} = \frac{75 \text{ mg/kg bw/d}}{100} = 0.75 \text{ mg/kg bw/d}$$

Dermal absorption rate
On the basis of the results of an *in vivo* dermal absorption study in rats and an *in vitro* comparison of the penetration of radiolabelled tritosulfuron through rat and human epidermal membranes an overall dermal absorption value of 1 % is proposed to use for risk assessment calculation purposes (B.6.12).

B.6.14.1.1.1 Operator exposure (German model)

The following assessment is made on the basis of the German model where the risk assessment is based on the comparison of the potential exposure and the tolerable exposure for each exposure route. The subsequent addition according to the following formula results in the "total degree of exposure" E:

$$E = \frac{D_{M(H)}}{D^{tol}} + \frac{D_{A(H)}}{D^{tol}} + \frac{D_{A(B)}}{D^{tol}} + \frac{D_{A(C)}}{D^{tol}} + \frac{I_M}{I^{tol}} + \frac{I_A}{I^{tol}}$$

If, according to this equation, the total degree of exposure E exceeds 1 - corresponding to 100% - (i.e. if the estimated or potential exposure is higher than the tolerable exposure or the AOEL) instructions for additional protective measures to reduce E are required.
The assessment was made with consideration of three individual levels of personal protective equipment (PPE) used by operators subsequently referred to as scenario 1 to 3.

Scenario 1:
No personal protective equipment is used when handling both the undiluted product (handling of product during mixing/loading) and during application.

Scenario 2:
Protective gloves are used when handling the undiluted product.

Scenario 3:
PPE with gloves, standard protective garment and sturdy footwear is used when handling the undiluted and the diluted product (handling of product during mixing/loading and application).

Determination of the tolerable exposure for tritosulfuron:
For the determination of the **tolerable dermal exposure** (D^{tol}) the NOAEL (90-d oral rat: 75 mg/kg bw/d) as considered to be relevant for the derivation of the systemic AOEL, a dermal absorption rate of 1 %, an assessment factor (AF) of 100 and an average body weight of 70 kg/person are to be taken into account. The tolerable dermal exposure is then determined as:

$$D^{tol} = \frac{NOAEL \text{ x } \%\,(oral\ abs.rate) \text{ x } bw/person}{AF \text{ x } \%\,(dermal\ abs.\ rate)} = \frac{75\ mg/kg\ bw \text{ x } 100\ \% \text{ x } 70\ kg\ bw/person}{100 \text{ x } 1\ \%}$$

D^{tol} = 5250 mg/person/d (equivalent to a dermal AOEL of 75 mg/kg bw/d).

Assuming 100 % pulmonary absorption, the **tolerable inhalation exposure (I^{tol})** is calculated as follows on the basis of this subchronic study and the oral absorption as mentioned above:

$$I^{tol} = \frac{NOAEL_0 \text{ x } bw\ (person)}{AF} = \frac{75\ mg/kg\ bw \text{ x } 70\ kg\ bw/person}{100}$$

I^{tol} = 52.5 mg/person (equivalent to an inhalation AOEL of 0.75 mg/kg bw).

Estimation of operator exposure for tritosulfuron:
Assumptions used for the calculation:

Formulation type:	Waterdispersible granule (WG)
Application technique:	Tractor mounted application/field crops
Area treated per day:	20 ha
Application rate:	0.05 kg a.i./ha
Dermal absorption rate:	1 %
Body weight of an operator:	70 kg
Penetration rate:	Gloves: 1 %; standard protective garment: 5 %

A summary of the expected/potential operator exposure for the different levels of PPE is provided in Table B.6.14-1: . More detailed information as to how these results have been generated is presented in appendix 1.

Table B.6.14-1: Summary of the estimated operator exposure* for tritosulfuron

Route of exposure and type of work	Scenario 1 No PPE	Scenario 2 PPE, mixing/loading	Scenario 3 PPE, all operations
Dermal exposure			
- Mixing/loading	2.00	0.02	0.02
- Application	2.04	2.04	0.14
Total dermal (D)	4.04	2.06	0.16
Inhalation exposure			
- Mixing/loading	0.008	0.008	0.008
- Application	0.001	0.001	0.001
Total inhalation (I)	0.009	0.009	0.009

* all figures in mg a.i./operator/day

The results of a comparison of estimated and tolerable exposures are presented in appendix 1 and summarised as follows:

Degree of exposure for scenario 1 (No PPE): E = 0.00094
Degree of exposure for scenario 2 (PPE during mixing/loading): E = 0.00056
Degree of exposure for scenario 3 (PPE during all operations): E = 0.00020

It is thus concluded that the estimated degree of exposure for tritosulfuron is in the range of 0.020 % to 0.094 % of the tolerable exposure (AOEL) depending on the level of PPE used. This indicates that the application of tritosulfuron is regarded as safe even without PPE under the conditions for which the authorisation of BAS 635 00 H is hereby requested.

B.6.14.1.1.2 Operator exposure (POEM-model)

As presented by the notifier, the operator exposure estimates were done using the UK-POEM for tractor application in field crops. The assessment was made with consideration of three individual levels of personal protective equipment (PPE) used by operators subsequently referred to as scenario 1 to 3.

Scenario 1:
No personal protective equipment is used when handling both the undiluted product (handling of product during mixing/loading) and during application.

Scenario 2:
Protective gloves are used when handling the undiluted product.

Scenario 3:
Protective gloves are used when handling the undiluted as well as the diluted product (handling of the product during mixing/loading and application).

Estimation of operator exposure for tritosulfuron in field crops, tractor application
Assumptions used for the calculation:

Formulation type:	Waterdispersible granule (WG)
Packaging	0,645 kg containers
Application technique:	Field crops: vehicle-mounted or trailed sprayers fitted with hydraulic nozzles
Area treated per day:	50 ha
Application rate:	0.0703 kg product/ha (i.e. 0.05 kg a.i./ha)
Water volume used	150-400 l/ha (worst case: 150 l/ha for calculation)
Dermal absorption rate:	1 %
Body weight of an operator:	60 kg
Penetration rate:	Gloves during mixing/loading 1 %; gloves during application: 10 %

A summary of the expected/potential operator exposure for the different levels of PPE is provided in Table B.6.14-2 for tractor operated equipment. More detailed information as to how these results have been generated is presented in appendices 2 to 4.

Table B.6.14-2: UK POEM - estimates of exposure to tritosulfuron from the use of BAS 635 00 H

dermal exposure[1)] (mg/person/day)			inhalation exposure[1)] (mg/person/day)	systemic* expos./absorbed dose (mg/person/day)		
mix/load	spray	total	spray	mix/load	spray**	total**
No PPE						
42.84	13.90	56.74	0.02	0.4284	0.159	0.588
Gloves during mixing/loading						
0.43	13.90	14.33	0.02	0.0043	0.159	0.163
Gloves during mixing/loading and application						
0.43	2.16	2.59	0.02	0.0043	0.042	0.046

1) Source: Tables, appendices 2 - 4.
* dermal absorption 1%; inhal. absorption 100 %.
** dermal and inhalation exposure.

Risk assessment, comparison of estimated and acceptable exposure

The results of the POEM calculations, without and with PPE, as presented in Table B.6.14-2 are summarised in the Table B.6.14-3 and expressed as percentage of the systemic AOEL.

Table B.6.14-3: UK POEM - Predicted exposure as a proportion of the systemic AOEL

PPE	Total systemic exposure		% of systemic AOEL (0.75 mg/kg bw/d)
	mg/person	mg/kg bw*	
No PPE	0.588	0.0098	1.31
Gloves during mixing/loading	0.163	0.0027	0.36
Gloves during mixing/loading and appl.	0.046	0.0008	0.10

* mg/person: 60 kg/person.

The exposure accounts for only 1.31 % of the systemic AOEL value if no PPE is used. The use of gloves during mixing/loading reduces this figure to about 0.36 % of the AOEL, whereas gloves during mixing/loading and application leads to a further reduction - exposure being 0.1 % of the AOEL value.

Final conclusion of the risk evaluation for operators:

The results show that the operator exposure for all proposed uses is acceptable even if no personal protection is used (German model: exposure = 0.094 % of the systemic AOEL; UK-POEM: exposure = 1.31 % of the systemic AOEL).

Table B.6.14-4: Results of the model calculations and a comparison with the proposed systemic AOEL

German model	treated area per day (ha/d)	PPE	Systemic exposure* (mg/kg bw/d)	% of AOEL (0.75 mg/kg bw/d)
	20	none	0.00071	0.094
		m/l: gloves	0.00042	0.056
		m/l: gloves; appl.: gloves + garment	0.00015	0.020
UK POEM	**treated area per day (ha/d)**	**PPE**	**Systemic exposure* (mg/kg bw/d)**	**% of AOEL (0.75 mg/kg bw/d)**
	50	none	0.0098	1.31
		m/l: gloves	0.0027	0.36
		m/l: gloves; appl.: gloves	0.0008	0.10
* In the calculations a body weight of 70 kg (German model) or 60 kg (UK POEM) and a dermal absorption rate of 1 % were used.				

Considering the results of the risk assessments based on the German model as well as on the UK-POEM it is concluded that BAS 635 00 H can be handled safely under the recommended conditions of use.

B.6.14.1.2 Measurement of operator exposure

Under the given conditions it can be assumed that the exposure of the operator is not exceeding the AOEL (see chapter above) and, therefore, a specific measurement was not performed.

B.6.14.2 Worker exposure

B.6.14.2.1 Estimation of worker exposure

As outlined by the notifier BAS 635 00 H will be applied in cereal crops at growth stage 12 - 39. Hand operations with these crops do not belong to standard growing procedures after the application of the herbicide and thus contact of relevant duration with treated plants is not expected. Therefore a relevant re-entry scenario actually does not exist.
However, for a restricted period of time scouting may be practiced to control the herbicidal effect or to check the need for additional applications (e.g. treatments with growth regulators or fungicides). In order to consider such a situation an estimation will be based on the model as developed by the German BBA (Biologische Bundesanstalt) [Hoernicke E. et al.; 1998; Hinweise in der Gebrauchsanleitung zum Schutz von Personen bei Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen (worker re-entry; Nachrichtenbl. Deut. Pflanzenschutzd. 50, Berlin] and the US EPA [EPA, Science Advisory Council for Exposure; 1998; Agricultural Default Transfer Coefficients, Policy # 003, 1998].

The following parameters were considered by the notifier:

Dislodgeable foliar residue	DFR	=	1 µg/cm² x kg ai applied
Transfer factor, according to EPA	TF*	=	1000 cm²/h x person
Working period	A	=	2 h/day
Penetration of protective material	P	=	5 % (= factor 0.05)
Rate of application	R	=	0.05 kg tritosulfuron/ha

* A transfer factor of 1000 was used as these operations substantially provide exposure of lower legs only and no other parts of the body.

Calculation of potential dermal exposure:

Dermal exposure (D) of the unprotected worker

D = DFR x TF x A x R
= 1 x 1000 x 2 x 0.05
= 100 µg/person x day
= 0.1 mg/person x day

considering a body weight of 70 kg

D = 0.00143 mg/kg bw/d

Dermal exposure (D(PPE)) for the protected worker

D (PPE) = D x P
= 0.00143 x 0.05
D (PPE) = 0.000072 mg/kg bw/d

The notifier compared the potential dermal exposure of workers with a specific dermal AOEL of 10 mg/kg bw/d (28d-dermal-study on rats; NOAEL = 1000 mg/kg bw/d; SF 100) and thus resulted in values for the "AOEL covered (%)" of: unprotected = 0.0143 %, protected = 0.00072 %.

However calculating with a dermal absorption rate of 1 % and a systemic AOEL of 0.75 mg/kg bw/d, it results in a higher tolerable dermal exposure (75 mg/kg bw/d).

Estimated absorbed dose (considering a dermal absorption rate of 1 %)**:**

	Potential dermal exposure	x	0.01		
without PPE:	0.00143	x	0.01	=	0.0000143 mg/kg bw/d
protected worker:	0.000072	x	0.01	=	0.00000072 mg/kg bw/d

Risk assessment:

The estimated dermal exposure as percentage of the systemic AOEL (0.75 mg/kg bw/d) are calculated to be:

without PPE:	0.0019 %
protected worker:	0.0001 %

The results of the risk assessment indicate that re-entry of treated fields is possible with a sufficient margin of safety after the spray solution has dried up. Special protective measures for worker re-entry are not necessary.

B.6.14.2.2 Measurement of worker exposure

Considering the results of the risk assessment on the basis of the estimated exposures, a measurement of worker exposure is not necessary and was, therefore, not performed.

B.6.14.3 Bystander exposure

As outlined by the notifier, BAS 635 00 H is a herbicide applied in field crops. The usual form of application is by tractor-mounted sprayers without bystanders. The spray solution as applied will contain a maximum of 0.05 % of the formulated product or 0.03 % w/v of the active ingredient tritosulfuron. In view of the recommended application technique in combination with Good Agricultural Practice (GAP) bystanders may be exposed briefly and to relatively low quantities of spray compared to an operator.
A possible situation in which bystander exposure may occur would be a person walking on a footpath alongside an area which is being treated at the same time. Even under these conditions the bystander will never walk directly next to the outer spraying nozzle. A distance of some meters from the downwind edge of the spray swath can always be expected.
To estimate exposure to bystanders, a comparison with the operator exposure can be helpful. In field crop applications with boom sprayers the following points are of particular importance:

a) Bystanders walking alongside a field which is being treated, are exposed only for the few seconds when the sprayer moves along the person. Assumed that passing a bystander takes a minute, the exposure time is only the 360th part of the exposure time of the operator, spraying 6 hours a day.
b) Repeated exposure is unlikely, since the sprayer will only pass once along the edge of a field for each spraying swath.
c) Bystanders always stand at a larger distance from the edge of the spray boom and thus from the spraying nozzle, than the operator. For example, an operator (the tractor driver) may be at 2 to 4 m distance to the nearest spraying nozzles, bystanders at least at about 8 m.

These factors even outweigh the reduction of exposure for the operator caused by garment worn during application. Therefore, during application field bystander exposure is no subject of special concern. It may be reminded that due to the results of the risk assessment operators are not requested to wear special protective measures during application. Nevertheless they are obliged to take care of themselves and for bystanders in accordance with good agricultural practice (GAP).
Due to considerations as indicated above a more quantitative estimation of bystander exposure was not performed.
Taking into account the results of the risk assessment for the operator which indicate that the exposure is always below the proposed systemic AOEL (German model and UK POEM, without PPE), the rapporteur agreed with the risk assessment for bystanders as given by the notifier (see above).

Appendix 1
BBA model: Operator exposure for tritosulfuron in field crops – tractor mounted

Assumptions and input parameters considered for the estimation of the operator exposure:

Formulation type:	WG	$\mathbf{D_{M(H)}}$	= 2.0 mg/person x kg a.i.
Application technique:	tractor mounted	$\mathbf{D_{A(H)}}$	= 0.38 mg/person x kg a.i.
Application rate:	0.05 kg tritosulfuron/ha	$\mathbf{D_{A(B)}}$	= 1.6 mg/person x kg a.i.
Area treated per day:	20 ha	$\mathbf{D_{A(C)}}$	= 0.06 mg/person x kg a.i.
		$\mathbf{I_M}$	= 0.008 mg/person x kg a.i.
		$\mathbf{I_A}$	= 0.001 mg/person x kg a.i.

Route of exposure			**Scenario 1 (No PPE)**	**Scenario 2 PPE, mix./load.**	**Scenario 3 PPE, all operations**
Dermal/mixing					
exposure (hands):	$\mathbf{D_{M(H)}}$	=	2.0 x 0.05 x 20		
		=	2 mg/person	0.02 mg/person*1	0.02 mg/person*1
Dermal/application					
exposure (hands, body, head)	$\mathbf{D_{A(H)}}$	=	0.38 x 0.05 x 20		
		=	0.38 mg/person	0.38 mg/person	0.0038 mg/person*1
	$\mathbf{D_{A(B)}}$	=	1.6 x 0.05 x 20		
		=	1.60 mg/person	1.6 mg/person	0.08 mg/person*2
	$\mathbf{D_{A(C)}}$	=	0.06 x 0.05 x 20		
		=	0.06 mg/person	0.06 mg/person	0.06 mg/person
Total dermal exposure		=	**4.04 mg/person**	**2.06 mg/person**	**0.164 mg/person**
Inhalation/mixing					
	$\mathbf{I_M}$	=	0.008 x 0.05 x 20		
		=	0.008 mg/person	0.008 mg/person	0.008 mg/person
Inhalation/application					
	$\mathbf{I_A}$	=	0.001 x 0.05 x 20		
		=	0.001 mg/person	0.001 mg/person	0.001 mg/person
Total inhalation exposure		=	**0.009 mg/person**	**0.009 mg/person**	**0.009 mg/person**

*1 reduction factor of gloves = 0.01
*2 reduction factor of protective clothing = 0.05

Calculation of degree of exposure (E):

$$E = \frac{D_{M(H)}}{D^{tol}} + \frac{D_{A(H)}}{D^{tol}} + \frac{D_{A(B)}}{D^{tol}} + \frac{D_{A(C)}}{D^{tol}} + \frac{I_M}{I^{tol}} + \frac{I_A}{I^{tol}}$$

For tolerated exposures see: B.6.14.1.1.1 (Determination of the tolerable exposure for tritosulfuron):

D^{tol} = 5250 mg/person/d (i.e. 75 mg/kg bw/d)
I^{tol} = 52.5 mg/person/d (i.e. 0.75 mg/kg bw/d)

Scenario 1: without PPE:

$$E = \frac{2.0}{5250} + \frac{0.38}{5250} + \frac{1.6}{5250} + \frac{0.06}{5250} + \frac{0.008}{52.5} + \frac{0.001}{52.5} = \mathbf{0.00094}$$

Scenario 2: considering PPE (gloves during mixing/loading):

$$E = \frac{0.02}{5250} + \frac{0.38}{5250} + \frac{1.6}{5250} + \frac{0.06}{5250} + \frac{0.008}{52.5} + \frac{0.001}{52.5} = \mathbf{0.00056}$$

Scenario 3: considering PPE (gloves and garment during all operations):

$$E = \frac{0.02}{5250} + \frac{0.0038}{5250} + \frac{0.08}{5250} + \frac{0.06}{5250} + \frac{0.008}{52.5} + \frac{0.001}{52.5} = \mathbf{0.00020}$$

Appendix 2:
UK POEM: Tractor-mounted/drawn field crop sprayer with hydraulic nozzles – no PPE

PRODUCT DATA				
Product	BAS 635 00 H			
Active substance	Tritosulfuron			
Concentration	714	mg/g		
Formulation type	WG			
Maximum in-use a.i. concentration	0.334628	mg/ml		
EXPOSURE DURING MIXING AND LOADING				
Container size	0,645	kg		
Hand contamination/operation	0,01	ml		
Application dose	0,0703	kg product/ha		
Work rate	50	ha/day		
Number of operations	6	/day		
Hand contamination	0,06	g/day		
Protective clothing	none			
Transmission to skin	100	%		
Dermal exposure to formulation	0,06	g/day		
EXPOSURE DURING SPRAY APPLICATION				
Application technique	tractor-mounted/drawn field crop sprayer with hydraulic nozzles			
Application volume	150	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65	10	25	%
Clothing	none	permeable	permeable	
Penetration	100	5	15	%
Dermal exposure	6,5	0,05	0,375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41,55	ml/day		
ABSORBED DOSE				
	Mix/load		Application	
Dermal exposure	0,06	g/day	41,55	ml/day
Concentration of a.s.	714	mg/ml	0,334628	mg/ml
Dermal exposure to a.s.	42,84	mg/day	13,9037934	mg/day
Percent absorbed	1	%	1	%
Absorbed dose	0,4284	mg/day	0,139037934	mg/day
INHALATION EXPOSURE DURING SPRAYING				
Inhalation exposure	0,01	ml/h		
Duration of exposure	6	h		
Concentration of a.s.	0,334628	mg/ml		
Inhalation exposure to a.s.	0,02007768	mg/day		
Percent absorbed	100	%		
Absorbed dose	0,02007768	mg/day		
PREDICTED EXPOSURE				
Total absorbed dose	0,587515614	mg/day		
Operator body weight	60	kg		
Operator exposure	0,009791927	mg/kg bw/day		
COMPARISON WITH AOEL	(Systemic AOEL: 0.75 mg/kg bw/d)			
Operator exposure	**1.3055**	**%**		

Appendix 3:
UK POEM: Tractor-mounted/drawn field crop sprayer with hydraulic nozzles – gloves during mixing/loading

PRODUCT DATA					
Product	BAS 635 00 H				
Active substance	Tritosulfuron				
Concentration	714	mg/g			
Formulation type	wdg				
Main solvent					
Concentration of solvent		w/w			
Maximum in-use a.s. concentration	0,334628	mg/ml			
EXPOSURE DURING MIXING AND LOADING					
Container size	0,645	kg			
Hand contamination/operation	0,01	ml			
Application dose	0,0703	kg product/ha			
Work rate	50	ha/day			
Number of operations	6	/day			
Hand contamination	0,06	g/day			
Protective clothing	gloves				
Transmission to skin	1	%			
Dermal exposure to formulation	0,0006	g/day			
EXPOSURE DURING SPRAY APPLICATION					
Application technique	tractor-mounted/drawn field crop sprayer with hydraulic nozzles				
Application volume	150	spray/ha			
Volume of surface contamination	10	ml/h			
Distribution	Hands		Trunk	Legs	
	65		10	25	%
Clothing	none		permeable	permeable	
Penetration	100		5	15	%
Dermal exposure	6,5		0,05	0,375	ml/h
Duration of exposure	6	h			
Total dermal exposure to spray	41,55	ml/day			
ABSORBED DOSE					
	Mix/load			Application	
Dermal exposure	0,0006	g/day		41,55	ml/day
Concentration of a.s.	714	mg/ml		0,334628	mg/ml
Dermal exposure to a.s.	0,4284	mg/day		13,9037934	mg/day
Percent absorbed	1	%		1	%
Absorbed dose	0,004284	mg/day		0,139037934	mg/day
INHALATION EXPOSURE DURING SPRAYING					
Inhalation exposure	0,01	ml/h			
Duration of exposure	6	h			
Concentration of a.s.	0,334628	mg/ml			
Inhalation exposure to a.s.	0,02007768	mg/day			
Percent absorbed	100	%			
Absorbed dose	0,02007768	mg/day			
PREDICTED EXPOSURE					
Total absorbed dose	0,163399614	mg/day			
Operator body weight	60	kg			
Operator exposure	0,002723327	mg/kg bw/day			
COMPARISON WITH AOEL	(Systemic AOEL: 0.75 mg/kg bw/d)				
Operator exposure	**0.3622**	**%**			

Appendix 4:
UK POEM: Tractor-mounted/drawn field crop sprayer with hydraulic nozzles - gloves during mixing/loading and application

PRODUCT DATA				
Product	BAS 635 00 H			
Active substance	Tritosulfuron			
Concentration	714	mg/g		
Formulation type	wdg			
Main solvent				
Concentration of solvent		w/w		
Maximum in-use a.s. concentration	0,334628	mg/ml		
EXPOSURE DURING MIXING AND LOADING				
Container size	0,645	kg		
Hand contamination/operation	0,01	ml		
Application dose	0,0703	kg product/ha		
Work rate	50	ha/day		
Number of operations	6	/day		
Hand contamination	0,06	g/day		
Protective clothing	gloves			
Transmission to skin	1	%		
Dermal exposure to formulation	0,0006	g/day		
EXPOSURE DURING SPRAY APPLICATION				
Application technique	tractor-mounted/drawn field crop sprayer with hydraulic nozzles			
Application volume	150	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65	10	25	%
Clothing	gloves	permeable	permeable	
Penetration	10	5	15	%
Dermal exposure	0,65	0,05	0,375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	6,45	ml/day		
ABSORBED DOSE				
	Mix/load		Application	
Dermal exposure	0,0006	g/day	6,45	ml/day
Concentration of a.s.	714	mg/ml	0,334628	mg/ml
Dermal exposure to a.s.	0,4284	mg/day	2,1583506	mg/day
Percent absorbed	1	%	1	%
Absorbed dose	0,004284	mg/day	0,021583506	mg/day
INHALATION EXPOSURE DURING SPRAYING				
Inhalation exposure	0,01	ml/h		
Duration of exposure	6	h		
Concentration of a.s.	0,334628	mg/ml		
Inhalation exposure to a.s.	0,02007768	mg/day		
Percent absorbed	100	%		
Absorbed dose	0,02007768	mg/day		
PREDICTED EXPOSURE				
Total absorbed dose	0,045945186	mg/day		
Operator body weight	60	kg		
Operator exposure	0,000765753	mg/kg bw/day		
COMPARISON WITH AOEL	(Systemic AOEL: 0.75 mg/kg bw/d)			
Operator exposure	**0.1021**	**%**		

B.6.15 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.1	Cotton, H.	2001	(14C)-BAS 635 H: Rates of penetration through rat and human skin using an in vitro system. 729/206 ! 2001/1006076 GLP, unpublished TOX2001-896	Y	BAS
AIIA-5.1	Hafemann, C.	2000	The metabolism of 14C-BAS 635 H (reg. no. 271272) in rats. 19461 ! 2000/1013501 GLP, unpublished TOX2001-893	Y	BAS
AIIA-5.1	Leibold, E. and Hoffmann, H.D.	2001	Investigation of the formation of AMTT after oral administration of 14C-BAS 635 H in rats. 02B0380/996010 ! 2000/1013503 GLP, unpublished TOX2001-894	Y	BAS
AIIA-5.1	Leibold, E., Hoffmann, H.D. and Hildebrand, B.	1998	14C-BAS 635 H - Study of the dermal absorption in rats. 01B0020/956022 ! #BASF 98/10802 GLP, unpublished TOX2001-895	Y	BAS
AIIA-5.1	Leibold, E., Hoffmann, H.D. and Hildebrand, B.	1998	14C-BAS 635 H - Study of the biokinetics in rats. 02B0300/946013 ! #BASF 98/10506 GLP, unpublished TOX2001-892	Y	BAS
AIIA-5.2.1	Kirsch, P. and Hildebrand, B.	1995	Study on the acute oral toxicity of reg. no. 271 272 in rats. 10A0290/941062 ! #BASF 95/10634 GLP, unpublished TOX2001-897	Y	BAS
AIIA-5.2.2	Kirsch, P. and Hildebrand, B.	1995	Study on the acute dermal toxicity of reg. no. 271 272 in rats. 11A0290/941063 ! #BASF 95/10635 GLP, unpublished TOX2001-898	Y	BAS
AIIA-5.2.3	Gamer, A.O. and Hoffmann, H.D.	1995	Study on the acute inhalation toxicity LC50 of reg. no. 271 272 as a dust aerosol in rats 4-hour exposure. 13I0290/947009 ! #BASF 95/10410 GLP, unpublished TOX2001-899	Y	BAS

[5] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.2.4	Rossbacher, R. and Hellwig, J.	1995	Study on the acute dermal irritation/corrosion of reg. no. 271 272 in rabbits. 14H0290/942094 ! #BASF 95/10533 GLP, unpublished TOX2001-900	Y	BAS
AIIA-5.2.5	Rossbacher, R. and Hellwig, J.	1995	Study on the acute eye irritation of reg. no. 271 272 in rabbits. 13H0290/942095 ! #BASF 95/10532 GLP, unpublished TOX2001-901	Y	BAS
AIIA-5.2.6	Rossbacher, R. and Hellwig, J.	1995	Report on the maximization test for the sensitizing potential of reg. no. 271 272 in guinea pigs. 30H0290/942096 ! #BASF 95/10523 GLP, unpublished TOX2001-902	Y	BAS
AIIA-5.3.1	Mellert, W., Deckardt, K., Gembardt, Chr. and Hildebrand, B.	1998	BAS 635 H - Repeated dose dermal toxicity study in Wistar rats administration for 4 weeks. 33S0167/95101 ! #BASF 98/10479 GLP, unpublished TOX2001-905	Y	BAS
AIIA-5.3.1	Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	1996	Reg. no. 271 272 - Repeated dose oral toxicity study in B6C3F1 CrlBr mice administration in the diet for 4 weeks. 40S0385/94030 ! #BASF 96/10430 GLP, unpublished TOX2001-904	Y	BAS
AIIA-5.3.1	Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	1997	Reg. no. 271 272 - Repeated dose oral toxicity study in Wistar rats administration in the diet for 4 weeks. 30S0385/94029 ! #BASF 97/10819 GLP, unpublished TOX2001-903	Y	BAS
AIIA-5.3.2	Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	1997	BAS 635 H - Subchronic oral toxicity study in B6C3F1 Crl BR mice administration in the diet for 3 months. 60S0385/94034 ! #BASF 97/11511 GLP, unpublished TOX2001-907	Y	BAS
AIIA-5.3.2	Mellert, W., Deckardt, K., Kaufmann, W. and Hildebrand, B.	2000	BAS 635 H - Subchronic oral toxicity study in Wistar rats administration in the diet for 3 months. 50S0385/94036 ! 2000/1003966 GLP, unpublished TOX2001-906	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.3.2	Menges, S., Schilling, K., Deckardt, K., Kaufmann, W. and Hildebrand, B.	2000	BAS 635 H - Subchronic oral toxicity study in Beagle dogs administration in the diet for 3 months. 31D0167/95044 ! 2000/1012355 GLP, unpublished TOX2001-908	Y	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1998	In vitro gene mutation test with BAS 635 H in CHO cells (HPRT locus assay). 50M0167/954099 ! 98/11436 GLP, unpublished TOX2001-911	Y	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1998	In vitro unscheduled DNA synthesis (UDS) assay with BAS 635 H in primary rat hepatocytes. 81M0167/954145 ! #BASF 98/10811 GLP, unpublished TOX2001-913	Y	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1998	In vitro chromosome aberration assay with BAS 635 H in V79 cells. 32M0167/954100 ! 98/11437 GLP, unpublished TOX2001-912	Y	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	2000	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with BAS 635 H. 40M0290/944382 ! 2000/1018507 GLP, unpublished TOX2001-910	Y	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1998	Report on the study of BAS 635 H (ZHT test substance no.: 95/167-1) in the Ames Test (salmonella/mammalian-microsome mutagenicity test - Standard plate test and preincubation test). 40M0167/954105 ! 1998/11634 GLP, unpublished TOX2001-909	Y	BAS
AIIA-5.4.2	Engelhardt, G. and Hoffmann, H.D.	1998	Cytogenetic study in vivo with BAS 635 H in the mouse micronucleus test single intraperitoneal administration. 26M0167/954101 ! #BASF 98/10581 GLP, unpublished TOX2001-914	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	2001	BAS 635 H - Supplementary carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0167/95080 ! 2001/1006065 GLP, unpublished TOX2001-922	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.5	Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	2001	BAS 635 H - Carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0167/95022 ! 2001/1006064 GLP, unpublished TOX2001-921	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	2001	BAS 635 H - Supplementary chronic toxicity study in Wistar rats administration in the diet for 24 months. 82S0167/95081 ! 2001/1006061 GLP, unpublished TOX2001-918	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Küttler, K. and Van Ravenzwaay, B.	2001	BAS 635 H - Carcinogenicity study in B6C3F1/CrlBR mice administration in the diet for 18 months. 76S0167/95021 ! 2001/1006084 GLP, unpublished TOX2001-923	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	2001	BAS 635 H - Chronic toxicity study in Wistar rats administration in the diet for 24 months. 82S0167/95023 ! 2001/1006060 GLP, unpublished TOX2001-917	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	2001	BAS 635 H - Carcinogenicity study in Wistar rats administration in the diet for 24 months. 82S0042/98025 ! 2001/1006062 GLP, unpublished TOX2001-919	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	2001	BAS 635 H - Supplementary carcinogenicity study in Wistar rats administration in the diet for 24 months. 82C0042/98049 ! 2001/1006063 GLP, unpublished TOX2001-920	Y	BAS
AIIA-5.5	Mellert, W., Deckardt, K., Pappritz, G. and Van Ravenzwaay, B.	2001	BAS 635 H - Chronic toxicity study in Wistar rats administration in the diet for 12 months. 70C0042/98065 ! 2001/1006059 GLP, unpublished TOX2001-916	Y	BAS
AIIA-5.5	Menges, S., Schilling, K., Deckardt, K., Kaufmann, W. and Hildebrand, B.	2000	BAS 635 H - Chronic oral toxicity study in Beagle dogs administration in the diet for 12 months. 33D0167/95074 ! 2000/1012356 GLP, unpublished TOX2001-915	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.6.1	Schilling, K., Deckardt, K., Gembardt, Chr. and Van Ravenzwaay, B.	2001	BAS 635 H - Two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0167/95088 ! 2001/1006077 GLP, unpublished TOX2001-925	Y	BAS
AIIA-5.6.1	Schilling, K., Gembardt, C. and Van Ravenzwaay, B.	2001	BAS 635 H - Supplementary two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0167/95110 ! 2001/1006067 GLP, unpublished TOX2001-926	Y	BAS
AIIA-5.6.1	Schilling, K., Gembardt, Chr. and Van Ravenzwaay, B.	2001	BAS 635 H - Two-generation reproduction toxicity study in Wistar rats continuous dietary administration. 70R0042/98010 ! 2001/1006066 GLP, unpublished TOX2001-924	Y	BAS
AIIA-5.6.2	Hellwig, J. and Hildebrand, B.	1998	BAS 635 H - Prenatal toxicity in Himalayan rabbits after oral administration (gavage). 40R0385/94040 ! #BASF 98/10227 GLP, unpublished TOX2001-928	Y	BAS
AIIA-5.6.2	Hellwig, J. and Hildebrand, B.	1996	Reg. no. 271 272 - Prenatal toxicity in Wistar rats after oral administration (gavage). 30R0290/94017 ! #BASF 96/10210 GLP, unpublished TOX2001-927	Y	BAS
AIIA-5.7	Mellert, W.	2001	BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats administration in the diet for 3 months. 50S0167/95102 ! 2001/1006068 GLP, unpublished TOX2001-931	Y	BAS
AIIA-5.7	Mellert, W., Kaufmann, W. and Hildebrand, B.	1998	BAS 635 H - Subchronic oral neurotoxicity study in Wistar rats administration in the diet for 3 months. 50S0167/95102 ! #BASF 98/10678 GLP, unpublished TOX2001-930	Y	BAS
AIIA-5.7	Mellert, W., Kaufmann, W. and Hildebrand, B.	1998	BAS 635 H - Acute oral neurotoxicity study in Wistar rats. 20S0167/95103 ! 98/11438 GLP, unpublished TOX2001-929	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.7	Nemec, M.D.	2001	Dietary developmental neurotoxicity study of BAS 635 H in rats. WIL-403001 ! 2001/1006071 GLP, unpublished TOX2001-932	Y	BAS
AIIA-5.8.1	Czich, A.	1999	In vitro chromosome aberration assay in Chinese hamster V79 cells with reg.-no. 335 182 (BH 635-3). 633600 ! 32M0576/969428 ! #BASF 99/11504 GLP, unpublished TOX2001-944	Y	BAS
AIIA-5.8.1	Engelhardt, G.	2001	Amendment no. 3 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 2001/1007726 GLP, unpublished TOX2001-942	Y	BAS
AIIA-5.8.1	Engelhardt, G.	2000	Amendment no. 1 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 2000/1019291 GLP, unpublished TOX2001-941	Y	BAS
AIIA-5.8.1	Engelhardt, G.	1999	Amendment no. 1 to the report salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! 1999/11629 GLP, unpublished TOX2001-940	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1999	In vitro chromosome aberration assay with reg.-no. 292 564; BH 635-2 in V79 cells. 32M0599/964427 ! 1999/11684 GLP, unpublished TOX2001-935	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1999	In vitro chromosome aberration assay with reg.-no. 335 184 (BH 635-4) in V79 cells. 32M0577/964426 ! 1999/11685 GLP, unpublished TOX2001-950	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg.-no. 373 906. 40M0298/004076 ! 2001/1006087 GLP, unpublished TOX2001-952	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	In vitro gene mutation test with reg.-no. 373 906 in CHO cells (HPRT locus assay). 50M0298/004079 ! 2001/1006073 GLP, unpublished TOX2001-953	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	Cytogenetic study in vivo with reg.-no. 373 906 in the mouse micronucleus test after two intraperitoneal administrations. 26M0298/004077 ! 2000/1018736 GLP, unpublished TOX2001-954	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1998	Salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg.-no. 335 184 (BH 635-4). 40M0577/964422 ! 1998/11635 GLP, unpublished TOX2001-948	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1998	Salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test) with PS 335 182. 40M0576/964420 ! #BASF 98/10810 GLP, unpublished TOX2001-939	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1999	Salmonella typhimurium / escherichia coli reverse mutation assay (standard plate test and preincubation test) with reg.-no. 292 564; BH 635-2. 40M0599/964425 ! 1999/11412 GLP, unpublished TOX2001-933	Y	BAS
AIIA-5.8.1	Gamer, A.O. and Hoffmann, H.D.	2000	Reg. no. 373906 - Acute oral toxicity study in Wistar rats. 10A0298/001071 ! 2001/1006074 GLP, unpublished TOX2001-955	Y	BAS
AIIA-5.8.1	Kirsch, P. and Hildebrand, B.	1995	Study on the acute oral toxicity of TBSA in rats. 10A0148/941038 ! #BASF 95/11408 GLP, unpublished TOX2001-936	Y	BAS
AIIA-5.8.1	Mellert, W., Deckardt, K., Gembardt, Ch. and Van Ravenzwaay, B.	2001	Reg.-no. 335182 (BH 635-3) - Subchronic toxicity study in Wistar rats administration in the diet for 3 months. 50C0576/96195 ! 2001/1006072 GLP, unpublished TOX2001-947	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.8.1	Wiemann, C.	1998	Amendment no. 1 - Reg.-no. 335 182 (BH 635-3): Acute oral toxicity in rats. 10A0576/961216 ! 1999/11221 GLP, unpublished TOX2001-946	Y	BAS
AIIA-5.8.1	Wiemann, C.	1999	Amendment no. 1 - Reg.-no. 292564; BH 635-2: Acute oral toxicity in rats. 10A0599/961217 ! 1999/10381 GLP, unpublished TOX2001-938	Y	BAS
AIIA-5.8.1	Wiemann, C. and Hellwig, J.	1998	Reg.-no. 335 182 (BH 635-3): Acute oral toxicity in rats. 10A0576/961216 ! #BASF 98/10843 GLP, unpublished TOX2001-945	Y	BAS
AIIA-5.8.1	Wiemann, C. and Hellwig, J.	1999	Reg.-no. 335 184 (BH 635-4): Acute oral toxicity in rats. 10A0577/961218 ! #BASF 99/10213 GLP, unpublished TOX2001-951	Y	BAS
AIIA-5.8.1	Wiemann, C. and Hellwig, J.	1999	Reg.-no. 292564; BH 635-2: Acute oral toxicity in rats. 10A0599/961217 ! #BASF 99/10099 GLP, unpublished TOX2001-937	Y	BAS
AIIA-5.8.1	Wollny, H.-E.	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 335 182; BH 635-3. 640402 ! 50M0576/969430 ! 1999/12026 GLP, unpublished TOX2001-943	Y	BAS
AIIA-5.8.1	Wollny, H.-E.	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 335 184; BH 635-4. 640403 ! 50M0577/969431 ! 1999/12016 GLP, unpublished TOX2001-949	Y	BAS
AIIA-5.8.1	Wollny, H.-E.	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with reg.-no. 292 564; BH 635-2. 640401 ! 50M0599/969429 ! 1999/11691 GLP, unpublished TOX2001-934	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.8.2	Engelhardt, G.	1997	Amendment no. 1 to the report on the study of AMTT, techn. cas-nr. [5311-05-7] (ZHT test substance no.: 96/38) in the salmonella typhimurium/escherichia coli reverse mutation assay (standard plate test and preincubation test). 40M0038/964034 ! 1997/1000920 GLP, unpublished TOX2001-961	Y	BAS
AIIA-5.8.2	Engelhardt, G. and Hoffmann, H.D.	1996	Report on the study of AMTT, techn. cas-nr. [5311-05-7] (ZHT test substance no.: 96/38) in the Ames salmonella/mammalian.microsome mutagenicity test and escherichia coli / mammalian-microsome reverse mutation assay (standard plate test and preincubation test). 40M0038/964034 ! 1996/1000679 GLP, unpublished TOX2001-960	Y	BAS
AIIA-5.8.2	Leibold, E., Hafemann, C. and Hoffmann, H.D.	2001	14C-eg. no. 231 700 - Study of the biokinetics and metabolism in rats. 02B0491/986012 ! 2000/1018485 GLP, unpublished TOX2001-956	Y	BAS
AIIA-5.8.2	Mellert, W., Deckardt, K., Kaufmann, W. and Van Ravenzwaay, B.	2001	AMTT - Subchronic toxicity study with estrus cycle determination and hormone analysis in female Wistar rats administration in the diet up to 32 weeks. 99S0100/98131 ! 2001/1006078 GLP, unpublished TOX2001-959	Y	BAS
AIIA-5.8.2	Poelloth, C.	1997	Amendment no. 1 to the report study on the acute oral toxicity of AMTT, techn. in rats. 10A0038/961019 ! 1997/1000919 GLP, unpublished TOX2001-958	Y	BAS
AIIA-5.8.2	Poelloth, C. and Hellwig , J.	1996	Study on the acute oral toxicity of AMTT, techn. cas-nr. [5311-05-7] in rats. 10A0038/961019 ! 1996/1000678 GLP, unpublished TOX2001-957	Y	BAS
AIIA-5.8.2	Schilling, K., Gembardt, Chr. and Van Ravenzwaay, B.	2001	AMTT and BisSH - Pre-/postnatal screening toxicity study in Wistar rats oral administration (gavage). 19R0100/98014 ! 2001/1003834 not GLP, unpublished TOX2001-964	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIA-5.8.2	Völkner, W.	1998	Micronucleus assay in bone marrow cells of the mouse after a single intraperitoneal administration of AMTT. 614800 ! 26M0100/989050 ! #BASF 98/11043 GLP, unpublished TOX2001-963	Y	BAS
AIIA-5.8.2	Vollmer, G.	1999	Study of a possible bond of reg.-no. 231700 and reg.-no. 271272 to the estrogen receptor in the cytosol from the endometrial RUCA-I adenocarcinoma cell line. 99P0100/989150 and 99P0042/989151 not GLP, unpublished TOX2001-965	Y	BAS
AIIA-5.8.2	Wollny, H.-E.	1999	Gene mutation assay in Chinese hamster V79 cells in vitro (V79 /HPRT) with AMTT. 631700 ! 50M0100/989153 ! 1999/10870 GLP, unpublished TOX2001-962	Y	BAS
AIIIA-7.1.1	Kuehlem, C. and Hellwig, J.	1997	Study on the acute oral toxicity of BAS 635 00 H in rats. 10A0278/961084 ! #BASF 97/10617 GLP, unpublished TOX2001-885	Y	BAS
AIIIA-7.1.2	Kuehlem, C. and Hellwig, J.	1997	Study on the acute dermal toxicity of BAS 635 00 H in rats. 11A0278/961085 ! #BASF 97/10523 GLP, unpublished TOX2001-886	Y	BAS
AIIIA-7.1.3	Gamer, A.O. and Hoffmann, H.D.	1997	BAS 635 00 H - Acute inhalation toxicity study in Wistar rats 4-hour dust exposure. 13I0278/967008 ! #BASF 97/10289 GLP, unpublished TOX2001-887	Y	BAS
AIIIA-7.1.4	Kuehlem, C. and Hellwig, J.	1997	Study on the acute dermal irritation/corrosion of BAS 635 00 H in rabbit. 14H0278/962156 ! #BASF 97/10490 GLP, unpublished TOX2001-888	Y	BAS
AIIIA-7.1.5	Kuehlem, C. and Hellwig, J.	1997	Study on the acute eye irritation of BAS 635 00 H in rabbit. 13H0278/9621567 ! #BASF 97/10491 GLP, unpublished TOX2001-889	Y	BAS
AIIIA-7.1.6	Wiemann, C. and Hellwig, J.	2000	BAS 635 00 H - Modified Buehler test (9 inductions) in guinea pigs. 33H0167/992193 ! 2000/1013137 GLP, unpublished TOX2001-890	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[5]
AIIIA-7.2.3.1	Anonym	1998	Policy # 003 - Science advisory council for exposure - Regarding: Agricultural default transfer coefficients. United States Environmental Protection Agency, 1998 #BASF 98/11675 not GLP,published TOX2001-891	N	-

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-7: Residue data

B.7 Residue data

B.7.1 Metabolism, distribution and expression of residues in plants (Annex IIA 6.1; Annex IIIA 8.1)

Metabolism in maize

Report:	Hofmann M., 1998 Plant uptake study with ^{14}C-BAS 635 H and maize. Use rate: 180 g a.i./ha (phenyl-U-^{14}C and triazine-2,4-^{14}C) BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep. unpublished BASF Reg Doc # 1998/10630
Guidelines:	not specified in the document
GLP:	Yes
Acceptability:	Yes

Report:	Reinhard K., 1999 Metabolism of ^{14}C-BAS 635 H in corn BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep. unpublished BASF Reg Doc # 1998/11379
Test Material:	[phenyl-U-^{14}C]-tritosulfuron, batch no. 538-01, radiochemical purity: 92.3 %, specific activity: 9.60 MBq/mg [triazine-2,4-^{14}C]-tritosulfuron, batch no. 537-01, radiochemical purity: 94.3 %, specific activity: 9.26 MBq/mg
Guidelines:	US, EPA Residue Chemistry Test Guidelines - Nature of the Residue - Plants, Livestock (OPPTS 860.1300)
GLP:	Yes
Acceptability:	Yes

B.7.1.1 Materials and Methods

The metabolism and distribution of tritosulfuron in plants was investigated using [phenyl-U-^{14}C]-tritosulfuron and [triazine-2,4-^{14}C]-tritosulfuron as shown in figures B.7.1-1 and B.7.1-2:

Figure B.7.1-1: Phenyl labelled test substance

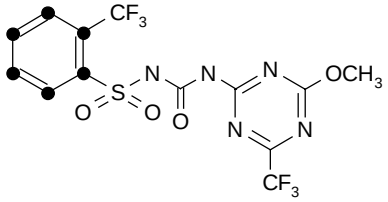
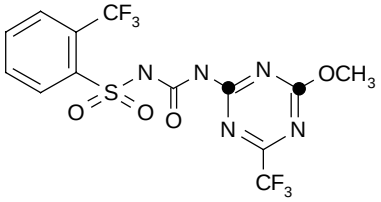


Figure B.7.1-2: Triazine labelled test substance



Four plant uptake studies have been performed in maize as preliminary experiments and investigations on the extractability (Hofmann, 1997, RIP2001-585, RIP2001-586, RIP2001-587 and RIP2001-588). A further plant uptake study including investigations on characterisation and identification of metabolites in maize was performed with sampling at different developing stages after application (plant uptake: Hofmann, 1998, RIP2001-584; identification and characterisation: Reinhard, 1998, RIP2001-589). Only this study is subject to the following evaluation.

The plants were treated at growth stage 14/15 (BBCH) with a WP-formulation at an exaggerated rate of 180 g as/ha corresponding to 3.6 times the maximum recommended use rate. The plants were cultivated on a sandy loam in plastic.

Samples were taken a short time after application (0 DAT) and at 14, 30, 60 and 80 (silage stage) days after application. The maize was harvested 105 days after application and separated in straw, grain, husk and cobs. Samples were stored at –18 ^{o}C before analysis.

The plant materials of both labels were extracted with methanol and water. For further identification and characterisation, the methanolic extracts were submitted to ethyl acetate/water partition. The extractable radioactivity was characterised by radio-HPLC using the methanol extracts or the extracts of liquid/liquid partition. The amount of radioactivity present in the extracts and the residue was determined by LSC and combustion analysis.

The metabolites were identified by HPLC-retention time comparison with cold reference standards or well-characterised compounds isolated from maize cell suspension cultures. Where possible, they were isolated by HPLC fractionation and their structures elucidated by LC/MS/MS. For characterisation, a polar peak present in straw (phenyl label) was further treated by enzymes, acids and bases.

Some of the non-extractable residues (phenyl-label) were subjected to ammonia extraction. In case of grain, additionally a DMSO/water extraction followed by ethanol precipitation was carried out to determine the amount of radioactivity linked to starch.

B.7.1.2 Findings

Radioactive residues

The total radioactive residues (TRR) were determined by combustion of the plant material and calculated as sum of the extractable radioactivity (ERR) and the radioactivity in the residue after extraction (RRR). A few samples showed discrepancies between the results after combustion and those calculated and were ascribed to inhomogeneity of the samples. For quantification of the radioactivity in the extracts and the chromatograms the calculated TRR (ERR+RRR) was used. The results are summarised in Table B.7.1-1.

No significant differences in TRR levels were found between the two labels. Apart from the early samplings, relatively low TRR levels were observed for forage, silage and straw. Very low TRR levels in the range of 0.010 – 0.015 mg/kg were found in grain. The solvent extractability (methanol and water) was high, it ranged from 81.4 % (grain) to 97,8 % (forage 14 DAT).

Table B.7.1-1: Radioactive residues in plant material, extracts and residues

Sample	TRR combustion	TRR (ERR+RRR)	Methanol (ERR)		Water (ERR)		Residue (RRR)	
	mg/kg	mg/kg	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Phenyl-label								
Forage 0 DAT	1.969	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Forage 14 DAT	0.837	0.751	0.714	95.0	0.021	2.8	0.016	2.2
Forage 30 DAT	0.256	0.219	0.188	86.1	0.018	8.4	0.012	5.4
Forage 60 DAT	0.075	0.060	0.050	84.0	0.004	7.4	0.005	8.6
Silage 80 DAT	0.095	0.077	0.056	73.4	0.009	12.3	0.011	14.3
Straw 105 DAT	0.203	0.207	0.146	70.5	0.030	14.3	0.031	15.2
Husks 105 DAT	0.032	0.031	0.025	81.7	0.002	7.7	0.003	10.6
Cob 105 DAT	0.008	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Grain 105 DAT	0.011	0.010	0.007	70.5	0.001	10.9	0.002	18.6
Triazine-label								
Forage 0 DAT	2.248	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Forage 14 DAT	0.934	0.784	0.717	91.4	0.033	4.3	0.034	4.3
Forage 30 DAT	0.184	0.184	0.168	91.2	0.007	4.0	0.009	4.9
Forage 60 DAT	0.058	0.056	0.047	84.4	0.003	4.9	0.006	10.7
Silage 80 DAT	0.076	0.069	0.056	80.8	0.004	6.4	0.009	12.8
Straw 105 DAT	0.267	0.193	0.140	72.7	0.023	11.9	0.030	15.4
Husks 105 DAT	0.039	0.036	0.029	80.3	0.003	8.5	0.004	11.2
Cob 105 DAT	0.005	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Grain 105 DAT	0.015	0.014	0.010	70.0	0.002	16.2	0.002	13.8

n.d. : not determined

Metabolism pathway

In maize, ^{14}C-tritosulfuron is metabolised by the following key transformation steps:

- Hydroxylation of the phenyl ring system followed by glucosylation yielding to the metabolites 635M17 and 635M13
- Cleavage of the triazine ring system yielding to the metabolite 635M01
- Cleavage of the sulfonyl urea bridge yielding to the metabolites 635M06 and 635M07.

Tritosulfuron decreased during the growth period of the maize plant. Five metabolites were identified, four of which were hydroxylated/glucosidated in the 5-position of the phenyl ring (635M13, 635M17, 635M06, 635M07). In the case of 635M01 the triazine ring had been opened with elimination of trifluoroacetic acid (see tables Table B.7.1-2, Table B.7.1-3 and Figure B.7.1-3).

With one exception (forage 30 DAT, 635M13) all metabolites identified or characterised were clearly below 0.05 mg/kg or 0.01 mg/kg in grain, respectively. In earlier samplings (forage 14 –60 DAT) the glucose conjugate 635M13 was the metabolite with the highest TRR levels behind tritosulfuron. In phenyl labelled samples of silage, straw and grain, the polar peak P1 had the overall highest TRR levels. In triazine labelled samples of silage, straw and grain, peak P9 and metabolite 635M01 showed relatively high TRR levels.

Different amounts of parent and metabolites were found in the two labels especially in silage, straw and grain. Low amounts of tritosulfuron and increased amounts of P1 were found in phenyl labelled samples and were contrasting with high amounts of tritosulfuron and low amounts of P1 in triazine labelled samples. Since the absolute concentrations were low no further investigations were carried out.

Characterisation

In order to classify the metabolites into organo-soluble and water-soluble ones, liquid/liquid partition experiments were carried out. In the forage samples harvested 14 – 60 days after treatment (DAT), most of the extractable radioactivity was organo-soluble. At the later sampling intervals, the radioactivity was equally distributed among the organic (ethyl acetate) and the aqueous phase.

Several peaks in the HPLC-chromatograms could not be identified, but especially those with higher TRR levels were further examined. The polar peak P1 was found in phenyl and triazine labelled matrices and was hardly soluble in organic solvents. P1 (phenyl label) could be split up into two different peaks (P1a, P1b) with ion exchange chromatography. Treatment with pectinase, acids and bases did not change the chromatographic behaviour of P1 so that a simple conjugate with endocons seems improbable. The peak P10 (phenyl label) consisted of the metabolite 635M06 and unknown compounds, whereas the peak P4 (phenyl label) consisted of several smaller components each of which is below 7.5 % TRR (0.016 mg/kg). Out of the triazine labelled substances peak P9 showed a similar retention time as the metabolite AMTT (635M04), but could by co-injection be distinguished from it.

The water extracts of forage DAT 60, silage and straw were submitted to HPLC-analysis. The peak pattern were similar to those of the methanol extract, but the individual concentrations were not added to those of the methanol extract due to poor resolution of the peaks.

The non-extractable residues (RRR) were below 20 % TRR and less than 0.02 mg/kg for almost all samples. Higher amounts were only found in straw (15.2/15.4 % TRR, corresponding to 0.031/0.030 mg/kg) and in forage DAT 14 (4.3 % TRR, 0.034 mg/kg). The non-extractable residues (phenyl-label) of silage, straw and grain were further characterised. Extraction with ammonia decreased the non-released residues to 10.5 % TRR in straw and 5.5 % TRR in silage. In grain about 1/3 of the radioactivity was released by ammonia, 1/3 precipitated together with starch and 1/3 remained in the DMSO/water extract.

Table B.7.1-2: Summary of identified and characterised components after treatment with [phenyl-U-^{14}C]-tritosulfuron

Metabolite Code	Forage 14 DAT		Forage 30 DAT		Forage 60 DAT		Silage 80 DAT		Straw 105 DAT		Grain 105 DAT	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Identified												
Tritosulfuron	0.440	58.6	0.102	46.7	0.019	31.2	0.004	4.8	0.029	14.2	0.0003	3.1
635M17	0.016	2.1	0.007	3.3	0.003	5.4	0.004	5.4	0.014	7.0	0.0004	3.9
635M13	0.213	28.4	0.056	25.4	0.007	12.2	0.004	5.2	0.010	5.0	n.d.	
635M01	0.026	3.5	0.009	4.3	0.002	3.3	0.001	0.8	0.005	2.3	n.d.	
635M07	n.d.[6]		n.d.		n.d.		0.001	1.0	0.002	0.8	n.d.	
Total identified	0.695	**92.6**	0.174	**79.7**	0.031	**52.1**	0.014	**17.2**	0.060	**29.3**	0.0007	**7.0**
Characterised												
P 1			0.007	3.4	0.008	13.0						
P 1a							0.008	10.4	0.011	5.1	0.0012	11.5
P 1b							0.022	28.4	0.029	14.0	0.0032	31.1
P 2											0.0002	1.7
P 3											0.0005	4.7
P 4					0.005	9.1	0.009	11.2	0.036	17.3	0.0009	8.1
P 6							0.001	0.9	0.001	0.7		
P 10 (635M06)	0.009	1.2	0.002	1.1	0.006	9.9	0.004	5.3	0.008	3.9	0.0007	6.4
P 11	0.009	1.2										
P 12			0.004	1.9								
P 17									0.001	0.3		
Water extract[1]	0.021	2.8	0.018	8.4	0.004	7.4	0.009	12.3	0.030	14.3	0.001	10.9
Ammonia extr.[2]							0.005	5.9	0.014	7.0	0.0006	5.6
Starch fraction[3]											0.0006	6.2
Supernatant [4]											0.0007	6.3
Total charact.	0.039	**5.2**	0.031	**14.8**	0.023	**39.4**	0.058	**74.4**	0.130	**62.6**	0.0096	**92.5**
Final residue	0.016	**2.2**	0.012	**5.4**	0.005	**8.6**	0.004	**5.5**	0.022	**10.5**	< 0.0001	**0.5**
Losses[5]							0.002	**2.9**				
Total	0.750	**100.0**	0.217	**99.9**	0.059	**100.1**	0.078	**100.0**	0.212	**102.4**	0.0104	**100**

[1] Aqueous extract after methanol extraction
[2] Ammonia extract of residue after methanol and water extraction
[3] Extraction with DMSO/water from the residue after ammonia extraction, precipitation with ethanol
[4] Supernatant after starch precipitation
[5] Losses from ammonia extraction
[6] not detected

Table B.7.1-3: Summary of identified and characterised components after treatment with [triazine-2,4-^{14}C]-tritosulfuron

Metabolite Code	Forage 14 DAT		Forage 30 DAT		Forage 60 DAT		Silage 80 DAT		Straw 105 DAT		Grain 105 DAT	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Identified												
Tritosulfuron	0.411	52.5	0.106	57.7	0.018	32.2	0.014	20.1	0.048	24.8	0.004	28.6
635M17	0.016	2.1	0.004	2.4	0.004	7.5	0.003	3.8	0.009	4.5	n.d.	
635M13	0.229	29.2	0.035	19.0	0.005	9.6	0.004	6.0	0.012	5.9	n.d.	
635M01	0.029	3.7	0.009	5.1	0.003	6.0	0.010	13.4	0.020	10.2	0.001	10.1
Total identified	0.685	**87.5**	0.154	**84.2**	0.030	**55.3**	0.031	**43.3**	0.089	**45.4**	0.005	**38.7**
Characterised												
P 1			0.002	1.3	0.006	11.0	0.006	8.2	0.015	7.9	0.001	4.7
P 5	0.031	3.9	0.010	5.6	0.001	1.8	0.005	6.8	0.017	8.5		
P 9					0.004	6.6	0.012	17.0	0.012	6.4	0.003	24.3
P 12					0.002	3.3	0.001	1.8	0.006	3.1		
P 13					0.003	5.5					<0.001	2.4
P 17					<0.001	0.9			0.001	0.5		
P 18							0.001	0.9				
P 19							0.002	2.7				
Water extract[1]	0.033	4.3	0.007	4.0	0.003	4.9	0.004	6.4	0.023	11.9	0.002	16.2
Total charact.	0.064	**8.2**	0.019	**10.9**	0.019	**34.4**	0.031	**43.8**	0.074	**38.3**	0.006	**47.6**
Final residue	0.034	**4.3**	0.009	**4.9**	0.006	**10.7**	0.009	**12.8**	0.030	**15.4**	0.002	**13.8**
Total	0.783	**100.0**	0.182	**100.0**	0.055	**100.0**	0.071	**99.9**	0.193	**99.1**	0.013	**100.1**

[1] Aqueous extract after methanol extraction
n.d.: not detected

Storage stability

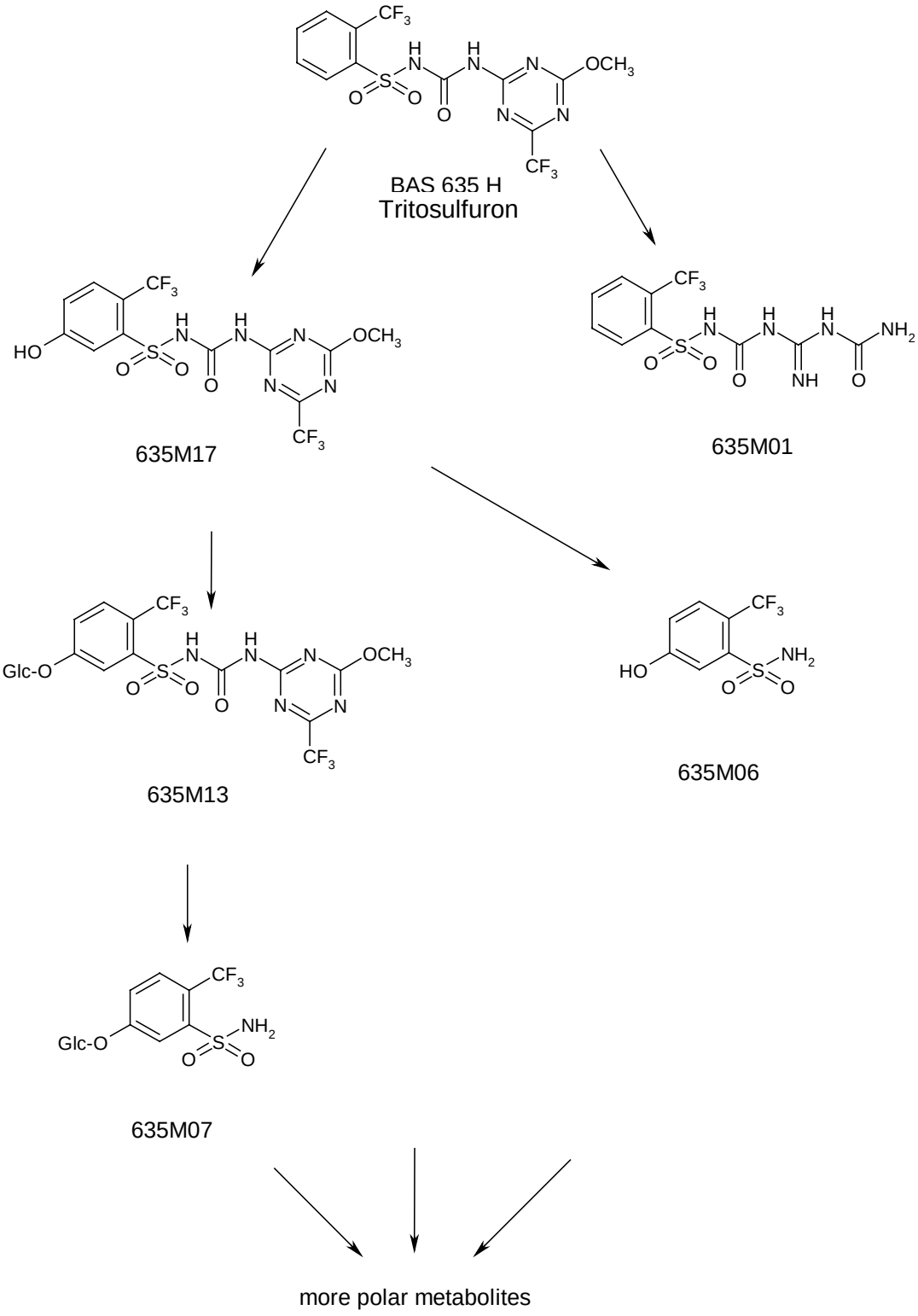
Separate experiments showed that the metabolite patterns were qualitatively and quantitatively stable over the experimental period.

B.7.1.3 Conclusion

The metabolism of tritosulfuron in maize was investigated by application of phenyl and triazine labelled test substance. Tritosulfuron metabolised either by hydroxylation followed by glucosylation of the phenyl ring and cleavage of the sulfonyl urea bridge or by cleavage of the triazine ring system (see Figure B.7.1-1). Five metabolites were identified. The other metabolites were mainly characterised by HPLC.

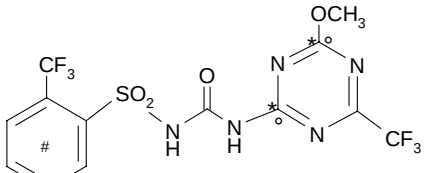
In almost all samples tritosulfuron was the main component. With one exception (forage 30 DAT, 635M13) all metabolites identified or characterised were clearly below 0.05 mg/kg or 0.01 mg/kg in grain, respectively. The metabolite AMTT (635M04) was not detected in the maize metabolism study.

Figure B.7.1-3: Metabolic pathway of tritosulfuron in maize



B.7.2 Metabolism, distribution and expression of residues in livestock (Annex IIA 6.2; Annex IIIA 8.1)

The metabolism and distribution in livestock of BAS 635 H was investigated using *[phenyl-U-^{14}C]*-BAS 635 H and *[triazine-2,4-^{14}C]*-BAS 635 H. The radiolabelled test compound was diluted with the non-radiolabelled compound to achieve the desired specific activity. In the case of the triazine labelled test compound, also ^{13}C-labelled compound was added (^{12}C/^{13}C ratio 60:40). The aim of the addition of the ^{13}C-label was to generate a characteristic isotope pattern to facilitate a potential MS identification of metabolites. However, as it turned out during the course of the study, this option was not used since metabolites could be identified by chromatographic comparison with reference compounds. The radiochemical purity of the dosed formulation was > 99 %.



[phenyl-U-^{14}C] label
* [triazine-2,4- ^{14}C] label
° [triazine-2,4-^{13}C] label

B.7.2.1 Lactating goat

B.7.2.1.1 Absorption, Distribution and Excretion

Report:	Leibold E. et al., 1997 ^{14}C-BAS 635 H - study of the absorption, distribution and excretion after repeated oral administration in lactating goats BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep. unpublished BASF RegDoc# 1997/11172
Test material	[*Phenyl-U-^{14}C]*-BAS 635H, *[Triazine-2,4-^{14}C]*-BAS 635H, and *[Triazine-2,4-^{13}C]*-BAS 635H
Guideline:	U.S. EPA, Pesticide Assessment Guidelines, Subpart O, Residue Chemistry § 171-4
GLP:	Yes (laboratory certified)
Acceptability:	The study is considered to be acceptable

The objectives of this study were :

- To determine rates and routes of excretion and distribution of ^{14}C-BAS 635 H in excreta, blood, plasma, milk and tissues of lactating goats.
- To generate samples of biological material following administration of ^{14}C-BAS 635 H (excreta, milk, tissues) which were transferred to an investigation on the metabolism performed as a separate study.

Material and Methods

The metabolism and distribution of ^{14}C-BAS 635 H was investigated in lactating goats ("Bunte deutsche Edelziege", age about 2 - $2^1/_2$ years) following repeated oral administration of the phenyl and the triazine labelled test compound at a nominal dose level of 10 mg/kg related to feed (dry matter) intake (two animals per label). The test compound was dissolved in Cremophor EL/tylose and dosed by gavage once daily for 6 consecutive days. A control animal was dosed with the blank vehicle. Details of the study design are summarised in Table B.7.2-1.

Sampling and sample storage

Excreta were collected daily, milk was sampled in the morning before dosing of the test compound and in the afternoon. In order to get some information on the blood and plasma concentration of radioactivity, blood samples were taken 1 hour before and 1 hour after each administration during the application period. On the last day of application, blood samples were additionally taken at 1, 2, 3, 4, 6, 8, 12 and 23 hours post dosing.
Animals were sacrificed at 23 hours after the last dosing. After terminal sacrifice, muscle, fat, kidney and liver were removed for the analysis of metabolites (see Part B.7.2.1.2). Samples were frozen and stored at –18 °C or below until analysis.

Measurement of radioactivity

The total radioactive residues in excreta, stomach and gut contents, bile, milk and tissues was determined. Aliquots of liquid samples (plasma, urine, milk, bile and cage wash) were mixed with scintillation cocktail and analysed for radioactivity without any additional treatment. Other samples were lyophilised and/or homogenised and solubilised before counting.

Table B.7.2-1: Dosing of lactating goats with ^{14}C-BAS 635 H

Animal group (Animal nos.)	Label position	Number of doses	Nominal dose	Actual dose		Sacrifice time
			[mg per kg feed intake]	[mg per kg feed intake]	[mg per kg body weight**]	[hours post dose]
P (1 and 2)	Phenyl	6	10	7.4*	0.49	23
T (4 and 5)	Triazine	6	10	9.6*	0.44	23
C (3)	Control	6	-	-	-	23

* Mean of two animals
** Body weight at start of dosing

Findings

Animal health

No behavioural or physical abnormalities were observed. Body weight, food consumption and milk production remained relatively constant during the application period. At sacrifice, macroscopic examination revealed no abnormalities.

Excretion and concentration of radioactivity

After 6 consecutive daily oral administrations of ^{14}C-BAS 635 H the radioactivity was rapidly and almost completely excreted (Table B.7.2-2): At sacrifice 61 % to 64 % of the administered dose was excreted in the urine and 16 % to 20 % in the faeces. Mean daily milk concentrations reached a plateau from Day 1 onwards. After dosing with the Phenyl label, total radioactive residues were 0.038 mg/kg in pool milk, 0.003 mg/kg in muscle, 0.005 mg/kg in fat, 0.047 mg/kg in kidney, and 0.026 mg/kg in liver. After dosing of the Triazine Label, total radioactive residues were 0.051 mg/kg in pool milk, 0.018 mg/kg in muscle, 0.026 mg/kg in fat, 0.058 mg/kg in kidney, and 0.048 mg/kg in liver (Table B.7.2-3).

The concentration of radioactivity in plasma peaked at 1-4 hours after the last dosing. Thereafter, it declined with a half-life of 3.8-7.5 hours (phenyl-label). In the animals dosed with triazine-labelled ^{14}C-BAS 635 H, plasma radioactivity declined biphasically with an initial half-life of 10.6-12.5 hours and a terminal half-life of 45.6-47.3 hours.

Table B.7.2-2: Material balance after administration of ^{14}C-BAS 635 H to lactating goats

Material balance in % of total dose				
Fraction	**Phenyl Label Animal no.**		**Triazine Label Animal no.**	
	1	2	4	5
Milk	0.3	0.3	0.3	0.3
Liver	< 0.1	< 0.1	< 0.1	< 0.1
Kidneys	< 0.1	< 0.1	< 0.1	< 0.1
Stomach and content	2.0	1.1	1.7	1.6
Gut and content	1.0	0.8	1.5	1.3
Other tissues	< 0.1	< 0.1	< 0.1	< 0.1
Cage wash	1.0	0.9	0.9	0.7
Urine	63.6	60.7	61.7	62.9
Faeces	19.6	17.9	17.9	15.7
Total	87.5	81.8	84.1	82.6

Table B.7.2-3: Total Radioactive Residues after dosing of lactating goats with ^{14}C-BAS 635 H. Mean of two animals per label. Nominal dose level: 10 mg/kg based on feed intake (dry matter)

Total Radioactive Residues [mg/kg]		
Tissue	**Phenyl Label (Animals 1 and 2)**	**Triazine Label (Animals 4 and 5)**
Milk (pool)	0.038	0.051
Muscle	0.003	0.018
Fat	0.005	0.026
Kidney	0.047	0.058
Liver	0.026	0.048

Conclusion

The total recoveries of radioactivity were in the range of 81.8 to 87.5 % of the administered dose. Radioactivity in milk amounted to about 0.3 %; at all application days, radioactivity concentrations were highest in the afternoon milk and were considerably lower in the morning

milk (before dosing). Concentrations of radioactivity in milk did not increase during application period. At sacrifice, highest concentrations of radioactivity were found in the GI-tract. There was no indication of accumulation of ^{14}C-BAS 635 H in goat tissues, organs and milk.

B.7.2.1.2 Lactating goat metabolism

Report:	Kohl W., 2000 The metabolism of ^{14}C-BAS 635 H (14C-Reg.-No. 271272) in lactating goats BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep. unpublished, BASF RegDoc# 2000/1013502
Test material	*[Phenyl-U-^{14}C]*-BAS 635 H, *[Triazine-2,4-^{14}C]*-BAS 635 H, and *[Triazine-2,4-^{13}C]*-BAS 635 H
Guideline:	U.S. EPA Residue Chemistry Test Guidelines OPPTS 860.1300
GLP:	Yes (laboratory certified)
Acceptability:	The study is considered to be acceptable.

This study was designed to investigate the nature of residues of BAS 635 H fed to goats at a nominal concentration corresponding to 10 mg/kg feed (dry matter).

Material and Methods
The in-life and biokinetic part of the study is reported in Part B.7.2.1.1.

Sample storage and preparation
All samples were stored at –18 °C or below. Milk was pooled for the whole treatment period and for the two animals which had received the same labelled form of the test article. Organs and tissues were pooled by combining respective tissues of Animals 1 and 2, and Animals 4 and 5 directly after necropsy (except fat *phenyl-label*). Milk and kidney were stored for less than 3 months prior to their first extraction and analysis. The first extraction and analysis of the other matrices was performed later: liver 10 months, muscle 15 months and fat 16 months after sampling.
All matrices from the *[Phenyl-^{14}C]* study and milk and kidney from the *[Triazine-^{14}C]* study were extracted and analysed again close to the end of the experimental part of the study (i.e. after 15 to 18 months of storage). The existing extracts of muscle, fat, kidney and liver from the *[Triazine-^{14}C]* study were reanalysed at the end of the study.

Analysis
For determination of total radioactive residues see above part B.7.2.1.1. Milk, muscle, kidney and liver were extracted with acetonitrile. Fat was extracted with a mixture of acetonitrile and iso-hexane. Aliquots of the acetonitrile extracts were evaporated, the remaining residue redissolved in water, the aqueous solution after adjusting to pH 2-4 extracted with ethyl acetate. The aqueous and the organic phases were submitted to LSC.

Metabolites were identified in the acetonitrile extracts by cochromatography with reference compounds.

Findings

Extractability

The radioactivity was effectively extracted with acetonitrile resp. acetonitrile/iso-hexane (Table B.7.2-4). The absolute level of non-extractable residues were low (0.001 - 0.006 mg/kg), therefore no further attempts were made to release this non-extractable radioactivity. After partitioning of the extractable radioactivity between water and ethyl acetate only traces of radioactivity were found in the aqueous phase: in milk 1-2 % of TRR (0.001 mg/kg or less); in muscle < 0.5 % of TRR (< 0.001 mg/kg); in fat 1-3 % of TRR (< 0.001 mg/kg); in kidney 1-2 % of TRR (0.001 mg/kg); in liver 1-3 % of TRR (0.001 mg/kg or less).

Table B.7.2-4: Extraction of radioactivity from milk, kidney and liver after dosing of ^{14}C-BAS 635 H. Nominal dose level 10 mg/kg based on feed intake

Extraction of radioactivity [mg/kg] (% TRR in parenthesis)				
	Acetonitrile	**Acetonitrile/ iso-hexane**	**Non-extractable**	**Total**
Phenyl Label (Animals 1 and 2)				
Milk (pool)	0.040 (102.6)	n.p.	< 0.001 (1.0)	0.040 (103.6)
Muscle	0.002 (79.3)	n.p.	0.001 (16.6)	0.003 (95.9)
Fat	n.p.	0.003 / 0.001 (71.1) / (14.8)	0.001 (13.9)	0.005 (99.8)
Kidney	0.044 (93.4)	n.p.	0.003 (5.8)	0.047 (99.2)
Liver	0.020 (76.6)	n.p.	0.006 (21.6)	0.026 (98.2)
Triazine Label (Animal 4 and 5)				
Milk (pool)	0.052 (101.3)	n.p.	0.001 (0.9)	0.053 (102.2)
Muscle	0.017 (94.2)	n.p.	0.001 (5.4)	0.018 (99.6)
Fat	n.p.	0.024 / < 0.001 (92.4) / (1.7)	0.001 (2.0)	0.025 (96.1)
Kidney	0.058 (99.2)	n.p.	0.003 (4.3)	0.060 (103.5)
Liver	0.044 (91.7)	n.p.	0.003 (6.1)	0.047 (97.8)

n.p. = not performed

Identification and quantification of the metabolites

The radio-HPLC analysis showed the following results.

Milk

The radioactivity consisted almost completely of unchanged parent compound in the [*Phenyl-^{14}C*]study; only traces of metabolite 635M02 were found (1 % of TRR or < 0.001 mg/kg). In the [*Triazine-^{14}C*]study the radioactivity consisted predominantly of unchanged parent compound (82 % of TRR or 0.042 mg/kg); small amounts of 2 metabolites were found: 635M04 (12 % of TRR or 0.006 mg/kg) and 635M09 (7 % of TRR or 0.004 mg/kg).

Muscle

In the *[Phenyl-^{14}C]* study the radioactivity consisted of unchanged parent compound (58 % of TRR or 0.001 mg/kg) and metabolite 635M02 (21 % of TRR or 0.001 mg/kg). In the *[Triazine-^{14}C]* study the radioactivity consisted of unchanged parent compound (34 % of TRR or 0.006 mg/kg), metabolite 635M04 (42 % of TRR or 0.008 mg/kg) and 635M09 (18 % of TRR or 0.003 mg/kg.

Fat

The radioactivity consisted of unchanged parent compound (55 % of TRR or 0.002 mg/kg) and metabolite 635M02 (17 % of TRR or 0.005 mg/kg) in the *[Phenyl-^{14}C]* study. In the *[Triazine-^{14}-C]* study the concentration of parent compound was lower (19 % of TRR or 0.001 mg/kg) beside of metabolite 635M04 (61 % of TRR or 0.016 mg/kg) and metabolite 635M09 /13 % of TRR or 0.003 mg/kg).

Liver

In the *[Phenyl-^{14}C]* study the radioactivity consisted of unchanged parent compound (59 % of TRR or 0.015 mg/kg) and metabolite 635M02 (18 % of TRR or 0.005 mg/kg). In the *[Triazine-^{14}C]* study the radioactivity consisted of unchanged parent compound (58 % of TRR or 0.028 mg/kg) and the metabolites 635M04 (23 % of TRR or 0.011 mg/kg) and 635M09 (11 % of TRR or 0.005 mg/kg).

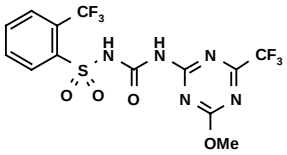
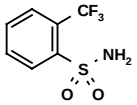
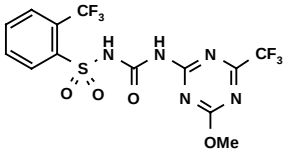
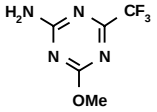
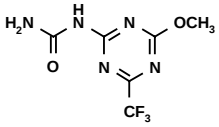
Kidney

In the *[Phenyl-^{14}C]* study the radioactivity consisted predominantly of unchanged parent compound (87 % of TRR or 0.041 mg/kg) beside of the metabolite 635M02 (7 % of TRR or 0.003 mg/kg). In the *[Triazine-^{14}C]* study the radioactivity consisted of unchanged parent compound (61 % of TRR or 0.035 mg/kg), the metabolite 635M04 (26 % of TRR or 0.015 mg/kg) and the metabolite 635M09 (13 % of TRR or 0.007 mg/kg).

Storage stability

No significant qualitative changes in the metabolite patterns were observed after a storage period of 15 to17 months irrespective of the used ^{14}C-label, but some quantitative changes had occurred, explained by the notifier "with a slow non-enzymic hydrolysis of the parent compound".

Table B.7.2-5: Summary of metabolites in milk and tissue of goats which had received ^{14}C-BAS 635 H at the 10 mg/kg nominal dose level (based on feed intake)

Metabolite code	Structure	Milk (pool) mg/kg (% TRR)	Muscle mg/kg (% TRR)	Fat mg/kg (% TRR)	Liver mg/kg (% TRR)	Kidney mg/kg (% TRR)
Phenyl Label						
BAS 635 H		0.040 (101.5)	0.001 (58.4)	0.002 (54.9)	0.015 (58.8)	0.041 (86.5)
635M02		<0.001 (1.1)	0.001 (20.9)	0.001 (16.8)	0.005 (17.8)	0.003 (6.9)
Total identified in the acetonitrile extract		**0.04 (102.6)**	**0.002 (79.3)**	**0.003 (71.7)**	**0.02 (76.6)**	**0.044 (93.4)**
Triazine Label						
BAS 635 H		0.042 (82.3)	0.006 (33.9)	0.005 (19.0)	0.028 (57.8)	0.035 (61.2)
635M04 **(AMTT)**		0.006 (11.9)	0.008 (42.4)	0.016 (60.6)	0.011 (22.9)	0.015 (25.5)
635M09		0.004 (7.2)	0.003 (17.8)	0.003 (12.8)	0.005 (11.0)	0.007 (12.5)
Total identified in the acetonitrile extract		**0.052 (101.4)**	**0.017 (94.1)**	**0.024 (92.4)**	**0.044 (91.7)**	**0.057 (99.2)**

Discussion

The metabolism of BAS 635 H in the lactating goat has been investigated using two labelled forms (^{14}C-label in the phenylring and in the heteroaromatic ring) because it was expected that the molecule would be cleaved at the sulfonylurea group. There was a rapid absorption from the gastrointestinal tract. The excretion of radioactivity was rapid and mainly occurred via urine (61 to 64 %) and feces (16 to 20 %). Only 0.3 % of the administered dose was found in milk.

With acetonitrile resp. acetonitrile/iso-hexane 72 % to 103 % of the total radioactive residues were extractable. The residues non-extractable with acetonitrile or acetonitrile/iso-hexane accounted for 1 % to 22 % of TRR, but the absolute amount was only < 0.001 mg/kg to 0.006 mg/kg.

Despite of low levels of radioactivity in milk and tissues, the radioactivity in the acetonitrile extracts could be nearly completely identified by chromatographic comparison with reference compounds. The major metabolic reaction was the cleavage of the sulfonylurea bridge.

Thus after dosing with *[Phenyl-^{14}C]*-BAS 635 H, the sulfonamide 635M02 was the major metabolite in muscle, fat and liver (0.001 to 0.005 mg/kg; 17 to 21 % of TRR) besides large

amounts of unchanged parent compound (0.001 to 0.015 mg/kg; 55 to 59 % of TRR). Milk and kidney contained predominantly the parent compound. After dosing with *[Triazine-^{14}C]*-BAS 635 H similar proportions of unchanged parent compound were found (0.005 to 0.0412 mg/kg; 19 to 82 % of TRR). In addition, the ureyltriazine 653M09 (0.003 to 0.007 mg/kg; 7 to 18 % of TRR) and the aminotriazine (AMTT) 635M04 (0.006 to 0.016 mg/kg; 12 to 61 % of TRR) were identified in all matrices.

Conclusion
The metabolic pathway of BAS 635 H in lactating goats is sufficiently investigated. After administration of an exaggerated dose (nominal 10 mg/kg feed, actual 7.4 resp. 9.6 mg/kg feed) only very low levels of parent compound and three metabolites in edible matrices resulted. As expected, the molecule is cleaved at the sulfonylurea bridge (Figure B.7.2-1). Breakdown products were found containing either the phenyl or the triazine moiety, according to the labelling position. There is no indication of accumulation of ^{14}C-BAS 635 H in goat tissues and milk.

B.7.2.2 Laying hens

B.7.2.2.1 Absorption, distribution and excretion

Report:	Leibold E. et al., 1997 ^{14}C-BAS 635 H - Study of the absorption, distribution and excretion after repeated oral administration in laying hens BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep. unpublished; BASF RegDoc# 1997/11170 and Leibold E., 1997 Amendment No. 1: ^{14}C-BAS 635 H - Study of the absorption, distribution and excretion after repeated oral administration in laying hens BASF AG, Ludwigshafen/Rhein, Germany Fed. Rep. unpublished; BASF RegDoc# 1997/11241
Test material	*[Phenyl-U-^{14}C]*-BAS 635 H, *[Triazine-2,4-^{14}C]*-BAS 635 H, and *[Triazine-2,4-^{13}C]*-BAS 635 H
Guideline:	U.S. EPA Pesticide Assessment Guidelines, Subpart O, Residue Chemistry § 171-4
GLP:	Yes (laboratory certified)
Acceptability:	The study is considered to be acceptable on principle (see conclusion)

The study had the following objectives:

- To determine rates and routes of excretion and distribution of ^{14}C-BAS 635 H in excreta, blood, plasma, eggs and tissues of laying hens.
- To generate samples of biological material following administration of ^{14}C-BAS 635 H (excreta, eggs, tissues) which were transferred to an investigation on the metabolism performed as a separate study.

Material and Methods

The metabolism and distribution of BAS 635 H was investigated in laying hens (Brown leghorn) following repeated oral administration of the phenyl and the triazine labelled test compound at a nominal dose level of 10 mg/kg related to feed intake The test compound was dissolved in Cremophor EL/tylose and dosed by gavage. ^{14}C-BAS 635 H was administered once daily for eight consecutive days to the two groups of hens (20 animals per label). Four control animal were dosed with the blank vehicle. Details of the study design are summarised in Table B.7.2-6.

Sampling and sample storage

Excreta were collected in time intervals of 24 hours. Eggs were collected in the morning before administration of the test substance and in the afternoon. In order to get some information on the blood and plasma concentration of radioactivity, blood samples were taken on the last day of application at -1 hour (only triazine-label), 1 hour (only phenyl-label), 2, 4, 6, 8, 23 hours post-dosing. Animals were sacrificed 23 hours after the last administration and the following tissues were checked for remaining radioactivity: liver, kidney, blood, fat, chest muscles, leg muscles, skin and gastrointestinal tract contents.

Muscle, fat, skin and liver were removed for the analysis of metabolites (see Part B.7.2.2.2). Samples were frozen and stored at - 18 °C or below until analysis.

Measurement of radioactivity

The total radioactive residues in excreta, the gastrointestinal tract, eggs and tissues was determined. Aliquots of liquid samples (plasma) were mixed with scintillation coctail and analysed for radioactivity without any additional treatment. Other samples were lyophilisized and/or homogenised and solubilisized before counting.

Table B.7.2-6: Dosing of laying hens with ^{14}C-BAS 635 H

Dose group	Label position	Number of animals	Number of doses	Nominal dose	Actual dose		Sacrifice time
				[mg per kg feed intake]	[mg per kg feed intake *]	[mg per kg body weight**]	[hours post dose]
1	Phenyl	20	8	10	13.95	0.91	23
2	Triazine	20	8	10	13.41	1.14	23
	Control	4	-	-	-	-	23

* Mean (all animals)

** Body weight at the first application day

Findings

Animal health

No behavioural or physical abnormalities were observed. With the exception of the phenyl-group. In which body weights slightly increased during acclimatisation and slightly decreased during the application period, body weights, food consumption and egg production remained

virtually unchanged during the study period for both labels. At sacrifice, macroscopic examination revealed no abnormalities.

Excretion and concentration of radioactivity

Following administration of ^{14}C-BAS 635 H to laying hens, the radioactivity was rapidly and almost completely excreted (Table B.7.2-7): At sacrifice 90.5 % and 98.0 % of the administered dose were found in the excreta after dosing of the *Phenyl* and the *Triazine* Label, respectively.

Pooled egg yolks from Days 6 to 8 contained total radioactive residues of 0.018 mg/kg after dosing of the *Phenyl* Label and 0.036 mg/kg after dosing of the *Triazine* Label. Mean radioactive residues in egg whites were 0.041 mg/kg and 0.053 mg/kg, respectively.

At sacrifice (23 hours after last application), the highest concentration of radioactivity was found in the content of the GI-tract (0.3 % of dose or 0.8 mg equ./kg in the *[Phenyl-^{14}C]* study, 1.3 % of dose or 5.2 mg equ./kg in the *[Triazine-^{14}C]* study.

The plasma level peaked at 1 hour and 2 hours post-dosing in the studies respectively. Concentration of radioactivity in blood did not go parallel with plasma concentrations and no clear time-dependency was seen (caused possibly by coagulating during sampling).

Concentrations of total radioactive residues in muscle, fat, skin and liver were in the range of 0.012 to 0.080 mg/kg (Table B.7.2-8).

Table B.7.2-7: Material balance after administration of ^{14}C-BAS 635 H to laying hens

Fraction	Material balance in % of total dose administered	
	Animal Group 1 (Phenyl Label)	Animal Group 2 (Triazine Label)
Egg yolk	< 0.1	< 0.1
Egg white	< 0.1	< 0.1
Liver	< 0.1	< 0.1
Gastro-intestinal tract	0.3	1.3
Other tissues	< 0.1	< 0.1
Excreta	90.5	98.0
Cage wash	0.9	0.8
Total	91.9	100.1

Table B.7.2-8: Total radioactive residues after dosing of laying hens with ^{14}C-BAS 635 H. Nominal dose level: 10 mg/kg based on feed intake (dry matter)

Matrix	Group 1 (Phenyl Label) [mg/kg]	Group 2 (Triazine Label) [mg/kg]
Egg white*	0.018	0.036
Egg yolk*	0.041	0.053
Whole egg**	0.024	0.040
Muscle	0.013	0.012
Fat	0.015	0.021
Skin	0.030	0.020
Liver	0.080	0.030

*Day 6 - 8 egg pool
**Calculated from egg white and yolk

Conclusion
After 8 consecutive daily oral administrations of ^{14}C-BAS 635 H at a nominal dose level of 10 mg/kg feed, there was a rapid absorption of radioactivity from the gastrointestinal tract. Excretion of radioactivity was very rapid and virtually complete within 24 hours after administration. Radioactivity in eggs amounted only to 0.08-0.14 % of the total radioactivity administered. There was no indication of accumulation of ^{14}C-BAS 635 H in the hen tissues, organs and eggs.

Note: *The study is acceptable on principle, but no information is given whether a plateau in eggs was reached.*

B.7.2.2.2 Laying hens metabolism

Report: Kohl W., 1999
The metabolism of ^{14}C-BAS 635 H (14C-Reg.-No. 271272) in laying hens
BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep.
unpublished; BASF RegDoc# 1999/10272

Test material *[Phenyl-U-^{14}C]*-BAS 635 H, *[Triazine-2,4-^{14}C]*-BAS 635 H, and *[Triazine-2,4-^{13}C]*-BAS 635 H

Guideline: U.S. EPA Residue Chemistry Test Guidelines OPPTS 860.1300

GLP: Yes (laboratory certified)

Acceptability: The study is considered to be acceptable

The objective of this study was to determine the concentration and identity of the biotransformation products of BAS 635 H in laying hens.

Material and Methods
The in-life and biokinetical part of the study is reported in Part B.7.2.2.1.

Sample storage and preparation for analysis
All samples were stored at –18 °C or below until they were analysed. Eggs were separated into whites and yolks and samples of treatment days 6, 7 and 8 were pooled according to animal groups. The weight of egg whites and yolks in the pool samples were determined and used for calculation of the concentration (TRR and individual metabolites) in whole eggs. Tissue samples were pooled according to animal groups.
Eggs and tissues were stored for a maximum of about 4 months prior to their first extraction and analysis. To get information about storage stability of residues, extracts of egg yolk, muscle, fat and liver were re-investigated about 10 months later.

Analysis
The determination of total radioactive residues is reported in Part B.7.2.2.1.
Egg whites and yolks as well as tissues (except fat) were extracted with acetonitrile, fat with acetonitrile/iso-hexane (1:1). The extraction residues in liver remaining from the acetonitrile extraction were further extracted with water.
Aliquots of the acetonitrile extracts were evaporated, the remaining residues re-dissolved in water, the aqueous solution after adjusting to pH 2 - 4 extracted with ethyl acetate.
The extracts were analysed chromotographically by HPLC and TLC.

Findings
Extractability
The radioactivity was effectively extracted from eggs and tissues with acetonitrile (fat with acetonitrile/iso-hexane) (Table B.7.2-9).
The non-extractable residues comprised 3 % to 15 % of TRR (or < 0.001 mg/kg to 0.012 mg/kg) in eggs and tissues from animals treated with *[Phenyl-^{14}C]*-BAS 635 H, and 3 % to 19 % of TRR (or 0.001 mg/kg to 0.007 mg/kg) in eggs and tissues from animals treated with *[Triazine-^{14}C]*-BAS 635 H.
The extraction residues of liver remaining from the acetonitrile extraction were further extracted with water that removed another 6 % of TRR *[Phenyl label]* and 8 % of TRR *[Triazine label]*. After partitioning of the acetonitrile extractable residues between water and ethyl acetate, metabolites in eggs and tissues from both label showed to be predominantly organo-soluble. Only 2 % to 15 % of ERR were found in aqueous phase [% ERR = % of extractable residues; where % ERR organosoluble + % ERR watersoluble = 100). Because of the low absolute concentration, no further attempt were made to identify the non-extractable radioactivity.

Table B.7.2-9: Extraction of radioactivity from eggs and tissues after dosing of ^{14}C-BAS 635 H. (Nominal dose level 10 mg/kg based on feed intake.)

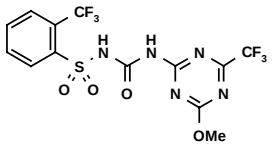
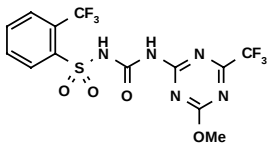
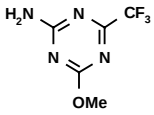
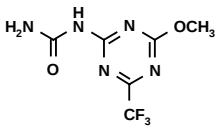
Extraction of radioactivity [mg/kg] (% TRR in parenthesis)				
	Acetonitrile	**Acetonitrile/ iso-hexane**	**Non-extractable**	**Total**
Phenyl Label (Animal Group 1)				
Egg white*	0.017 (98.0)	n.p.	< 0.001 (2.8)	0.018 (100.8)
Egg yolk*	0.034 (83.9)	n.p.	0.007 (17.8)	0.041 (101.7)
Whole egg**	0.022 (94.3)	n.p.	0.002 (6.7)	0.024 (101.0)
Muscle	0.011 (88.5)	n.p.	0.001 (11.5)	0.012 (100.0)
Fat	n.p.	0.014 /0.001 (90.3) / (7.5)	0.001 (6.6)	0.015 (104.4)
Skin	0.023 (76.8)	n.p.	0.006 (19.2)	0.029 (96.0)
Liver	0.071 (89.0)	n.p.	0.012 (15.0)	0.083 (104.0)
Triazine Label (Animal Group 2)				
Egg white*	0.034 (94.9)	n.p.	0.001 (2.6)	0.035 (97.5)
Egg yolk*	0.050 (93.9)	n.p.	0.006 (12.0)	0.056 (105.9)
Whole egg**	0.038 (94.6)	n.p.	0.002 (5.0)	0.040 (99.6)
Muscle	0.010 (85.5)	n.p.	0.002 (20.6)	0.012 (106.1)
Fat***	n.p.	0.18 / 0.001 (88.2) / (6.6)	0.001 (4.4)	0.020 (99.2)
Skin	0.017 (84.1)	n.p.	0.003 (14.8)	0.020 (98.9)
Liver	0.025 (82.9)	n.p.	0.007 (22.6)	0.032 (105.5)

* Egg pool Days 6 - 8 n.p. = not performed

** Calculated from egg white and yolk

*** second extraction because in the first extraction only the acetonitrile phase was ananlysed

Table B.7.2-10: Summary of identified metabolites in eggs and tissue of laying hens which had received ^{14}C-BAS 635 H at a nominal dose level of 10 mg/kg based on feed intake (dry matter)

Metabolite code	Structure	Egg white	Egg yolk	Whole egg	Muscle	Fat	Skin	Liver
		mg/kg (% TRR)	mg/kg (% TRR)	mg/kg (% TRR)	mg/kg (% TRR)	mg/kg (% TRR)	mg/kg (% TRR)	mg/kg (% TRR)
Phenyl Label								
BAS 635 H		0.010 (57.0)	0.003 (7.8)	0.008 (44.2)	0.002 (12.8)	0.004 (23.7)	0.010 (32.9)	0.039 (48.2)
635M02		0.006 (34.4)	0.026 (64.5)	0.011 (42.3)	0.009 (66.2)	0.008 (50.5)	0.010 (31.8)	0.030 (38.0)
Total identified		**0.016 (91.4)**	**0.029 (72.3)**	**0.019 (86.5)**	**0.011 (79.0)**	**0.012 (74.2)**	**0.02 (64.7)**	**0.069 (86.2)**
Triazine Label								
BAS 635 H		0.010 (27.4)	0.003 (6.0)	0.008 (21.9)	0.002 (15.8)	0.002 (9.7)	0.008 (42.1)	0.016 (52.8)
635M04 **(AMTT)**		0.014 (39.1)	0.031 (58.9)	0.018 (44.2)	0.004 (30.7)	0.015 (71.0)	0.008 (40.8)	0.002 (8.0)
635M09		0.007 (20.1)	0.014 (25.8)	0.009 (21.6)	0.003 (25.0)	0.002 (7.5)	<0.001 (1.2)	0.003 (10.0)
Total identfied		**0.031 (86.6)**	**0.048 (90.7)**	**0.035 (87.7)**	**0.009 (71.5)**	**0.019 (88.2)**	**0.016 (84.1)**	**0.021 (70.8)**

Additionally the following unknown minor metabolites were found.

Phenyl label group:

Egg whites : 1 (0.001 mg/kg or 6.6 % of TRR)
Egg yolk : 3 (< 0.001 to 0.003 mg/kg or 1 to 7.5 % of TRR)
Muscle : 1 (0.001 mg/kg or 9.6 % of TRR)
Fat : 2 (0.001 to 0.002 mg/kg or 4 to 12 % of TRR)
Skin : 2 (0.002 mg/kg or 5 to 7 % of TRR)
Liver : 2 (0.001 to 0.002 mg/kg or 1 to 2 % of TRR)

Triazine label group:

Egg white : 1 (0.003 mg/kg or 8 % of TRR)
Egg yolk : 1 (0.002 mg/kg or 3 % of TRR)
Muscle : 1 (0.002 mg/kg or 14 % of TRR)
Fat : -
Skin : -
Liver : 2 (0.001 to 0.003 mg/kg or 3 to 9 % of TRR)

Identification and quantification of the extractable residues
The chromatographic analysis showed the following results (see also Table B.7.2-10).
Excreta
The extract of pooled excreta from the *[Phenyl-^{14}C]* group contained predominantly unchanged parent compound (82 % of administered dose, 90 % of excreta radioactivity). Seven minor metabolites (< 0.1 % to 2 % of dose) could be detected, two of these could be identified as the metabolites 635M01 and 635M02 respectively. The extract from pooled excreta from the *[Triazine-^{14}C]* group contained also predominantly unchanged parent compound (85 % of administered dose, 88 % of excreta radioactivity). Six minor metabolites could be detected (1 % to 3 % of dose or excreta radioactivity), two of these were identified as the metabolites 635M09 and 635M04 (AMTT) respectively.
Eggs and tissues
The acetonotrile extracts and the ethyl acetate phases resulting from the ethyl acetate/water partitioning of the acetonitrile extracts were analysed by HPLC. The quantitative results are based on chromatograms obtained with the acetonitrile extracts. The ethyl acetate phases contained all metabolites found in the acetonitrile extracts (although in slightly different relative amounts) and showed sharper peaks and reproducible retention times; therefore, these extracts were mainly used for identification of metabolites. The results are summarised in Table B.7.2-10.

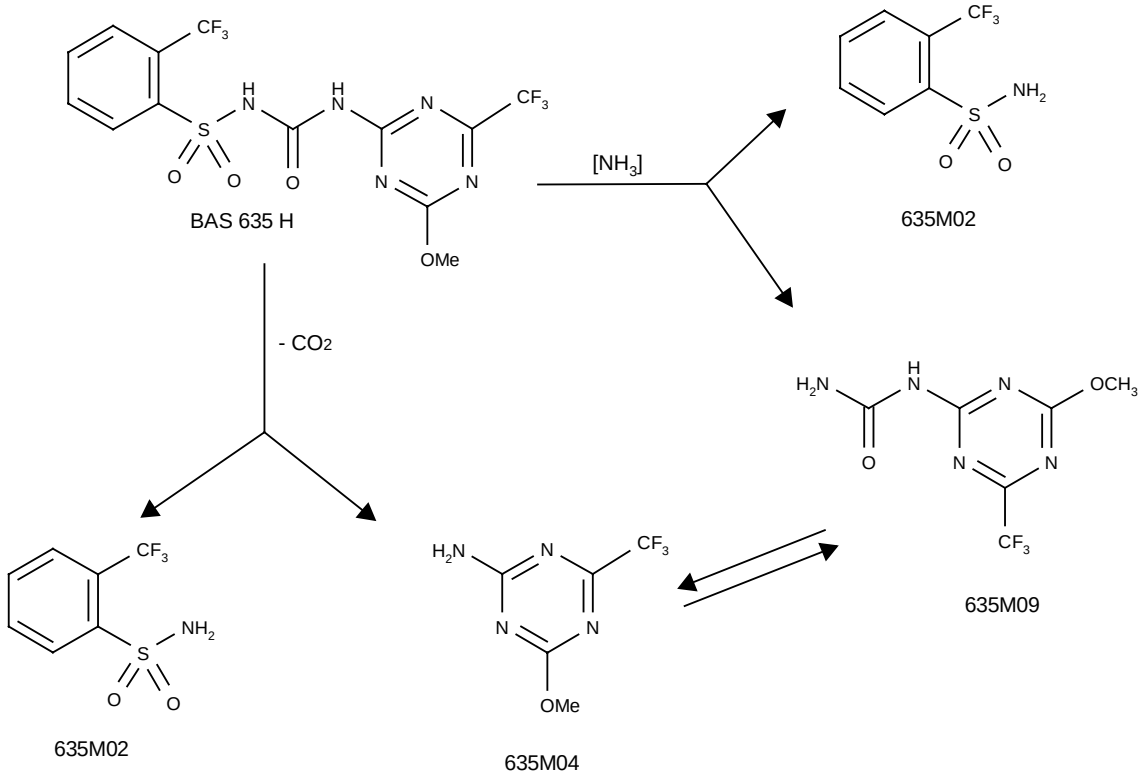
Storage stability
A comparison of the metabolite patterns at the beginning of the study and about 10 months later in extracts of egg yolk, muscle, fat and liver showed no significant qualitative changes. As changes the reduction of polar unknown metabolite peaks were observed. On the other hand in muscle and liver the concentration of the metabolite 635M04 increased and of the parent compound decreased in the *Triazine label* group. These changes were explained by the notifier "with a slow non-enzymic hydrolysis on storage of the parent compound".

Discussion
The metabolism of BAS 635 H has been investigated using two labelled forms (^{14}C-label in the phenyl ring and in the triazine ring). The total recovery of radioactivity was 91.9 % for the group dosed with *[Phenyl-^{14}C]*-BAS 635 H and 100 % for the group dosed with *[Triazine-^{14}C]*-BAS 635 H. Daily recoveries of radioactivity in excreta (82 - 98 % and 93 - 101 % respectively for the two groups) indicate rapid and almost complete excretion of radioactivity within 24 hours post-dosing. In eggs only 0.08 % of the total administered radioactivity were found.
With acetonitrile 77 % to 98 % of TRR and with acetonitrile/iso-hexane 90 % of TRR in fat were extractable. The remaining non-extractable residues accounted for 3 % to 19 %; however, the absolute amount was only 0.007 mg/kg or less, except liver from the phenyl label, where it was 0.012 mg/kg. The subsequent water extraction of liver released another 6 % to 8 % of TRR. The etyl acetate/water partitioning of the extractable radioactivity showed that metabolites were predominantly non-polar (organic soluble). Despite of the low levels of radioactivity in eggs and tissues, 65 % to 91 % of TRR could be identified.
The major metabolic reaction was the cleavage of the sulfonylurea bridge (Figure B.7.2-1).
After dosing of *[Phenyl-^{14}C]*-BAS 635 H, the sulfonamide 635M02 was a major metabolite (32 % to 66 % of TRR). The unchanged parent compound accounted for 8 % to 57 % of TRR.
After dosing of *[Triazine-^{14}C]*-BAS 635 H similar proportions of unchanged parent compound were found (6 % to 53 % of TRR). Additionally, the ureyltriazine 635M09 (1 % to 26 % of TRR) and the aminotriazine 635M04 (AMTT) (8 % to 71 % of TRR) were identified.

In excreta a fourth metabolite 635M01 was identified at low level (1.6 % od administered dose) which was not reported in the goat study.
The re-analysis of extracts of eggs and tissues about 10 months after beginning of study showed that in muscle and liver about 50 % of the parent compound had hydrolytically degraded to the aminotriazine 635M04 (AMTT), in fat was the degradation less pronounced. Therefore it has to be expected that directly after sacrifice of the animals the amount of 635M04 (AMTT) will be lower and the amount of parent compound higher than found and reported.

Conclusion
The metabolic pathway of BAS 635 H in laying hens is sufficiently investigated. After administration of an exaggerated dose (nominal 10 mg/kg feed dry matter, actual 13.95 mg/kg and 13.4 mg/kg respectively) for 8 consecutive days, eggs and tissues contained residues at very low levels consisting of unchanged parent compound and three major metabolites.
As expected the molecule is cleaved at the sulfonylurea bridge. Breakdown products were found containing either the phenyl or the triazine moiety according to the labelling position, the same as reported in the goat study.
There was no indication of accumulation of ^{14}C-BAS 635 H in hen tissues and eggs.

Figure B.7.2-1: Metabolic pathway of BAS 635 H in goats and hens



B.7.2.3 Pigs

No metabolism study in pigs was performed, since the metabolites identified in ruminants (goats) were essentially detected in rodents (rats).

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

B.7.3.1 Plants

In the metabolism study conducted in maize with an exaggerated rate of 180 g as/ha, only low amounts (< 0.01 mg/kg) of parent compound tritosulfuron and of metabolites were found in grain. The metabolite AMTT (635M04) was not detected in the maize metabolism study. But due to the toxicological properties of AMTT, all samples from the supervised residue trials performed in 1999 and 2000 were analysed for tritosulfuron and AMTT. In none of the grain samples from cereals and maize, neither tritosulfuron nor AMTT was detected in amounts greater than 0.001 mg/kg.

Therefore, the residue definition for plant materials is proposed as **tritosulfuron**.

B.7.3.2 Animal matrices

Metabolism studies performed on goats and hens show that residues in products of animal origin contain parent as major component. Transformation products after cleavage of the sulfonylurea bridge were the sulfonamide 635M02, the ureyltriazine 635M09, and the aminotriazine 635M04 (AMTT).

An individual metabolite is considered to be relevant if in studies where the animals were dosed close to the expected maximum residue level based on Good Agricultural Practice (GAP) the following criteria are met:

- relative amount > 10 % of total radioactive residues (TRR) in a matrix

and

- absolute concentration > 0.05 mg/kg in the same matrix

Since the total radioactive residue level in edible matrices of the goat and hen metabolism studies was below 0.05 mg/kg in most of the cases and since these residue levels resulted from overdosing the goats and hens compared to realistic feeding levels obtained according to GAP, the criteria for the designation of a relevant metabolite are not met. With focus on the metabolite 635M04 (AMTT), it can be assumed that this compound would be present in animal matrices at levels below 0.001 mg/kg after feed up-take with realistic residues and therefore, it would not be detected by any residue analytical method.

The parent compound was detected at significant proportions in all matrices, even though it occurred at very little absolute residue levels.

Based on these facts, the following definition of relevant residues is proposed for products of animal origin for monitoring purposes :

parent BAS 635 H (tritosulfuron)

The Notifier proposed an analytical enforcement method parent only.

B.7.4 Use pattern

For tritosulfuron containing products, uses are applied for in maize and cereals in both the northern and southern regions of Europe. Tritosulfuron will either be applied as solo product or in combination with other herbicidal active substances as WG formulations. They will be used at application rates of 150 – 400 l/ha corresponding to 0.05 kg as/ha. Details of the proposed uses are summarised in B.3.3.

Table B.7.4-1: Formulated products of tritosulfuron

BAS-Code	Content of tritosulfuron (g/kg)	Other active substance (g/kg)
BAS 635 00 H*	714	
BAS 641 01 H**	400	Cinidonethyl, 240
BAS 655 00 H**	250	Dicamba, 500
BAS 655 01 H**	125	Dicamba, 600

* representative formulation of EU Dossier
** further formulated product under development

B.7.5 Identification of critical GAPs

The critical GAP for the use of tritosulfuron is based on an application rate of 0.05 kg as/ha at the latest possible developing stage. This is growth stage 39 (BBCH) for cereals and stage 17 (BBCH) for maize.

B.7.6 Residues resulting from supervised trials (Annex IIA 6.3; Annex IIIA 8.2)

B.7.6.1 Cereals

B.7.6.1.1 Study design

During the growing seasons 1999 and 2000, 46 field trials were conducted in different representative cereal growing areas in Germany, Denmark, Spain, France, Great Britain and Italy (24 in Northern EU, 22 in the South) to determine the residue levels of tritosulfuron after application of either BAS 635 00 H, BAS 641 01 H or BAS 655 00 H. Different cereal varieties such as spring and winter barley, spring and winter wheat as well as durum wheat were used. They were all applied once at BBCH growth stage 37 – 45 at an application rate equivalent to 0.05 kg as/ha of tritosulfuron together with 1.25 l/ha of the additive BAS 152 00 S. The spray volume was 300 l/ha. All samples were analysed for parent compound tritosulfuron and the metabolite AMTT (635M04).

In the years 1996 to 1998 trials had already been conducted with the formulation BAS 641 00 H, but samples were analysed for tritosulfuron only and not for AMTT. These results are additionally reported as supplementary data.

Table B.7.6-1: Formulations of tritosulfuron used in residue trials in cereals

Formulation code	Type	Tritosulfuron (g/kg)	Other active substance / content (g/kg)	Additive
BAS 635 00 H	WG	714	---	BAS 152 00 S
BAS 641 01 H	WG	400	BAS 615 H (Cinidon-ethyl) / 240	BAS 152 00 S
BAS 655 00 H	WG	250	Dicamba / 500	BAS 152 00 S
BAS 641 00 H*	WG	50	BAS 615 H (Cinidon-ethyl) / 30	---

* Formulation used in 1996 to 1998

Table B.7.6-2: GAP information of the residue trials in cereals

Crop	Country	Formulation	Application				PHI
			Method	Rate kg as/ha	Spray conc. kg as/hl	No	
Residue trials in 1999 and 2000							
Spring barley	D-Germany (2 trial)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-60
Spring barley	DK-Denmark (1 trial)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-79
Spring barley	DK-Denmark (1 trial)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-79
Spring barley	F-France (2 trials)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-61
Spring barley	F-France (2 trials)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-61
Spring barley	I-Italy (1 trial)	BAS 655 00 H WG 250	foliar	0.050 0.100	Tritosulfuron, 0.017 Dicamba, 0.033	1	0-37
Winter barley	F-France (2 trials)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-66
Winter barley	GB-Great Britain (2 trials)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-74
Winter barley	GB-Great Britain (2 trials)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-74
Winter barley	F-France (5 trials)	BAS 655 00 H WG 250	foliar	0.050 0.100	Tritosulfuron, 0.017 Dicamba, 0.033	1	0-85
Winter barley	I-Italy (3 trials)	BAS 655 00 H WG 250	foliar	0.050 0.100	Tritosulfuron, 0.017 Dicamba, 0.033	1	0-54
Spring wheat	D-Germany (2 trial)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-60
Winter wheat	F-France (4 trials)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-102
Winter wheat	F-France (2 trials)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-102
Winter wheat	F-France (7 trials)	BAS 655 00 H WG 250	foliar	0.050 0.100	Tritosulfuron, 0.017 Dicamba, 0.033	1	0-90

Crop	Country	Formulation	Application				PHI
			Method	Rate kg as/ha	Spray conc. kg as/hl	No	
Winter wheat	I-Italy (1 trial)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-54
Winter wheat	I-Italy (1 trial)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-54
Winter wheat	I-Italy (2 trials)	BAS 655 00 H WG 250	foliar	0.050 0.100	Tritosulfuron, 0.017 Dicamba, 0.033	1	0-55
Durum wheat	E-Spain (2 trials)	BAS 641 01 H WG 400	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-87
Durum wheat	E-Spain (2 trials)	BAS 635 00 H WG 714	foliar	0.050	Tritosulfuron, 0.017	1	0-87
Residue trials in 1996 to 1998							
Spring barley	B-Belgium (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-21
Spring barley	F-France (4 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-76
Spring barley	FIN-Finland* (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	436
Spring barley	S-Sweden (2 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-92
Winter barley	GB-Great Britain (4 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-79
Spring wheat	GB-Great Britain (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-102
Spring wheat	FIN-Finland* (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	454
Winter wheat	E-Spain (2 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-70
Winter wheat	D-Germany (5 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-100
Winter wheat	GB-Great Britain (2 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-45
Winter wheat	NL-Netherlands (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-21
Durum wheat	E-Spain (2 trials)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-69
Winter rye	D-Germany (1 trial)	BAS 641 00 H WG 50	foliar	0.050 0.030	Tritosulfuron, 0.017 BAS 615 H, 0.010	1	0-85

* non valid field trial

B.7.6.1.2 Acceptability

1999-2000

All trials are regarded as valid.

1996-1998

The residue data of the trials conducted in 1996 to 1998 were reported as supplementary data. For the laboratory parts, recovery experiments were documented but no further documentation (e.g. chromatograms) was submitted. Since the method was validated (cf. B.5.2) the studies are considered as valid except for the following: Field trials conducted in Finland (Sasturain, Mackenroth, 2001, RIP2001-601) were non-GLP trials and no documentation about the field part was submitted. Therefore, the results of these trials cannot be regarded as valid.

B.7.6.1.3 Analytical method

1999 - 2000

In all trials, plant without root was sampled directly after the application as well as 8 - 30 days thereafter. Grain and straw were collected at 54 – 102 DAT.

Method BASF D003 was used for analysis of tritosulfuron. Aliquots of acetone/water extracts were cleaned up with a quaternary amine column. LC/MS/MS was used for determination. The limit of quantitation was 0.01 mg/kg for plant and straw matrices and 0.001 mg/kg for grain (validation cf. B.5.2).

Method BASF D002 was used for analysis of AMTT (635M04). Aliquots of acetone/water extracts were further cleaned up with quaternary amine column, HLB® SPE column and SPE micro column. GC/MS with single ion monitoring (M/Z 164) was used for determination. The limit of quantitation was 0.001 mg/kg in all matrices.

All recoveries for tritosulfuron (fortification level: 0.001 to 5 mg/kg) and for AMTT (fortification level: 0.001 to 1.0 m/kg) reported in the residue studies were acceptable.

1996 –1998

Methods BASF 405/1 and 405/2 were used for analysis of tritosulfuron. The limit of quantitation was 0.01 mg/kg for plant and straw (405/1, validation cf. B.5.2) and 0.001 mg/kg for grain (405/2, detection LC/MS/MS). All recoveries for tritosulfuron (fortification level: 0.001 to 1.0 mg/kg) reported in the residue studies were acceptable.

B.7.6.1.4 Results of residue trials in cereals

1999-2000

The residues of tritosulfuron in plant without root sampled directly after the application ranged between < 0.01 and 4.12 mg/kg. In more than 90 % of the samples the residues were between 0.1 and 1.6 mg/kg. There were no significant differences between the three formulations tested.

None of the grain samples analysed for tritosulfuron did show any residue above the limit of quantitation of 0.001 mg/kg. In 39 out of 46 straw samples collected at 37 – 102 DAT, no

residues above the limit of quantification were found, the others contained tritosulfuron between 0.01 and 0.023 mg/kg.

The degradation product AMTT was found between < 0.001 and 0.053 mg/kg at day 0. After 8 – 30 days, only 7 out of 46 plant samples contained AMTT between 0.001 and 0.0029 mg/kg. In none of the grain samples tested AMTT could be detected above the limit of quantitation of 0.001 mg/kg. In straw, 27 samples showed residues up to 0.013 mg/kg.

1996-1998 (supplementary data)

In the earlier series of residue trials comparable values were obtained for tritosulfuron. No residues above the limit of quantification of 0.001 mg/kg were found in grain. In straw, 4 out of 27 samples contained residues of tritosulfuron between 0.01 and 0.025 mg/kg. In two trials, tritosulfuron was applied later as usual at growth stage 55 – 59. These straw samples contained 0.046 mg/kg and 0.136 mg/kg tritosulfuron.

B.7.6.1.5 Conclusion

Residue trials with tritosulfuron were performed in representative growing areas of the North and the South EU. Different formulations were applied once with an application rate of 50 g as/ha and in most trials at growth stage 37 - 39 (BBCH). Several varieties of cereals were used. Thus, the trials represent typical residue behaviour of tritosulfuron in cereals under European conditions. The residue situation was identical for all crops tested with the various formulations and also with regard to the regional and the seasonal distribution.

When applied according to GAP (growth stage 37 – 39), no residues of tritosulfuron and the metabolite AMTT were detectable in grain (< 0.001 mg/kg) at harvest time. In straw, tritosulfuron was found in the range of < 0.01 – 0.025 mg/kg. The metabolite AMTT showed residues in the range of < 0.001 – 0.013 mg/kg.

Table B.7.6-3: Residue data of tritosulfuron and metabolite AMTT (635M04) in cereals

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
Summer barley, North Europe									
DK / 2000	WG 714	0.0521	BBCH 39	1	whole plant	1.596	0.0048	0	RIP2001-598
						0.025	< 0.001	19	
					grain	< 0.001	< 0.001	79	
					straw	< 0.01	< 0.001	79	
DK / 2000	WG 400 + BAS 615 H	0.0516	BBCH 39	1	whole plant	1.512	0.0046	0	RIP2001-598
						0.019	< 0.001	19	
					grain	< 0.001	< 0.001	79	
					straw	< 0.01	< 0.001	79	
DE / 1999	WG 400	0.0488	BBCH 39	1	whole plant	0.276	0.0155	0	RIP2001-595
						< 0.01	< 0.001	13	
					grain	< 0.001	< 0.001	60	
					straw	< 0.01	0.0012	60	

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
DE / 1999	WG 400	0.0524	BBCH 37-39	1	whole plant grain straw	0.392 < 0.01 < 0.001 < 0.01	0.0054 0.0029 < 0.001 0.0031	0 15 66 66	RIP2001-595
N-FR / 1997	WG 50	0.051	BBCH 37	1	whole plant grain straw	0.77 < 0.01 < 0.001 0.017		0 21 67 67	RIP2001-600
SE / 1997	WG 50	0.0481	BBCH 37	1	whole plant grain straw	0.434 0.031 < 0.001 0.025		0 17 78 78	RIP2001-600
FI / 1998*	WG 50	0.05		1	grain straw	<0.001* < 0.01*		436 436	RIP2001-601
SE / 1998	WG 50	0.048	BBCH 37	1	whole plant grain straw	1.13 0.014 < 0.001 0.011		0 31 66 66	RIP2001-602
BE / 1998	WG 50	0.051	BBCH 39	1	whole plant	0.845 0.074		0 21	RIP2001-602
N-FR / 1998	WG 50	0.05	BBCH 39	1	whole plant	0.673 0.066		0 15	RIP2001-602
Summer barley, South Europe									
S-FR / 2000	WG 714	0.048	BBCH 37-39	1	whole plant grain straw	1.403 < 0.01 < 0.001 < 0.01	0.0136 < 0.001 < 0.001 < 0.001	0 27 61 61	RIP2001-597
S-FR / 2000	WG 400	0.0486	BBCH 37-39	1	whole plant grain straw	4.198 0.011 < 0.001 0.014	0.0533 < 0.001 < 0.001 < 0.001	0 27 61 61	RIP2001-597
IT / 2000	WG 250	0.0506	BBCH 39	1	whole plant grain straw	0.49 0.16 < 0.001 0.011	0.0022 < 0.001 < 0.001 0.0027	0 8 37 37	RIP2001-599
S-FR / 1996-1997	WG 50	0.0498	BBCH 37	1	whole plant grain straw	0.855 0.02 < 0.001 < 0.01		0 32 76 76	RIP2001-600
S-FR / 1997-1998	WG 50	0.05	BBCH 39	1	whole plant grain straw	0.938 < 0.01 < 0.001 < 0.01		0 23 61 61	RIP2001-602
Winter barley, North Europe									
GB / 1999-2000	WG 714	0.0521	BBCH 39	1	whole plant grain straw	1.128 0.021 < 0.001 0.015	0.0022 < 0.001 < 0.001 < 0.001	0 20 70 70	RIP2001-598
GB / 1999-2000	WG 714	0.05	BBCH 39	1	whole plant grain straw	0.897 0.015 < 0.001 < 0.01	0.0102 < 0.001 < 0.001 < 0.001	0 24 74 74	RIP2001-598

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
GB / 1999-2000	WG 400	0.0516	BBCH 39	1	whole plant grain straw	0.872 0.02 < 0.001 0.023	0.0016 < 0.001 < 0.001 < 0.001	0 20 70 70	RIP2001-598
GB / 1999-2000	WG 400	0.0488	BBCH 39	1	whole plant grain straw	0.698 0.01 < 0.001 < 0.01	0.0107 < 0.001 < 0.001 < 0.001	0 24 74 74	RIP2001-598
N-FR / 1998-1999	WG 250	0.0487	BBCH 37-39	1	whole plant grain straw	0.152 0.016 < 0.001 < 0.01	0.001 < 0.001 < 0.001 < 0.001	0 15 76 76	RIP2001-596
N-FR / 1998-1999	WG 250	0.0537	BBCH 37-39	1	whole plant grain straw	0.227 0.032 < 0.001 0.017	0.0019 0.0011 < 0.001 0.0043	0 14 65 65	RIP2001-596
N-FR / 1999-2000	WG 250	0.0502	BBCH 39	1	whole plant grain straw	0.659 0.025 < 0.001 < 0.01	0.0018 < 0.001 < 0.001 < 0.001	0 12 84 84	RIP2001-599
N-FR / 1999-2000	WG 250	0.0528	BBCH 39	1	whole plant grain straw	0.93 < 0.01 < 0.001 < 0.01	0.0014 < 0.001 < 0.001 0.001	0 15 85 85	RIP2001-599
N-FR / 1999-2000	WG 250	0.05046	BBCH 39	1	whole plant grain straw	0.543 0.023 < 0.001 0.014	< 0.001 < 0.001 < 0.001 0.0039	0 14 59 59	RIP2001-599
GB / 1996-1997	WG 50	0.0496	BBCH 37	1	whole plant grain straw	0.457 0.016 < 0.001 < 0.01		0 22 79 79	RIP2001-600
GB / 1996-1997	WG 50	0.0535	BBCH 45	1	whole plant grain straw	0.819 0.036 < 0.001 0.017		0 15 76 76	RIP2001-600
GB / 1997-1998	WG 50	0.047	BBCH 39	1	whole plant grain straw	0.698 0.055 < 0.001 < 0.01		0 24 77 77	RIP2001-602
GB / 1997-1998	WG 50	0.051	BBCH 39	1	whole plant	0.84 0.115		0 16	RIP2001-602
Winter Barley, South Europe									
S-FR / 1999-2000	WG 714	0.0492	BBCH 39	1	whole plant grain straw	1.501 0.021 < 0.001 < 0.01	0.0093 0.0017 < 0.001 0.0038	0 14 59 59	RIP2001-597
S-FR / 1998-1999	WG 400	0.0514	BBCH 39	1	whole plant grain straw	0.117 < 0.01 < 0.001 < 0.01	0.0015 < 0.001 < 0.001 0.0019	0 30 66 66	RIP2001-595

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
S-FR / 1998-1999	WG 400	0.0469	BBCH 39-41	1	whole plant grain straw	0.061 0.01 < 0.001 0.01	0.003 < 0.001 < 0.001 0.0131	0 9 58 58	RIP2001-595
S-FR / 1999-2000	WG 400	0.0492	BBCH 39	1	whole plant grain straw	1.487 0.026 < 0.001 < 0.01	0.0138 0.0017 < 0.001 0.0031	0 14 59 59	RIP2001-597
IT / 1998-1999	WG 250	0.0523	BBCH 37	1	whole plant grain straw	< 0.01 < 0.01 < 0.001 < 0.01	< 0.001 < 0.001 < 0.001 0.0056	0 14 54 54	RIP2001-596
IT / 1998-1999	WG 250	0.0504	BBCH 37	1	whole plant grain straw	0.266 0.035 < 0.001 < 0.01	0.0032 < 0.001 < 0.001 0.0015	0 8 49 49	RIP2001-596
IT / 1999-2000	WG 250	0.0466	BBCH 39	1	whole plant grain straw	0.669 0.01 < 0.001 < 0.01	0.0015 < 0.001 < 0.001 0.0021	0 8 38 38	RIP2001-599
Summer Wheat, North Europe									
DE / 1999	WG 400	0.0496	BBCH 37-39	1	whole plant grain straw	0.412 < 0.01 < 0.001 < 0.01	0.0044 < 0.001 < 0.001 0.0029	0 20 86 86	RIP2001-595
DE / 1999	WG 400	0.0517	BBCH 37-39	1	whole plant grain straw	0.346 0.011 < 0.001 < 0.01	0.0088 < 0.001 < 0.001 0.0032	0 18 58 58	RIP2001-595
GB / 1997	WG 50	0.0506	BBCH 33	1	whole plant grain straw	0.875 0.013 < 0.001 < 0.01		0 31 102 102	RIP2001-600
FI / 1998*	WG 50	0.05		1	grain straw	<0.001* < 0.01*		454 454	RIP2001-601
Winter wheat, North Europe									
N-FR / 1999-2000	WG 714	0.049	BBCH 37-39	1	whole plant grain straw	0.468 < 0.01 < 0.001 < 0.01	0.0045 < 0.001 < 0.001 0.0017	0 26 102 102	RIP2001-597
N-FR / 1999-2000	WG 714	0.0503	BBCH 37-39	1	whole plant grain straw	0.765 < 0.01 < 0.001 < 0.01	0.012 < 0.001 < 0.001 0.0013	0 18 97 97	RIP2001-597
N-FR / 1999-2000	WG 400	0.0464	BBCH 37-39	1	whole plant grain straw	0.456 < 0.01 < 0.001 < 0.01	0.0104 < 0.001 < 0.001 0.0013	0 26 102 102	RIP2001-597
N-FR / 1999-2000	WG 400	0.0508	BBCH 37-39	1	whole plant grain straw	0.671 < 0.01 < 0.001 < 0.01	0.0183 < 0.001 < 0.001 0.0014	0 18 97 97	RIP2001-597

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
N-FR / 1998-1999	WG 250	0.048	BBCH 37-39	1	whole plant grain straw	0.118 < 0.01 < 0.001 < 0.01	< 0.001 < 0.001 < 0.001 < 0.001	0 24 85 85	RIP2001-596
N-FR / 1998-1999	WG 250	0.0564	BBCH 37-39	1	whole plant grain straw	0.145 0.024 < 0.001 0.018	< 0.001 < 0.001 <0.001 0.0042	0 18 73 73	RIP2001-596
N-FR / 1999-2000	WG 250	0.0504	BBCH 37-39	1	whole plant grain straw	0.56 < 0.01 < 0.001 < 0.01	0.0414 < 0.001 < 0.001 < 0.001	0 26 102 102	RIP2001-599
N-FR / 1999-2000	WG 250	0.0505	BBCH 39	1	whole plant grain straw	0.719 0.015 < 0.001 < 0.01	0.0344 0.0018 < 0.001 < 0.001	0 17 79 79	RIP2001-599
N-FR / 1999-2000	WG 250	0.0513	BBCH 39	1	whole plant grain straw	0.485 0.018 < 0.001 0.01	0.0021 0.0012 < 0.001 0.0012	0 21 90 90	RIP2001-599
DE / 1996-1997	WG 50	0.0467	BBCH 31	1	whole plant grain straw	1.66 < 0.01 < 0.001 < 0.01		0 52 100 100	RIP2001-600
DE / 1996-1997	WG 50	0.0496	BBCH 37	1	whole plant grain straw	0.627 0.014 < 0.001 < 0.01		0 24 80 80	RIP2001-600
DE / 1997-1998	WG 50	0.048	BBCH 37	1	whole plant grain straw	1.37 0.03 < 0.001 < 0.01		0 19 83 83	RIP2001-602
NL / 1997-1998	WG 50	0.0475	BBCH 39	1	whole plant	0.656 0.013		0 21	RIP2001-602
DE / 1997-1998	WG 50	0.0515	BBCH 37-39	1	whole plant grain straw	0.607 < 0.01 < 0.001 < 0.01		0 24 84 84	RIP2001-602
DE / 1997-1998	WG 50	0.05	BBCH 39	1	whole plant grain straw	0.592 0.014 < 0.001 < 0.01		0 22 70 70	RIP2001-602
GB / 1997-1998	WG 50	0.0515	BBCH 37	1	whole plant grain straw	0.584 < 0.01 < 0.001 0.012		0 33 86 86	RIP2001-602
GB / 1997-1998	WG 50	0.0475	BBCH 39-41	1	whole plant	0.485 0.011		0 24	RIP2001-602

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
Winter Wheat, South Europe									
IT / 1999-2000	WG 714	0.0465	BBCH 37	1	whole plant	0.593	0.0021	0	RIP2001-597
						< 0.01	< 0.001	11	
					grain	< 0.001	< 0.001	54	
					straw	< 0.01	< 0.001	54	
S-FR / 1998-1999	WG 400	0.0463	BBCH 39-41	1	whole plant	0.067	0.003	0	RIP2001-595
						0.01	< 0.001	8	
					grain	< 0.001	< 0.001	63	
					straw	< 0.01	0.0033	63	
S-FR / 1998-1999	WG 400	0.0489	BBCH 41-45	1	whole plant	0.207	< 0.001	0	RIP2001-595
						0.012	< 0.001	10	
					grain	< 0.001	< 0.001	70	
					straw	< 0.01	0.0087	70	
IT / 1999-2000	WG 400	0.0496	BBCH 37	1	whole plant	0.535	0.003	0	RIP2001-597
						< 0.01	< 0.001	11	
					grain	< 0.001	< 0.001	54	
					straw	< 0.01	0.0013	54	
IT / 1998-1999	WG 250	0.0485	BBCH 37-39	1	whole plant	0.3	0.0021	0	RIP2001-596
						0.011	< 0.001	10	
					grain	< 0.001	< 0.001	54	
					straw	< 0.01	0.0012	54	
IT / 1998-1999	WG 250	0.0514	BBCH 37	1	whole plant	0.326	0.0011	0	RIP2001-596
						0.022	< 0.001	13	
					grain	< 0.001	< 0.001	55	
					straw	< 0.01	< 0.001	55	
S-FR / 1999-2000	WG 250	0.0501	BBCH 37-39	1	whole plant	0.675	0.0293	0	RIP2001-599
						< 0.01	< 0.001	17	
					grain	< 0.001	< 0.001	74	
					straw	< 0.01	< 0.001	74	
S-FR / 1999-2000	WG 250	0.0481	BBCH 39	1	whole plant	0.547	0.0013	0	RIP2001-599
						0.017	0.0016	12	
					grain	< 0.001	< 0.001	69	
					straw	< 0.01	< 0.001	69	
ES / 1996-1997	WG 50	0.0493	BBCH 57-59	1	whole plant	1.29		0	RIP2001-600
						0.599		12	
					grain	< 0.001		70	
					straw	0.046		70	
ES / 1996-1997	WG 50	0.049	BBCH 55-57	1	whole plant	1.15		0	RIP2001-600
						0.7		12	
					grain	< 0.001		64	
					straw	0.136		64	
Durum wheat, South Europe									
ES / 1999-2000	WG 714	0.0514	BBCH 39	1	whole plant	0.841	0.0221	0	RIP2001-598
						0.012	< 0.001	12	
					grain	< 0.001	< 0.001	87	
					straw	< 0.01	0.0021	87	
ES / 1999-2000	WG 714	0.0521	BBCH 37	1	whole plant	0.79	0.0109	0	RIP2001-598
						< 0.01	< 0.001	28	
					grain	< 0.001	< 0.001	78	
					straw	< 0.01	0.0035	78	
ES / 1999-2000	WG 400	0.0532	BBCH 39	1	whole plant	0.543	0.0068	0	RIP2001-598
						0.01	< 0.001	12	
					grain	< 0.001	< 0.001	87	
					straw	< 0.01	0.0024	87	

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
ES / 1999-2000	WG 400	0.0536	BBCH 37	1	whole plant grain straw	0.734 < 0.01 < 0.001 < 0.01	0.0169 < 0.001 < 0.001 0.0034	0 28 78 78	RIP2001-598
ES / 1997-1998	WG 50	0.054	BBCH 37-39	1	whole plant grain straw	0.828 0.017 < 0.001 < 0.01		0 29 69 69	RIP2001-602
ES / 1997-1998	WG 50	0.0535	BBCH 37-39	1	whole plant grain straw	1.08 < 0.01 < 0.001 < 0.01		0 29 69 69	RIP2001-602
Winter rye, North Europe									
DE / 1996-1997	WG 50	0.05	BBCH 33	1	whole plant grain straw	0.861 0.023 < 0.001 < 0.01		0 23 85 85	RIP2001-600

* regarded as not valid

B.7.6.2 Maize

B.7.6.2.1 Study design

During the growing seasons 1999 and 2000, 17 field trials were conducted in different representative maize growing areas in Germany, Denmark, Spain, France, Great Britain and the Netherlands (8 in Northern EU, 9 in the South) to determine the residue levels of tritosulfuron and the metabolite AMTT (635M04) after application of BAS 635 00 H.

The herbicide was applied once with 0.07 kg/ha (0.05 kg as/ha) together with 1.25 l/ha of the adjuvant BAS 152 00 S. In four of the French trials, BAS 635 00 H was applied as tank mix together with BAS 351 40 H (48 % bentazone). In all cases the application was performed at BBCH growth stage 14 – 16 with a spray volume of 300 l/ha.

In the years 1996 to 1998 trials had already been conducted with the formulations BAS 639 00 H, BAS 635 01 H or BAS 635 GJ H. Since the samples were analysed for tritosulfuron only and not for AMTT, these results are additionally reported as supplementary data.

Table B.7.6-4: Formulations of tritosulfuron used in residue trials in maize

Formulation code	Type	Tritosulfuron (g/kg)	Other active substance / content (g/kg)	Additive
BAS 635 00 H	WG	714	---	BAS 152 00 S
BAS 635 01 H*	WG	50	---	---
BAS 635 GJ H*	WG	33	---	---
BAS 639 00 H*	WG	27	Bentazone / 533	BAS 064 00 S
BAS 351 40 H		---	Bentazone / 480	---

* Formulation used in 1996 to 1998

Table B.7.6-5: GAP information of the residue trials in maize

Crop	Country	Formulation	Application				PHI
			Method	Rate kg as/ha	Spray conc. kg as/hl	No	days
Residue trials in 1999 to 2000							
Maize	D-Germany (2 trials)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-139
Maize	DK-Denmark (1 trial)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-118
Maize	E-Spain (5 trials)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-134
Maize	F-France (4 trials)	BAS 635 00 H WG 714 + BAS 351 40 H	foliar	0.050 1.54	tritosulfuron, 0.020 bentazone, 0.614	1	0-144
Maize	F-France (3 trials)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-141
Maize	GB-Great Britain (1 trial)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-92
Maize	NL-Netherlands (1 trial)	BAS 635 00 H WG 714	foliar	0.050	0.017	1	0-92
Residue trials in 1996 to 1998							
Maize	B-Belgium (1 trial)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-96
Maize	B-Belgium (1 trial)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-96
Maize	D-Germany (5 trials)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-139
Maize	D-Germany (4 trial)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-138
Maize	D-Germany (3 trial)	BAS 635 GJ WG 33 H	foliar	0.050	0.017	1	0-138
Maize	E-Spain (6 trials)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-113
Maize	E-Spain (2 trials)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-104
Maize	F-France (2 trials)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-114
Maize	F-France (3 trials)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-114

Crop	Country	Formulation	Application				PHI
			Method	Rate kg as/ha	Spray conc. kg as/hl	No	days
Maize	F-France (1 trial)	BAS 635 GJ WG 33 H	foliar	0.050	0.017	1	0-109
Maize	GB-Great Britain (2 trials)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-102
Maize	GB-Great Britain (2 trials)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-102
Maize	I-Italy (2 trials)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-124
Maize	I-Italy (2 trials)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-124
Maize	NL-Netherlands (1 trial)	BAS 639 00 H WG 27	foliar	0.051	tritosulfuron, 0.017 bentazone, 0.336	1	0-105
Maize	S-Sweden (1 trial)	BAS 635 01 H WG 50	foliar	0.050	0.017	1	0-107
Maize	S-Sweden (1 trial)	BAS 635 GJ WG 33 H	foliar	0.050	0.017	1	0-107

B.7.6.2.2 Acceptability

1999-2000

All trials are regarded as valid.

1996 -1998

The residue data of the trials conducted in 1996 to 1998 (RIP-606 – RIP-609) were reported as supplementary data. For the laboratory parts, recovery experiments were documented but no further documentation (e.g. chromatograms) was submitted. Since the method was validated (cf. B.5.2) the studies are considered as valid.

B.7.6.2.3 Analytical method

1999 - 2000

Samples of plant without root were taken directly after the application (0 DAT) as well as 30 – 57 days thereafter. Cobs with husks and the rest of the plant (without roots) were collected after 73 – 121 days. Finally, grain and straw were taken 102 – 144 days after the application.

All samples were analysed for tritosulfuron and for its hydrolytic degradation product AMTT (635M04). For analysis of the parent compound, BASF Analytical Method No. D0003 was used. The limit of quantitation thereof was 0.01 mg/kg for plant and straw matrices and 0.001 mg/kg for grain (cf. B.5.2). BASF Analytical Method No. D0002 which quantified AMTT had a limit of quantitation of 0.001 mg/kg in all matrices.

All recoveries for tritosulfuron (fortification level 0.001 to 20 mg/kg) and for AMTT (fortification level: 0.001 to 0.24 mg/kg) reported in the residue studies were acceptable.

1996 –1998

Methods BASF 405/1 and 405/2 were used for analysis of tritosulfuron. The limit of quantitation was 0.01 mg/kg for plant and straw (405/1, validation cf. B.5.2) and 0.001 mg/kg for grain (405/2, detection LC/MS/MS). All recoveries for tritosulfuron (fortification level: 0.001 to 1.0 mg/kg) reported in the residue studies were acceptable.

B.7.6.2.4 Results of residue trials in maize

1999 - 2000

The residues of tritosulfuron found in plant without root directly after the application ranged between 0.031 and 6.24 mg/kg. From the plant samples collected at the second sampling, only four out of 17 showed residues above the limit of quantitation ranging between 0.018 and 0.034 mg/kg. None of the cob, grain or straw samples analysed did show any residue of tritosulfuron above the limit of quantitation.

Directly after the application, the degradation product AMTT was found in plant without root between < 0.001 and 0.018 mg/kg. None of the plant samples taken at 30 – 57 DAT did show any AMTT above the limit of quantification. The cobs and all but one sample of rest plant collected at the third sampling (73 – 121 DAA) did not show AMTT above LOQ, in the one rest plant sample 0.0011 mg/kg of AMTT was found. No AMTT was found in neither grain nor straw sampled 102 – 144 days after the application.

1996 – 1998 (supplementary data)

In the earlier series of residue trials comparable results were obtained for tritosulfuron in maize. No residues above the limit of quantification of 0.001 mg/kg were found in grain. From the second sampling on, only in two samples of whole plant (DAT 20 and 31) 0.015 mg/kg and 0.03 mg/kg and in one cob sample (DAT 107) 0.022 mg/kg were found. All other samplings showed no residue above the limit of quantification of 0.01 mg/kg.

B.7.6.2.5 Conclusion

Residue trials in maize were conducted in representative growing areas of the North and the South EU. Different formulations or tank mixes were used. They were applied with a rate of 50 g as/ha at growth stage 14 - 17 (BBCH). The trials represent typical residue behaviour of tritosulfuron in maize under European conditions. The residue situation was identical regardless the regional and seasonal distribution of the trials.

At time of harvest, no residues of tritosulfuron and the metabolite AMTT were detectable in maize grain and straw. In none of the maize forage samples (DAT 73 – 121) residues of tritosulfuron or AMTT were detected above 0.01 mg/kg. Only one cob sample (DAT 107) showed residues of tritosulfuron at 0.022 mg/kg.

Table B.7.6-6: Residue data of tritosulfuron and the metabolite AMTT in maize

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
North Europe									
DE / 1999	WG 714	0.0492	BBCH 15	1	whole plant	3.875	0.0184	0	RIP2001-603
						< 0.01	< 0.001	35	
					cobs with husks	< 0.01	< 0.001	105	
					rest of plant	< 0.01	< 0.001	105	
					grain	< 0.001	< 0.001	135	
					straw	< 0.01	< 0.001	135	
N-FR / 1999	WG 714	0.049	BBCH 14-15	1	whole plant	1.4	0.0029	0	RIP2001-604
						< 0.01	< 0.001	45	
					cobs with husks	< 0.01	< 0.001	115	
					rest of plant	< 0.01	< 0.001	115	
					grain	< 0.001	< 0.001	140	
					straw	< 0.01	< 0.001	140	
N-FR / 1999	WG 714	0.05	BBCH 15-16	1	whole plant	1.16	0.0039	0	RIP2001-604
						< 0.01	< 0.001	30	
					cobs with husks	< 0.01	< 0.001	76	
					rest of plant	< 0.01	< 0.001	76	
					grain	< 0.001	< 0.001	107	
					straw	< 0.01	< 0.001	107	
NL / 2000	WG 714	0.0519	BBCH 15	1	whole plant	4.25	0.0023	0	RIP2001-605
						0.02	< 0.001	35	
					cobs with husks	< 0.01	< 0.001	110	
					rest of plant	< 0.01	< 0.001	110	
					grain	< 0.001	< 0.001	139	
					straw	< 0.01	< 0.001	139	
DE / 2000	WG 714	0.0503	BBCH 15	1	whole plant	4.37	0.0047	0	RIP2001-605
						< 0.01	< 0.001	40	
					cobs with husks	< 0.01	< 0.001	116	
					rest of plant	< 0.01	0.0011	116	
					grain	< 0.001	< 0.001	139	
					straw	< 0.01	< 0.001	139	
N-FR / 2000	WG 714	0.0497	BBCH 14	1	whole plant	6.24	0.0051	0	RIP2001-605
						0.034	< 0.001	50	
					cobs with husks	< 0.01	< 0.001	121	
					rest of plant	< 0.01	< 0.001	121	
DK / 2000	WG 714	0.0508	BBCH 14	1	whole plant	4.27	0.0094	0	RIP2001-605
						< 0.01	< 0.001	40	
					cobs with husks	< 0.01	< 0.001	118	
					rest of plant	< 0.01	< 0.001	118	
GB / 2000	WG 714	0.05	BBCH 15	1	whole plant	2.48	0.0036	0	RIP2001-605
						< 0.01	< 0.001	45	
					cobs with husks	< 0.01	< 0.001	92	
					rest of plant	< 0.01	< 0.001	92	

Country/ Year	Formula-tion (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Trito-sulfuron	AMTT		
DE / 1997	WG 50	0.0525	BBCH 14-16	1	whole plant	2.08		0	RIP2001-607
						< 0.01		37	
					cobs with husks	< 0.01		113	
					rest of plant	< 0.01		113	
N-FR / 1997	WG 50	0.0501	BBCH 16	1	whole plant	2.18		0	RIP2001-607
						< 0.01		41	
					cobs with husks	< 0.01		108	
					rest of plant	< 0.01		108	
N-FR / 1997	WG 50	0.0527	BBCH 15	1	whole plant	1.48		0	RIP2001-607
						< 0.01		20	
					cobs with husks	< 0.01		91	
					rest of plant	< 0.01		91	
					grain	< 0.001		114	
					straw	< 0.01		114	
GB / 1997	WG 50	0.05	BBCH 16	1	whole plant	2.37		0	RIP2001-607
						< 0.01		32	
					cobs with husks	< 0.01		94	
					rest of plant	< 0.01		94	
GB / 1997	WG 50	0.052	BBCH 15	1	whole plant	2.9		0	RIP2001-607
						< 0.01		32	
					cobs with husks	< 0.01		102	
					rest of plant	< 0.01		102	
BE / 1997	WG 50	0.0487	BBCH 15	1	whole plant	0.561		0	RIP2001-607
						< 0.01		40	
					cobs with husks	< 0.01		96	
					rest of plant	< 0.01		96	
DE / 1998	WG 50	0.051	BBCH 15-16	1	whole plant	1.59		0	RIP2001-609
						< 0.01		28	
					cobs with husks	< 0.01		92	
					rest of plant	< 0.01		92	
N-FR / 1998	WG 50	0.0517	BBCH 16	1	whole plant	0.949		0	RIP2001-609
						< 0.01		24	
					cobs with husks	< 0.01		80	
					rest of plant	< 0.01		80	
					grain	< 0.001		109	
					straw	< 0.01		109	
DE / 1998	WG 50	0.0524	BBCH 15	1	whole plant	1.11		0	RIP2001-609
						< 0.01		34	
					cobs with husks	< 0.01		116	
					rest of plant	< 0.01		116	
					grain	< 0.001		138	
					straw	< 0.01		138	

Country/ Year	Formula-tion (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Trito-sulfuron	AMTT		
SE / 1998	WG 50	0.0547	BBCH 15	1	whole plant cobs with husks rest of plant	2.2 < 0.01 0.022 < 0.01		0 53 107 107	RIP2001-609
DE / 1998	WG 50	0.0454	BBCH 16	1	whole plant cobs with husks rest of plant grain straw	0.405 < 0.01 < 0.01 < 0.01 < 0.001 < 0.01		0 27 78 78 111 111	RIP2001-609
DE / 1998	WG 33	0.0509	BBCH 15-16	1	whole plant cobs with husks rest of plant	2.4 < 0.01 < 0.01 < 0.01		0 28 92 92	RIP2001-609
DE / 1998	WG 33	0.051	BBCH 15	1	whole plant cobs with husks rest of plant grain straw	1.1 < 0.01 < 0.01 < 0.01 < 0.001 < 0.01		0 34 116 116 138 138	RIP2001-609
DE / 1998	WG 33	0.0495	BBCH 16	1	whole plant cobs with husks rest of plant grain straw	0.393 < 0.01 < 0.01 < 0.01 < 0.001 < 0.01		0 27 78 78 111 111	RIP2001-609
N-FR / 1998	WG 33	0.0517	BBCH 16	1	whole plant cobs with husks rest of plant grain straw	0.811 < 0.01 < 0.01 < 0.01 < 0.001 < 0.01		0 24 80 80 109 109	RIP2001-609
SE / 1998	WG 33	0.0489	BBCH 15	1	whole plant cobs with husks rest of plant	2.19 < 0.01 < 0.01 < 0.01		0 53 107 107	RIP2001-609
DE / 1996	WG 27	0.056	BBCH 14-16	1	whole plant cobs with husks rest of plant	3.01 < 0.01 < 0.01 < 0.01		0 50 102 102	RIP2001-606
NL / 1996	WG 27	0.052	BBCH 15	1	whole plant cobs with husks rest of plant	1.69 < 0.01 < 0.01 < 0.01		0 29 105 105	RIP2001-606

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
DE / 1996	WG 27	0.052	BBCH 14-16	1	whole plant	0.375		0	RIP2001-606
						< 0.01		52	
					cobs with husks	< 0.01		108	
					grain	< 0.001		139	
					straw	< 0.01		139	
DE / 1996	WG 27	0.049	BBCH 16-17	1	whole plant	1.98		0	RIP2001-606
						< 0.01		36	
					cobs with husks	< 0.01		111	
DE / 1996	WG 27	0.052	BBCH 16	1	whole plant	1.35		0	RIP2001-606
						< 0.01		22	
					cobs with husks	< 0.01		82	
					grain	< 0.001		120	
					straw	< 0.01		120	
BE / 1997	WG 27	0.0481	BBCH 15	1	whole plant	1.05		0	RIP2001-607
						< 0.01		40	
					cobs with husks	< 0.01		96	
					rest of plant	< 0.01		96	
DE / 1997	WG 27	0.0514	BBCH 14-16	1	whole plant	1.53		0	RIP2001-607
						< 0.01		37	
					cobs with husks	< 0.01		113	
					rest of plant	< 0.01		113	
N-FR / 1997	WG 27	0.0472	BBCH 16	1	whole plant	2.07		0	RIP2001-607
						< 0.01		41	
					cobs with husks	< 0.01		108	
					rest of plant	< 0.01		108	
N-FR / 1997	WG 27	0.0501	BBCH 15	1	whole plant	1.21		0	RIP2001-607
						0.03		20	
					cobs with husks	< 0.01		91	
					rest of plant	< 0.01		91	
					grain	< 0.001		114	
					straw	< 0.01		114	
GB / 1997	WG 27	0.0493	BBCH 16	1	whole plant	2.37		0	RIP2001-607
						< 0.01		32	
					cobs with husks	< 0.01		94	
					rest of plant	< 0.01		94	
GB / 1997	WG 27	0.05	BBCH 15	1	whole plant	1.96		0	RIP2001-607
						< 0.01		32	
					cobs with husks	< 0.01		102	
					rest of plant	< 0.01		102	

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
South Europe									
ES / 1999	WG 714	0.05	BBCH 14-15	1	whole plant	2.917	< 0.001	0	RIP2001-603
						< 0.01	< 0.001	57	
					cobs with husks	< 0.01	< 0.001	93	
					rest of plant	< 0.01	< 0.001	93	
					grain	< 0.001	< 0.001	134	
					straw	< 0.01	< 0.001	134	
ES / 1999	WG 714	0.0514	BBCH 14-15	1	whole plant	2.96	< 0.001	0	RIP2001-603
						< 0.01	< 0.001	48	
					cobs with husks	< 0.01	< 0.001	84	
					rest of plant	< 0.01	< 0.001	84	
					grain	< 0.001	< 0.001	126	
					straw	< 0.01	< 0.001	126	
S-FR / 1999	WG 714	0.0523	BBCH 15	1	whole plant	2.5	0.0063	0	RIP2001-604
						< 0.01	< 0.001	46	
					cobs with husks	< 0.01	< 0.001	111	
					rest of plant	< 0.01	< 0.001	111	
					grain	< 0.001	< 0.001	144	
					straw	< 0.01	< 0.001	144	
S-FR / 1999	WG 714	0.0492	BBCH 15-16	1	whole plant	0.031	< 0.001	0	RIP2001-604
						< 0.01	< 0.001	48	
					cobs with husks	< 0.01	< 0.001	108	
					rest of plant	< 0.01	< 0.001	108	
					grain	< 0.001	< 0.001	141	
					straw	< 0.01	< 0.001	141	
ES / 2000	WG 714	0.052	BBCH 16	1	whole plant	3.15	0.0046	0	RIP2001-605
						0.018	< 0.001	50	
					cobs with husks	< 0.01	< 0.001	95	
					rest of plant	< 0.01	< 0.001	95	
					grain	< 0.001	< 0.001	127	
					straw	< 0.01	< 0.001	127	
ES / 2000	WG 714	0.0516	BBCH 16	1	whole plant	1.76	0.0057	0	RIP2001-605
						< 0.01	< 0.001	37	
					cobs with husks	< 0.01	< 0.001	78	
					rest of plant	< 0.01	< 0.001	78	
					grain	< 0.001	< 0.001	113	
					straw	< 0.01	< 0.001	113	
ES / 2000	WG 714	0.0499	BBCH 16	1	whole plant	2.34	0.0021	0	RIP2001-605
						< 0.01	< 0.001	39	
					cobs with husks	< 0.01	< 0.001	73	
					rest of plant	< 0.01	< 0.001	73	
					grain	< 0.001	< 0.001	102	
					straw	< 0.01	< 0.001	102	

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
S-FR / 2000	WG 714	0.0507	BBCH 15	1	whole plant	4.73	0.0094	0	RIP2001-605
						< 0.01	< 0.001	51	
					cobs with husks	< 0.01	< 0.001	83	
					rest of plant	< 0.01	< 0.001	83	
					grain	< 0.001	< 0.001	111	
					straw	< 0.01	< 0.001	111	
S-FR / 2000	WG 714	0.0495	BBCH 14	1	whole plant	4.27	0.0043	0	RIP2001-605
						0.025	< 0.001	48	
					cobs with husks	< 0.01	< 0.001	107	
					rest of plant	< 0.01	< 0.001	107	
					grain	< 0.001	< 0.001	141	
					straw	< 0.01	< 0.001	141	
ES / 1997	WG 50	0.0524	BBCH 16-17	1	whole plant	0.657		0	RIP2001-607
						< 0.01		35	
					cobs with husks	< 0.01		83	
					rest of plant	< 0.01		83	
					grain	< 0.001		104	
					straw	< 0.01		104	
ES / 1997	WG 50	0.0511	BBCH 14-15	1	whole plant	0.887		0	RIP2001-607
						< 0.01		35	
					cobs with husks	< 0.01		83	
					rest of plant	< 0.01		83	
					grain	< 0.001		104	
					straw	< 0.01		104	
IT / 1997	WG 50	0.0511	BBCH 14-16	1	whole plant	2.31		0	RIP2001-608
						< 0.01		50	
					cobs with husks	< 0.01		93	
					rest of plant	< 0.01		93	
					grain	< 0.001		124	
					straw	< 0.01		124	
IT / 1997	WG 50	0.0518	BBCH 15	1	whole plant	2.64		0	RIP2001-608
						< 0.01		46	
					cobs with husks	< 0.01		97	
					rest of plant	< 0.01		97	
					grain	< 0.001		116	
					straw	< 0.01		116	
ES / 1996	WG 27	0.05	BBCH 14-16	1	whole plant	2.38		0	RIP2001-606
						< 0.01		37	
					cobs with husks	< 0.01		65	
					rest of plant	< 0.01		65	
					grain	< 0.001		113	
					straw	< 0.01		113	

Country/ Year	Formulation (g as/kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No		Tritosulfuron	AMTT		
ES / 1996	WG 27	0.05	BBCH 14-16	1	whole plant	2.46		0	RIP2001-606
						0.015		31	
					cobs with husks	< 0.01		58	
					rest of plant	< 0.01		58	
					grain	< 0.001		106	
					straw	< 0.01		106	
ES / 1996	WG 27	0.055	BBCH 16-17	1	whole plant	1.13		0	RIP2001-606
						< 0.01		30	
					cobs with husks	< 0.01		72	
					grain	< 0.001		105	
ES / 1996	WG 27	0.052	BBCH 16-17	1	whole plant	0.783		0	RIP2001-606
						< 0.01		30	
					cobs with husks	< 0.01		72	
					grain	< 0.001		105	
					straw	< 0.01		105	
ES / 1997	WG 27	0.0512	BBCH 16-17	1	whole plant	0.977		0	RIP2001-607
						< 0.01		35	
					cobs with husks	< 0.01		83	
					rest of plant	< 0.01		83	
					grain	< 0.001		104	
					straw	< 0.01		104	
ES / 1997	WG 27	0.052	BBCH 14-15	1	whole plant	1.23		0	RIP2001-607
						< 0.01		35	
					cobs with husks	< 0.01		83	
					rest of plant	< 0.01		83	
					grain	< 0.001		104	
					straw	< 0.01		104	
IT / 1997	WG 27	0.0504	BBCH 14-16	1	whole plant	2.45		0	RIP2001-608
						< 0.01		50	
					cobs with husks	< 0.01		93	
					rest of plant	< 0.01		93	
					grain	< 0.001		124	
					straw	< 0.01		124	
IT / 1997	WG 27	0.0493	BBCH 15	1	whole plant	3.54		0	RIP2001-608
						< 0.01		46	
					cobs with husks	< 0.01		97	
					rest of plant	< 0.01		97	
					grain	< 0.001		116	
					straw	< 0.01		116	

B.7.6.3 Storage stability of tritosulfuron and metabolite AMTT (635M04)

Materials and methods

The deep freeze stability of tritosulfuron and the metabolite AMTT was investigated in wheat, maize and radish roots (Stewart, 2001, RIP2001-610; Jordan, 2001, RIP2001-611). Untreated samples were fortified with 0.1 mg/kg tritosulfuron or 0.01 mg/kg AMTT (straw: 0.015 mg/kg AMTT).

The samples were stored in a freezer under the usual storage conditions for field samples and analysed with methods used in the residue trials. For analysis of tritosulfuron two different methods were used for cereals and maize matrices. Up to month 14 the method of the residue trials from 1996 – 1998 was used and later on and for radish root the method of the trials from 1999 - 2000. The performance of the analytical methods were evaluated during each sample set by fortifying control matrix with a standard of tritosulfuron or AMTT (procedural recovery).

Findings

Recoveries of tritosulfuron and AMTT in the stored samples compared well with those fortified on the day of analysis (procedural recoveries). For tritosulfuron, average recoveries of the stored samples ranged between 71 to 94 % (month 0 – 14, average procedural recovery: 84 %) and between 81 to 114 % (month 28 – 36, average procedural recovery: 93 %).

Average recoveries of AMTT from stored samples ranged from 67 to 104 % in wheat samples (average procedural recovery: 86 %) and from 62 to 87 % in radish root (average procedural recovery: 94 %).

Almost all data of the stored samples are in the acceptable range of 70 to 110 % of the initial concentration.

Conclusion

The storage trials showed that tritosulfuron was stable over a period of 3 years in frozen maize and wheat samples. In all residue trials, tritosulfuron was analysed within this period and obtained data can therefore be regarded as valid.

Storage trials with AMTT had only be conducted to a maximum of 12 months until reporting and are still ongoing. AMTT was stable during the interval investigated and it can be expected that it will be stable for longer periods. Thus, the results obtained in the residue trials, with intervals between sampling and analysis of 6 – 14 months, are regarded as valid.

Table B.7.6-7: Storage stability of tritosulfuron in various plant matrices

Storage interval (months)	Average recovery after fortification with 0.1 mg/kg tritosulfuron (%)				
	Maize grain	Maize forage	Wheat grain	Wheat straw	Radish root
0	85	81	81	80	82
1	82	72	74	71	-
3	98	80	78	75	-
4	-	-	-	-	87
6	85	94	84	92	-
7	-	-	-	-	83
13	74	-	77	-	-
14	-	-	-	78	-
28	97	103	103	114	-
36	81	97	103	101	-

Table B.7.6-8: Storage stability of the metabolite AMTT (635M04) in various plant matrices

Storage interval (months)	Average recovery after fortification with 0.01 mg/kg AMTT (%)			
	Wheat grain	Wheat forage	Wheat straw*	Radish root
0	99	74	-	87
1	70	103	89	62
3	88	73	100	80
5	-	-	98	-
6	67	104	-	71
10	-	85	-	-
12	82	-	-	-

* fortified with 0.015 mg/kg AMTT

B.7.7 Effects of industrial processing and/or household preparation (Annex IIA 6.5; Annex IIIA 8.4)

Results from metabolism studies and residue trials indicate that under practical conditions no residues of tritosulfuron or its metabolites are expected to exceed 0.01 mg/kg in cereal grain or maize grain. Hence, studies on the nature and level of residue in regard to proccesing are not required. Nevertheless, a study has been conducted to the nature of residue simulating baking, brewing and boiling.

B.7.7.1 Effects on the nature of residue

Report: Goetz A.J., 1996
Hydrolysis of ^{14}C-BAS 635 H at 100 °C and pH 5
Agricultural Products Center, Research Triangle Park,
NC 27709-3528, United States of America
unpublished
BASF RegDoc# 1996/5200

Test Material: [phenyl-U-^{14}C]-tritosulfuron,
radiochemical purity: 99.2 %, specific activity: 9.6 MBq/mg
[triazine-2,4-^{14}C]-tritosulfuron,
radiochemical purity: 99,4 %, specific activity: 9.26 MBq/mg

Guidelines: EEC 91/414

GLP: Yes

Acceptability: Yes

Material and Methods

Phenyl labelled or triazine labelled tritosulfuron was dissolved in an aqueous buffer solution at pH = 5. For simulation of baking, brewing and boiling, the test substances were treated under reflux at 100 °C for 60 minutes.

For analysis, aliquots were taken for LSC-measurements and chromatographic analysis (HPLC/TLC) right before starting and at the end of the test. The degradation products formed were identified by co-chromatography with authentic reference standards.

Findings

The radioactivity recovered at time 60 minutes was 98.2 % TAR (total applied radioactivity) for phenyl labelled ^{14}C-tritosulfuron and 98.9 % TAR for the triazine label. Less than a 2 % loss of TAR occurred during refluxing. Thus indicating, that no volatile components were produced.

After 60 minutes of refluxing, ^{14}C-tritosulfuron had decreased to approximately 18 % TAR. Besides tritosulfuron, only the metabolites AMTT (635M04, triazine label) and 635M02 (phenyl label) were found.

Table B.7.7-1: Degradation products of tritosulfuron after simulation of proccesing

Label	Time (minutes)	TAR (%)		
		Tritosulfuron	AMTT (635M04)	635M02
Phenyl	0	100.0	0.0	0.0
	60	18.9	-	79.4
Triazine	0	100.0	0.0	0.0
	60	18.0	80.9	-

Conclusion

During the simulation of processing ^{14}C-tritosulfuron underwent rapid hydrolytic degradation. At elevated temperatures, the sulfonyl urea bridge was cleaved resulting in the hydrolysis products AMTT (635M04) and 635M02. Both metabolites were also the primary hydrolysis

products in the hydrolysis studies conducted at 25 °C and 50 °C. These results demonstrated that at high temperatures, no new hydrolysis products from tritosulfuron were formed.

B.7.8 Livestock feeding studies (Annex IIA 6.4; Annex IIIA 8.3)

B.7.8.1 Ruminants

A feeding study in ruminants is only required,

- when significant residues (≥ 0.1 mg/kg of the total diet as received, except special cases, such as active substances which accumulate) occur in crops or part of the crops fed to ruminants, and
- when metabolism studies indicate that significant residues (above the limit of determination) may occur in any edible animal tissue taking into account the residue levels in potential feedingstuffs obtained at the 1x dose rate.

Forage and silage are the feed items with highest residues that are fed to ruminants. In samples of cereal plants after a PHI of 14 days, residues were found in the range of < 0.01 to 0.032 mg/kg with three samples in the range of 0.055 – 0.074 mg/k and one single sample at 0.115 mg/kg in trials performed according to GAP. In maize only 7 out of 56 samples of plant at a PHI of 20 to 50 days showed residues above the LOQ in the range 0.015 – 0.034 mg/kg.

If the highest residue of 0.115 mg/kg is taken as 100 % of feed intake, a feed burden of 0.575 mg/kg DM can be calculated for cattle. Comparison with the metabolism study in goat shows that this corresponds to approximately an 17.4 x dose considering mg per kg dry matter feed and to an overdosing factor of 24 or 20 related to mg per kg body weight for dairy cows and beef cattle, respectively (Table B.7.8-1).

Based on these overdosing factors, the expected total residues in milk and edible tissues from cattle were extrapolated from the corresponding residues of tritosulfuron found in the goat metabolism study. Nevertheless the extrapolation shows that even for the worst case, with the highest residue level in cereal plant, no residues above the LOQ of 0.01 mg/kg of the residue analytical method are calculated for animal products (Table B.7.8-2).

As can be seen by the residue data, residues of tritosulfuron in green plants of cereal and maize are generally significantly lower and forage and silage for animal feeding are harvested normally at later PHIs which leads to even lower residues. Therefore, residues in products from cattle above the LOQ are not to be expected and a feeding study is not regarded necessary.

Table B.7.8-1: Calculation of overdosing factors (nominal values)

	Goat metabolism	Potential intake dairy cow	Potential intake beef cattle
mg/kg feed (DM)	10	0.575	0.575
mg/kg body weight	0.5	0.021	0.025
Overdosing factor: dose in metabolism study / potential intake			
mg/kg feed		17.4	17.4
mg/kg body weight		24	20

Table B.7.8-2: Potential transfer of residues to cow milk and tissues

Matrix	Tritosulfuron (mg/kg) from metabolism study	Extrapolated total residue from actual intake (mg/kg)		
		Based on residues in feed	Based on dose per body weight dairy cow	Based on dose per body weight beef cattle
Milk	0.042[1)]	0.0024	0.0018	
Muscle	0.006[1)]	0.0003	0.0003	0.0003
Fat	0.005[1)]	0.0003	0.0002	0.0003
Liver	0.028[1)]	0.0016	0.0012	0.0014
Kidney	0.041[2)]	0.0024	0.0017	0.0021

[1)] Triazine Label
[2)] Diphenyl label

B.7.8.2 Poultry

A feeding study in poultry is only required,

- when significant residues (≥ 0.1 mg/kg of the total diet as received, except special cases, such as active substances which accumulate) occur in crops or part of the crops fed to poultry, and
- when metabolism studies indicate that significant residues (above the limit of determination) may occur in any edible animal tissue taking into account the residue levels in potential feedingstuffs obtained at the 1 x dose rate.

None of the prerequisites is fulfilled:

The parent residues in cereal and maize grain, which is the only plant part of cereals and maize that is fed to poultry, were found below the LOQ of 0.001 mg/kg of the residue analytical method, when cereal and maize had been treated according to current GAP.

Since the residue level in poultry feed is by a factor of approximately 100 below the trigger value, there is no poultry feeding study triggered.

B.7.8.3 Pigs

A feeding study in pigs is only required, if the metabolic pathways differ significantly in pigs as compared to ruminants. This is not expected to be the case, since the metabolites identified in goats were essentially detected in the rat metabolism study.

B.7.9 Residues in succeeding or rotational crops (Annex IIA 6.6; Annex IIIA 8.5)

Report:	Veit, P., 2001 Quantification and Identification of Radioactive Residues in Rotational Crops after Treatment with ^{14}C-BAS 635 H (^{14}C-271272) BASF AG, Agrarzentrum Limburgerhof, Limburgerhof, Germany Fed. Rep unpublished BASF RegDoc# 2001/1000995
Test Material:	[phenyl-U-^{14}C]-tritosulfuron, batch no. 478-03, 538-01, radiochemical purity: 98.2 – 99.6 %, specific activity: 9.6 MBq/mg [triazine-2,4-^{14}C]-tritosulfuron, batch no. 437-32, 537-01, radiochemical purity: 97.5 – 98.9 %, specific activity: 2.55 / 9.26 MBq/mg
Guidelines:	BBA Guideline Part IV, 3-10, "Testing of residue behaviour of plant protection products in rotational crops (crop rotation guideline)" US, EPA Residue Chemistry Test Guidelines “Confined Accumulation in Rotational Crops” (OPPTS 860.1850)
GLP:	Yes
Acceptability:	Yes

The studies describing the test design are referred to in the result tables. They are all carried out according to GLP and are regarded as valid.

B.7.9.1 Material and methods

The residue levels and the nature of the residues in four different succeeding crops were investigated following application of ^{14}C-tritosulfuron (phenyl and triazine label). The test compound was taken up in acetone and mixed into a loamy sand soil at an application rate equivalent to 60 g as/ha (GAP: 50 g as/ha). The amount of soil referred to a penetration depth of the active ingredient into the soil surface of 2 cm.

After application, the soil premix was aged for 30, 120 and 365 days. The aged soil was mixed with untreated soil corresponding to ploughing the soil from 2 cm to a depth of 20 cm. Afterwards, carrot, lettuce, bean and spring wheat were sowed or planted in pots and grown in a greenhouse or a vegetation hall.

Parts of immature plants and food and feed items of mature crops were harvested, processed and analysed by combustion / extraction and subsequent radioactivity measurement for the determination of the total radioactive residues. In addition, soil samples were taken after application, after ploughing and after harvest of mature crops.

All plant samples were extracted with methanol and with water. The remaining residues after solvent extraction from the wheat matrices: straw, chaff and grain and in addition from carrot foliage (phenyl-label, 365 DAT) were treated with an aqueous ammonia solution to release

part of the remaining radioactivity. Methanol extracts of samples with a sufficient level of radioactivity and in some cases also the water extracts were analysed by HPLC.

B.7.9.2 Findings

Soil

After soil ageing and ploughing, the residue levels of the phenyl label did not show major differences among the 3 plant back intervals (0.020 – 0.019 mg/kg). For the triazine label, the residue levels declined relatively to the applied amount from an ageing interval of 30 days to 365 days. Only 0.013 mg/kg was found in ploughed soil (triazine label) after an ageing interval of 365 days.

In general, the residues in the soil from carrots and wheat were lower than from beans and lettuce, probably due to the shorter time interval between planting and harvest of beans and lettuce. A tendency to higher residue levels in soil after plant back intervals of 365 days can be seen for all plants (see Table B.7.9-1).

Table B.7.9-1: Total radioactive residues in soil samples after treatment with ^{14}C-tritosulfuron (phenyl and triazine label)

Soil samples	Tritosulfuron phenyl label	Tritosulfuron triazine label
	TRR [mg/kg]	TRR [mg/kg]
After application		
30 DAT	0.199	0.194
120 DAT	0.216	0.258
365 DAT	0.208	0.202
After soil ageing and ploughing		
30 DAT	0.020	0.019
120 DAT	0.020	0.021
365 DAT	0.019	0.013
After harvest of ripe crops		
Carrots 30 DAT	0.002	0.002
Carrots 120 DAT	0.002	0.003
Carrots 365 DAT	0.006	0.007
Beans 30 DAT	0.008	0.005
Beans 120 DAT	0.009	0.010
Beans 365 DAT	0.003	0.015
Lettuce 30 DAT	0.016	0.001
Lettuce 120 DAT	0.008/0.007	0.011/0.009
Lettuce 365 DAT	0.019	0.011
Wheat 30 DAT	0.005	0.002
Wheat 120 DAT	0.003	0.003
Wheat 365 DAT	0.008	0.007

Radioactive residues in plants

The distribution of the total radioactive residues (TRR), the extractable radioactive residues (ERR) and the residual radioactive residues (RRR) in the individual samples are summarised

in Table B.7.9-2. The total radioactive residues were calculated as sum of extractable and residual radioactive residues.

In the edible parts of the plants, the TRR values were very low after all 3 plant back intervals. The TRR values in carrot roots and green beans were ≤ 0.011 mg/kg. In lettuce head, the total radioactive residues were ≤ 0.022 mg/kg and in wheat grain, the residue levels were ≤ 0.019 mg/kg. The highest residue levels were detected in the immature plant parts of the crops and in wheat straw (0.233 mg/kg phenyl-label / 0.267 mg/kg triazine-label, plant back interval DAT 30) and carrot foliage 127/126 DAP (0.069 mg/kg phenyl-label/ 0.008 mg/kg triazine-label, plant back interval DAT 365).

In triazine labelled samples, highest residue levels were mostly found in plant back studies with DAT 120 and lowest levels at DAT 365. Comparison between phenyl and triazine labelled samples showed that the residue levels at DAT 365 were significantly higher in the phenyl labelled samples.

Extractability

To determine the nature of the residues, individual crop parts were extracted with methanol and afterwards with water. For carrots, beans, lettuce and wheat foliage, the extractability with methanol was good and with few exceptions > 75 %. The other samples showed extractability in the range of 65.9 % to 73.1 % TRR.

In the case of the dry matrices such as wheat straw, chaff and grain, methanol extractability was generally low (26.6 % - 72.8 % TRR) and an additional water extraction significantly increased the extractability. The overall extractability was ≥ 75 % TRR except for triazine labelled samples of wheat grain (47.1 % - 75.0 % TRR).

Table B.7.9-2: Quantitative distribution of radioactive residues in rotational crops after treatment with ^{14}C-tritosulfuron (phenyl and triazine label)

Crop parts Days after sowing/planting DAP	TRR	Methanol		Water		ERR		RRR		References
	mg/kg	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	
Plant back interval: 30 DAT										
Phenyl label										
Carrot Plant 37	0.040	0.036	88.4	0.003	6.2	0.038	94.6	0.002	5.4	RIP2001-613
Carrot Plant 56	0.015	0.013	88.5	0.001	5.0	0.014	93.5	0.001	6.5	RIP2001-614
Carrot Foliage 111	0.029	0.024	82.8	0.003	9.9	0.027	92.7	0.002	7.3	
Carrot Foliage 133	0.049	0.037	75.9	0.007	13.5	0.044	91.0	0.005	10.7	
Carrot Roots 111	0.006	0.005	86.8	<0.001	5.6	0.006	92.4	<0.001	7.6	
Carrot Roots 133	0.011	0.009	85.2	0.001	7.1	0.010	92.3	0.001	7.7	
Beans Plant 29	0.057	0.053	92.1	0.003	5.4	0.056	97.5	0.001	2.5	
Beans Plant 56	0.063	0.009	83.9	0.001	10.9	0.010	94.7	0.001	5.3	
Beans Plant 75	0.018	0.015	81.7	0.003	14.5	0.017	96.2	0.001	3.8	
Green Beans 61	0.001	0.001	93.1	<0.001	0.7	0.001	93.8	<0.001	6.2	
Green Beans 75	0.003	0.002	84.7	<0.001	8.2	0.003	92.9	<0.001	7.1	
Lettuce Plant 29	0.011	0.010	91.3	<0.001	4.2	0.010	95.5	<0.001	4.5	
Lettuce Head 61	0.007	0.006	89.4	<0.001	5.5	0.007	94.9	<0.001	5.1	

Crop parts Days after sowing/planting DAP	TRR	Methanol		Water		ERR		RRR		References
	mg/kg	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	
Wheat Plant 62	0.065	0.056	86.8	0.007	11.1	0.064	97.9	0.001	2.1	
Wheat Straw 141	0.233	0.145	62.0	0.073	31.3	0.217	93.3	0.016	6.7	
Wheat Chaff 141	0.095	0.055	57.9	0.030	31.7	0.085	89.6	0.010	10.4	
Wheat Grain 141	0.011	0.006	53.1	0.003	30.9	0.009	84.0	0.002	16.0	
Triazine label										
Carrot Plant 36	0.023	0.021	93.2	0.001	3.1	0.022	96.3	0.001	3.7	RIP2001-615
Carrot Plant 55	0.008	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	RIP2001-616
Carrot Foliage 110	0.011	0.009	86.9	0.001	7.2	0.010	94.1	0.001	5.8	
Carrot Foliage 132	0.009	0.006	67.6	0.001	13.1	0.007	80.7	0.002	19.3	
Carrot Roots 110	0.002	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Carrot Roots 132	0.002	0.002	76.4	<0.001	3.9	0.002	80.3	<0.001	19.7	
Beans Plant 28	0.051	0.049	95.2	0.002	3.0	0.050	98.2	0.001	1.8	
Beans Plant 55	0.014	0.012	87.0	0.001	5.0	0.013	92.0	0.001	8.0	
Beans Plant 74	0.024	0.022	91.0	0.001	3.0	0.022	93.9	0.001	6.1	
Green Beans 60	0.003	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Green Beans 74	0.005	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Lettuce Plant 28	0.011	0.009	84.7	<0.001	4.1	0.010	88.8	0.001	11.2	
Lettuce Head 60	0.009	0.006	65.9	0.001	15.0	0.007	81.0	0.002	19.0	
Wheat Foliage 61	0.049	0.043	86.2	0.004	7.1	0.046	93.3	0.003	6.8	
Wheat Straw 140	0.267	0.093	34.9	0.123	46.3	0.217	81.2	0.050	18.8	
Wheat Chaff 140	0.261	0.115	44.1	0.081	31.0	0.196	75.2	0.065	24.9	
Wheat Grain 140	0.019	0.007	38.4	0.005	26.9	0.012	65.3	0.007	34.7	
Plant back interval: 120 DAT										
Phenyl label										
Carrot Plant 57	0.016	0.014	87.8	0.001	4.1	0.015	91.9	0.001	8.1	RIP2001-618
Carrot Foliage 110	0.055	0.044	78.8	0.007	13.4	0.051	92.2	0.004	7.8	RIP2001-622
Carrot Foliage 125	0.049	0.037	76.4	0.008	16.9	0.045	93.3	0.003	6.7	
Carrot Roots 110	0.006	0.006	90.0	<0.001	4.1	0.006	94.1	<0.001	5.9	
Carrot Roots 125	0.007	0.006	86.7	<0.001	6.2	0.006	92.9	<0.001	7.1	
Beans Plant 57	0.018	0.016	88.2	0.001	8.0	0.017	96.2	0.001	3.8	
Beans Plant 81	0.018	0.014	77.5	0.003	16.8	0.018	94.4	0.001	5.6	
Green Beans 68	0.003	0.002	84.3	<0.001	8.4	0.001	92.7	<0.001	7.3	
Green Beans 81	0.003	0.003	87.3	<0.001	5.4	0.003	92.7	<0.001	7.4	
Lettuce Plant 29	0.016	0.015	93.6	0.001	4.1	0.016	97.7	<0.001	2.3	
Lettuce Head (A)61	0.007	0.006	88.6	<0.001	7.1	0.006	95.7	<0.001	4.3	
Lettuce Head (B)61	0.022	0.020	88.9	0.001	5.9	0.021	94.8	0.001	5.2	
Wheat Plant 42	0.042	0.039	93.4	0.002	4.3	0.041	97.7	0.001	2.3	
Wheat Straw 127	0.133	0.095	71.1	0.030	22.1	0.125	93.2	0.009	6.8	
Wheat Chaff 127	0.039	0.023	60.5	0.010	25.5	0.033	86.0	0.005	14.0	
Wheat Grain 127	0.007	0.004	54.9	0.002	30.8	0.006	85.7	0.001	14.3	
Triazine label										
Carrot Plant 56	0.010	0.008	88.8	<0.001	4.8	0.009	93.6	0.001	6.4	RIP2001-619
Carrot Foliage 109	0.025	0.023	92.8	0.001	5.1	0.024	97.9	0.001	2.1	RIP2001-620
Carrot Foliage 124	0.019	0.016	85.6	<0.001	1.2	0.017	86.7	0.003	13.3	
Carrot Roots 109	0.004	0.004	94.3	<0.001	2.7	0.004	97.0	<0.001	3.0	
Carrot Roots 124	0.003	0.002	95.0	<0.001	4.3	0.002	99.2	<0.001	0.8	

Crop parts Days after sowing/planting DAP	TRR	Methanol		Water		ERR		RRR		References
	mg/kg	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	
Beans Plant 56	0.033	0.030	92.7	0.002	5.9	0.032	98.7	<0.001	1.3	
Beans Plant 80	0.031	0.028	91.3	0.002	7.5	0.031	98.8	<0.001	1.2	
Green Beans 67	0.003	0.002	94.1	<0.001	4.7	0.002	98.7	<0.001	1.3	
Green Beans 80	0.004	0.003	95.4	<0.001	2.4	0.003	97.8	<0.001	2.2	
Lettuce Plant 27	0.009	0.008	92.7	0.001	6.1	0.009	98.8	<0.001	1.2	
Lettuce Head (A)60	0.016	0.013	81.1	0.003	16.5	0.016	97.6	<0.001	2.4	
Lettuce Head (B)60	0.015	0.014	88.6	0.001	9.2	0.015	97.8	<0.001	2.2	
Wheat Foliage 45	0.002	0.002	93.1	<0.001	2.8	0.002	95.9	<0.001	4.1	
Wheat Straw 126	0.060	0.035	57.7	0.017	28.2	0.052	85.9	0.009	14.1	
Wheat Chaff 126	0.109	0.048	44.3	0.042	38.5	0.090	82.8	0.019	17.2	
Wheat Grain 126	0.012	0.004	35.9	0.005	39.2	0.009	75.0	0.003	25.0	
Plant back interval: 365 DAT										
Phenyl label										
Carrot Plant 42	0.052	0.044	85.2	0.004	6.8	0.048	92.0	0.004	8.0	RIP2001-621
Carrot Foliage 99	0.046	0.037	80.7	0.006	13.1	0.043	93.8	0.003	6.2	RIP2001-622
Carrot Foliage 127	0.069	0.048	68.9	0.014	20.1	0.062	89.0	0.008	11.0	
Carrot Roots 99	0.010	0.009	89.7	<0.001	4.5	0.009	94.2	0.001	5.8	
Carrot Roots 127	0.006	0.005	75.3	0.001	15.5	0.006	90.8	0.001	9.2	
Beans Plant 42	0.036	0.030	84.1	0.005	12.9	0.035	97.1	0.001	2.9	
Beans Plant 83	0.029	0.021	71.3	0.007	24.4	0.028	95.7	0.001	4.3	
Green Beans 70	0.003	0.003	88.7	<0.001	4.7	0.003	93.4	<0.001	6.5	
Green Beans 83	0.003	0.003	85.9	<0.001	5.8	0.003	91.6	<0.001	8.4	
Lettuce Plant 31	0.023	0.021	93.4	0.001	3.0	0.022	96.4	0.001	3.6	
Lettuce Head 63	0.007	0.006	87.9	<0.001	5.6	0.006	93.5	<0.001	6.6	
Wheat Plant 48	0.101	0.087	86.6	0.011	11.3	0.098	97.9	0.002	2.1	
Wheat Straw 129	0.186	0.135	72.8	0.040	21.4	0.175	94.1	0.011	5.9	
Wheat Chaff 129	0.067	0.032	48.0	0.021	30.6	0.053	78.7	0.014	21.3	
Wheat Grain 129	0.017	0.010	59.1	0.005	30.2	0.015	89.3	0.002	10.7	
Triazine label										
Carrot Plant 41	0.006	0.005	92.6	<0.001	3.5	0.005	96.1	<0.001	4.0	RIP2001-617
Carrot Foliage 98	0.010	0.009	89.6	0.001	5.6	0.009	95.4	<0.001	4.6	RIP2001-624
Carrot Foliage 126	0.008	0.006	70.5	0.001	9.5	0.007	80.0	0.002	20.0	
Carrot Roots 98	0.001	0.001	85.6	<0.001	8.9	0.001	94.5	<0.001	5.5	
Carrot Roots 126	0.001	0.001	86.2	<0.001	5.6	0.001	91.8	<0.001	8.3	
Beans Plant 41	0.008	0.008	93.6	<0.001	3.7	0.008	97.3	<0.001	2.7	
Beans Plant 82	0.012	0.010	87.9	0.001	7.2	0.011	95.1	0.001	4.9	
Green Beans 69	0.001	0.001	88.2	<0.001	3.0	0.001	91.2	<0.001	8.8	
Green Beans 82	0.001	0.001	67.7	<0.001	10.8	0.001	78.6	<0.001	21.4	
Lettuce Plant 30	0.002	0.001	79.9	<0.001	11.4	0.001	91.0	<0.001	8.7	
Lettuce Head 62	0.001	0.001	73.1	<0.001	17.1	0.001	90.2	<0.001	9.8	
Wheat Foliage 47	0.054	0.049	89.8	0.004	6.9	0.053	96.7	0.002	3.3	
Wheat Straw 128	0.015	0.010	62.7	0.003	21.6	0.013	84.3	0.002	15.7	
Wheat Chaff 128	0.017	0.011	66.6	0.001	8.4	0.013	75.0	0.004	25.0	
Wheat Grain 128	0.002	0.001	26.6	0.001	20.5	0.001	47.1	0.001	53.0	

Residual Residues

High levels of residual residues after extraction with methanol and water were found in wheat matrices and in carrot foliage (DAT 365). Therefore, the residues of these samples were extracted with ammonia. The remaining non-released residues were low, ≤ 0.006 mg/kg (phenyl label) and ≤ 0.021 mg/kg (triazine label), and no further analysis was carried out.

Table B.7.9-3: Summary of released non-extractable radioactivity in rotational crops after ^{14}C-tritosulfuron (phenyl and triazine label) treatment and plant back intervals of 30. 120 and 365 days

Crop parts days after sowing/planting DAP	Residues after methanol / water extraction (RRR)		Ammonia extract		Final residues (RRR2)		Recovery
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	%
Phenyl label							
Plant back interval 30 DAT							
Wheat Straw 141	0.016	6.7	0.006	2.6	0.006	2.5	75.0
Wheat Chaff 141	0.010	10.4	0.005	5.6	0.003	3.5	80.0
Wheat Grain 141	0.002	16.0	0.001	6.2	0.001	12.6	100.0
Plant back interval: 120 DAT							
Wheat Straw 127	0.009	6.8	0.005	4.1	0.003	2.4	88.9
Wheat Chaff 127	0.005	14.0	0.003	6.6	0.003	7.9	120.0
Wheat Grain 127	0.001	14.3	< 0.001	6.9	0.001	9.6	100.0
Plant back interval: 365 DAT							
Carrot foliage 127	0.008	11.0	0.003	4.3	0.003	4.9	75.0
Wheat Straw 129	0.011	5.9	0.007	3.9	0.003	1.7	90.9
Wheat Chaff 129	0.014	21.3	0.007	11.0	0.006	8.6	92.9
Wheat Grain 129	0.002	10.7	0.001	8.5	0.001	3.6	100.0
Triazine label							
Plant back interval 30 DAT							
Wheat Straw 140	0.050	18.8	0.036	13.5	0.021	7.9	113.7
Wheat Chaff 140	0.065	24.9	0.038	14.5	0.020	7.7	89.3
Plant back interval: 120 DAT							
Wheat Straw 126	0.009	14.1	0.005	8.3	0.005	8.3	117.6
Wheat Chaff 126	0.019	17.2	0.011	10.4	0.009	8.2	106.7

Metabolites

After the extraction procedures, HPLC analysis was carried out for extracts with a sufficient level of radioactivity. In all matrices, concentration of parent was very low after plant back intervals of 365 days (≤ 0.001 mg/kg).

The metabolite AMTT (635M04) was detected in almost all samples of the triazine label but mostly at low absolute concentrations (< 0.01 mg/kg). Only after plant back intervals of 30 days amounts above 0.01 mg/kg were found in bean plant DAP 28 (0.011 mg/kg), wheat foliage DAP 61 (0.013 mg/kg) and wheat straw DAP 140 (0.029 mg/kg).

Carrots

In the extracts of carrot foliage at last harvest/phenyl-label, tritosulfuron was not a major metabolite. After plant back intervals of 30 and 365 days, the metabolite 635M06

(OH-sulphonamide) was the major peak in concentrations of 0.015 mg/kg (30.3 % TRR) and 0.025 mg/kg (36.2 % TRR). For carrot foliage 125 DAP and a plant back interval of 120 days, the major metabolite was 635M02 (sulphonamide) in a concentration of 0.005 mg/kg (10.1 % TRR).

Also, in the extracts of carrot foliage/triazine-label, the concentration of parent decreased after longer plant back intervals. In carrot foliage 30 DAT, AMTT (635M04) was the dominant peak with a concentration of 0.002 mg/kg/ 20.8 % TRR. In carrot foliage 120 DAT, 635M13, a sugar conjugate, was the major peak and in carrot foliage 365 DAT, 5 individual peaks could be detected with a total concentration of 0.010 mg/kg.

The extracts of carrot roots were only analysed for carrot roots 133 DAP/30 DAT and carrot roots 99 DAP/365 DAT from the phenyl-label. The concentration of parent was very low and one of the dominant peaks was OH-sulphonamide (635M06), as already seen in the extracts of carrot foliage.

Bean plant

The concentration of parent tritosulfuron in the extracts of bean plants, after plant back intervals of 30 and 120 days, was similar and < 0.01 mg/kg with the exception of 0.016 mg/kg at DAT 120 for the triazine label. Concentrations of parent at DAT 365 was very low. After plant back intervals of 30 and 120 days, the metabolite 635M01 (‚long guanidine‘; a product where the triazine ring was cleaved) was a dominant degradation product for both labels. After a plant back interval of 365 days, the dominant peak changed to 635M03 (‚short guanidine‘, a degradation product of 635M01). The concentrations of those metabolites were very low and always < 0.01 mg/kg.

Lettuce

In all lettuce plant samples concentration of parent was < 0.01 mg/kg. For the samples from the phenyl-label, the major metabolite after all plant back intervals was 635M06 (OH-sulphonamide) in a concentration range from 0.002 mg/kg to 0.011 mg/kg. This metabolite was already seen in carrot foliage as a dominant degradation product. For the lettuce plant samples from the triazine-label, the major part of the radioactivity was detected in the polar region, including 635M10.

Wheat

In all the wheat samples (foliage, straw and grain) from the two labels and the 3 plant back intervals, tritosulfuron was a minor peak or not detected.

In wheat grain (phenyl-label), the major degradation product was 635M18 in concentrations of 0.005 – 0.008 mg/kg (46 – 48 % TRR). In the wheat grain sample from the triazine-label, several polar peaks could be detected, including 635M10.

In wheat straw, the parent compound was only detected in very low concentration and several degradation products were found. The metabolite 635M01 (‚long guanidine‘) was the major degradation product for both labels. For DAT 365 phenyl label, 635M12 (a sugar conjugate of 635M01) and 635M02 (sulphonamide) were major peaks.

The results of the HPLC analysis are summarised in Table B.7.9-4 and Table B.7.9-5. For samples of the triazine label marked with “*” the concentrations were calculated differing from the original study. The metabolite 635M03 has only one radioactive labelled C-atom left in comparison to two labelled C-atoms in the parent molecule of the triazine label. This leads to a lower peak area in the HPLC chromatogram for metabolite 635M03 in comparison to

parent and the other metabolites with two labelled C-atoms and has to be taken into account in the calculation.

Table B.7.9-4: Summary of major components in rotational crops after treatment with phenyl-label labelled ^{14}C-tritosulfuron.

Crop parts	TRR	Methanol		Tritosulfuron		Metabolites		
DAP	mg/kg	mg/kg	% TRR	mg/kg	% TRR	Code	mg/kg	% TRR
Phenyl label								
Plant back interval: 30 DAT								
Carrot foliage 111	0.029	0.024	82.8	0.005	16.9	635M06	0.008	28.7 %
						635M01	0.003	11.7 %
						635M18	0.002	5.7 %
						635M02/ 635M03/ 635M13	each 0.001	≤ 3.8 %
						unknown: 3 peaks	0.003	9.9 %
Carrot foliage 133	0.049	0.037	75.9	0.005	9.8	635M06	0.015	30.3 %
						635M03	0.003	6.0 %
						635M13/ 635M18	each 0.002	< 4.6 %
						635M02	0.001	2.5 %
						635M01	< 0.001	0.5 %
						unknown: 6 peaks	0.008	18.2 %
Carrot roots 133	0.011	0.009	85.2	0.001	16.9	635M06	0.002	18.8 %
						635M01/ 635M03/ 635M18	each 0.001	≤ 13.9 %
						635M02	< 0.001	2.2 %
						unknown: 4 peaks	0.002	19.6 %
Beans plant 75	0.018	0.015	81.7	0.005	13.6	635M01/ 635M18	each 0.002	≤ 12.1%
						635M03/ 635M13	each 0.001	≤ 6.4 %
						635M02/ 635M23	each < 0.001	≤ 1.8 %
						unknown: 2 peaks	0.003	15.1 %
Lettuce plant 29	0.011	0.010	91.3	0.005	42.0	635M06	0.002	20.3 %
						635M13	0.001	7.5 %
						635M01/635M17	each < 0.001	≤ 4.3 %
						unknown: 3 peaks	0.002	15.9 %
Wheat straw 141	0.233	0.145 + H_2O 0.030	62.0 31.7	n.d.		635M01	0.056	23.7 %
						635M06	0.023	10.2 %
						635M13	0.018	7.9 %
						635M02	0.015	6.7 %
						635M17	0.014	6.1 %
						635M03	0.008	3.2 %
						635M23	0.006	2.4 %
						unknown: 9 peaks	0.077	33.3 %
Wheat grain 141	0.011	0.006	53.1	n.d.		635M18	0.005	46.0 %
						unknown: 2 peaks	< 0.001	7.2 %
Plant back interval: 120 DAT								
Carrot foliage 110	0.055	0.044	78.8	0.016	28.9	635M06	0.012	22.3 %
						635M18	0.004	6.5 %
						635M01/ 635M03	each 0.002	≤ 3.7 %
						unknown: 5 peaks	0.008	14.2 %
Carrot foliage 125	0.049	0.037	76.4	0.007	13.8	635M02	0.005	10.1 %
						635M18	0.001	2.3 %
						unknown: 11 peaks	0.025	50.1 %
Beans plant 81	0.018	0.014	77.5	0.007	38.0	635M01	0.002	9.3 %
						635M06	0.001	6.8 %
						635M23	< 0.001	0.7 %
						unknown: 5 peaks	0.004	22.7 %

Crop parts	TRR	Methanol		Tritosulfuron		Metabolites		
DAP	mg/kg	mg/kg	% TRR	mg/kg	% TRR	Code	mg/kg	% TRR
Lettuce head 29	0.016	0.015	93.6 %	0.008	50.8	635M06	0.002	14.0 %
						635M02	0.001	6.7 %
						635M01	< 0.001	2.2 %
						unknown: 3 peaks	0.003	19.8 %
Lettuce head (B) 61	0.022	0.020	88.9	0.006	27.5	635M02	0.003	15.0 %
						635M17/ 635M18	each 0.001	5.1 %
						635M13	< 0.001	1.5 %
						unknown: 11 peaks	0.007	34.5 %
Wheat straw 127	0.133	0.095 + H_2O	71.1	< 0.001	0.2	635M01	0.042	31.2 %
						635M02	0.020	14.5 %
		0.030	22.1			635M06/ 635M13	each 0.007	≤ 5.3 %
						635M03/ 635M23/ 635M17	each 0.002	≤ 1.6 %
						unknown: 7 peaks	0.042	32.6 %
Plant back interval: 365 DAT								
Carrot foliage 99	0.046	0.037	80.7	n.d.		635M06	0.017	37.0 %
						635M02/ 635M03	each 0.003	< 7.4 %
						635M18	0.002	3.9 %
						unknown: 3 peaks	0.012	25.3 %
Carrot foliage 127	0.069	0.048 + H_2O	68.9	<0.001	0.2	635M06	0.025	36.2 %
						635M18	0.006	8.6 %
		0.014	20.1			635M02	0.005	7.3 %
						635M03	0.003	5.0 %
						unknown: 6 peaks	0.021	31.6 %
Carrot roots 99	0.010	0.009	89.7	<0.001	1.3	635M06/ 635M18	each 0.002	≤ 21.0 %
						635M02/ 635M03	each 0.001	≤ 7.3 %
						unknown: 7 peaks	0.003	33.5 %
Beans plant 83	0.029	0.021	71.3	0.001	2.0	635M03	0.009	31.5 %
						635M18	0.006	20.6 %
						635M02	0.001	2.7 %
						635M01	< 0.001	1.0 %
						unknown: 5 peaks	0.004	13.5 %
Lettuce plant 31	0.023	0.021	93.4	n.d.		635M06	0.011	47.8 %
						635M02	0.002	10.1 %
						635M18	< 0.001	2.2 %
						unknown: 5 peaks	0.007	33.3 %
Wheat straw 129	0.186	0.135 + H_2O	72.8	n.d.		635M12	0.046	24.9 %
						635M02	0.035	18.9 %
		0.040	21.4			635M06	0.015	8.4 %
						635M03	0.007	3.5 %
						635M01/ 635M13/ 635M17	each 0.001	< 0.8 %
						unknown: 8 peaks	0.068	37.0 %
Wheat grain 129	0.017	0.010	59.1	n.d.		635M18	0.008	48.0 %
						635M02	0.001	4.6 %
						635M13	< 0.001	2.4 %
						unknown: 5 peaks	0.001	4.3 %

Table B.7.9-5: Summary of major components in rotational crops after treatment with ^{14}C-tritosulfuron triazine label. Plant back intervals of 30, 120 and 365 days

Crop parts	TRR	Methanol		Tritosulfuron		Metabolites		
DAP	mg/kg	mg/kg	% TRR	mg/kg	% TRR	Code	mg/kg	% TRR
Triazine label								
Plant back interval: 30 DAT								
Carrot plant 36	0.023	0.021	93.2	0.013	57.6	635M04	0.005	19.9 %
						635M01	0.001	4.3 %
						unknown. 5 peaks	0.003	11.5 %
Carrot foliage 110	0.011	0.009	86.9	0.004	38.4	635M04	0.002	20.8 %
						635M01/ 635M10	each 0.001	≤ 13.4 %
						unknown: 2 peaks	0.001	5.8 %
Beans plant 28	0.051	0.049	95.2	0.028	54.0	635M04	0.011	22.2 %
						635M10	0.002	4.6 %
						unknown: 2 peaks	0.007	14.3 %
Beans plant 55*	0.014	0.012	87.0	0.006	41.5	635M03	0.002	12.3 %
						635M01/ 635M04	each 0.001	≤ 9.7 %
						635M10	< 0.001	2.5 %
						unknown: 3 peaks	0.002	14.7 %
Beans plant 74	0.024	0.022	91.0	0.009	37.8	635M01	0.005	18.7 %
						635M04	0.002	10.1 %
						635M10	0.001	4.0 %
						unknown: 4 peaks	0.005	20.1 %
Lettuce plant 28	0.011	0.009	84.7	0.003	31.0	635M10	0.005	42.3 %
						635M04	0.001	4.8 %
						635M01	< 0.001	2.3 %
						unknown: 1 peak	0.001	4.8 %
Wheat foliage 61	0.049	0.043	86.2	n.d.		635M04	0.013	26.2 %
						635M10	0.007	14.4 %
						635M01	0.003	6.7 %
						unknown: 6 peaks	0.020	38.9 %
Wheat straw 140	0.267	0.093	34.9	0.008	3.1	635M01	0.052	19.4 %
		+ H_2O				635M10/ 635M13	each 0.032	≤ 12.0 %
		0.123	46.3			635M04	0.029	11.1 %
						unknown: 6 peaks	0.063	23.7 %
Wheat grain 140*	0.019	0.007	38.4	n.d.		635M10	0.003	16.9 %
						635M04	0.001	2.4 %
						635M01/ 635M03	each < 0.001	≤ 1.5 %
						unknown: 4 peaks	0.004	16.2 %
Plant back interval: 120 DAT								
Carrot foliage 109	0.025	0.023	92.8	0.007	28.0	635M04	0.006	25.4 %
						unknown: 4 peaks	0.009	39.4 %
Carrot foliage 124*	0.019	0.016	85.6	n.d.		635M13	0.004	19.6 %
						635M01	0.003	13.2 %
						635M03	0.001	6.0 %
						635M04	0.001	3.1 %
						unknown: 5 peaks	0.008	43.7 %
Beans plant 56*	0.033	0.030	92.7	0.015	46.3	635M04 / 635M03	each 0.003	9.5 %
						635M01	0.003	8.5 %
						635M10	0.002	6.5 %
						unknown: 4 peaks	0.004	12.5 %
Beans plant 80	0.031	0.028	91.3	0.016	50.9	635M01/ 635M04	each 0.002	< 6.6 %
						unknown: 2 peaks	0.009	28.6 %
Lettuce head (A) 60*	0.016	0.013	81.1	0.006	35.1	635M10	0.004	25.2 %
						635M03	0.002	10.3 %
						635M01	0.001	4.8 %
						unknown:1 peak	0.001	5.6 %

Crop parts	TRR	Methanol		Tritosulfuron		Metabolites		
DAP	mg/kg	mg/kg	% TRR	mg/kg	% TRR	Code	mg/kg	% TRR
Triazine label								
Lettuce head (B) 60	0.015	0.014	88.6	0.007	43.4	635M10	0.005	31.4 %
						unknown: 1 peak	0.002	13.8 %
Wheat straw 126*	0.060	0.035 + H_2O 0.017	57.7 28.2	< 0.001	0.2	635M10	0.009	15.1 %
						635M01	0.005	8.4 %
						635M04	0.004	7.7 %
						635M03	0.004	6.7 %
						635M13	< 0.001	0.8 %
						unknown: 8 peaks	0.023	36.9 %
Plant back interval: 365 DAT								
Carrot foliage 98	0.010	0.009	89.9	n.d.		unknown: 5 peaks	0.010	89.7 %
Beans plant 82*	0.012	0.010	87.9	n.d.		635M03	0.007	59.4 %
						635M10	0.001	12.4 %
						635M01/ 635M04	each 0.001	≤ 4.7 %
						unknown: 1 peak	0.001	7.7 %
Wheat foliage 47*	0.054	0.049	89.8	n.d.		635M10	0.016	28.6 %
						635M01	0.009	17.0 %
						635M03	0.006	11.4 %
						unknown: 5 peaks	0.018	32.8 %
Wheat straw 129*	0.015	0.010	62.7	n.d.		635M01	0.004	25.8 %
						635M03	0.003	16.6 %
						635M04	< 0.001	1.6 %
						unknown: 2 peaks	0.003	18.7 %

Metabolic pathway

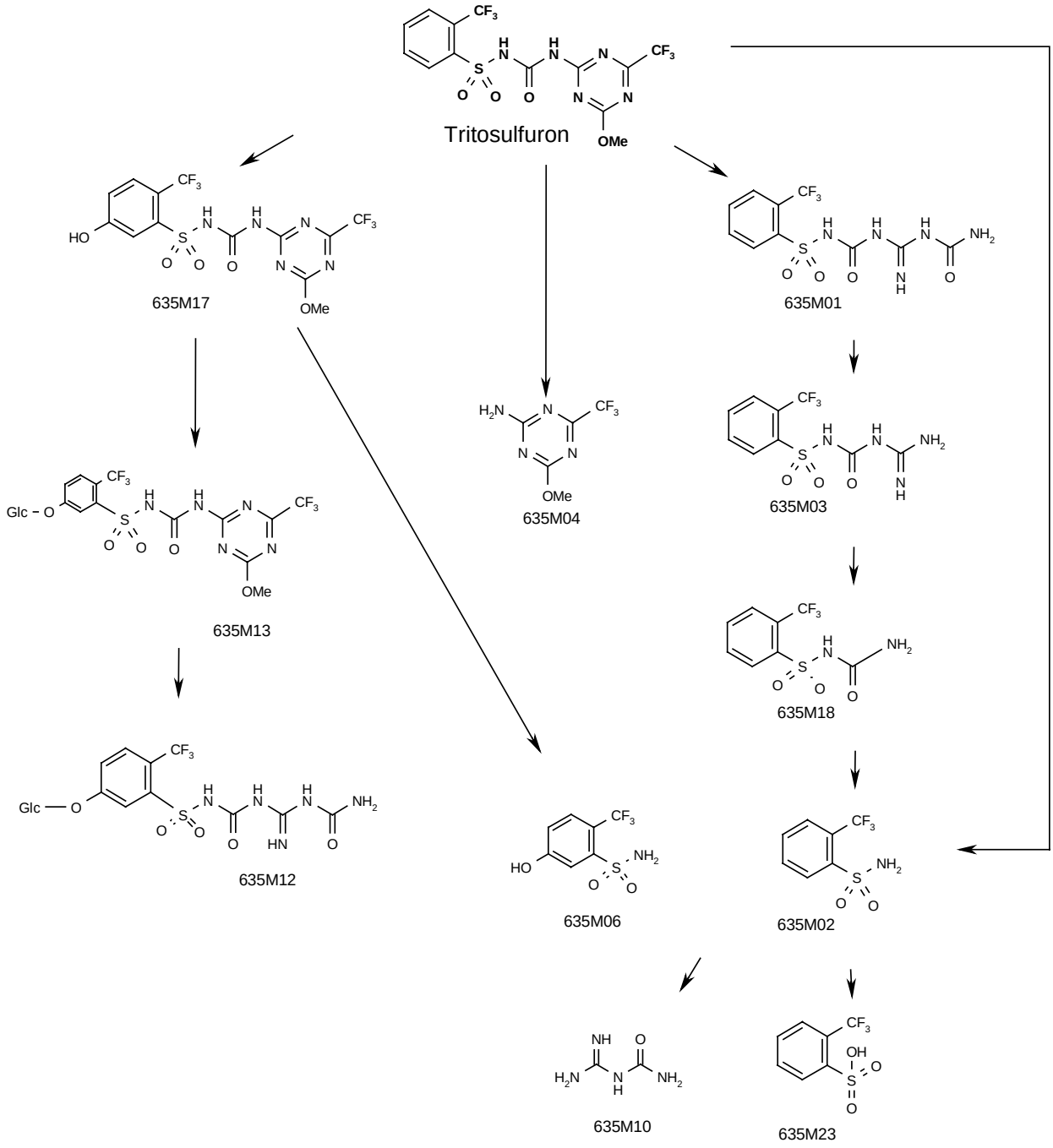
Different possibilities for the degradation of tritosulfuron seemed to exist in the plants and depending on the crop one way or the other was preferred (Figure B.7.9-1).

In carrots and in lettuce, a hydroxylation and a later cleavage of the whole compound seemed to be the preferred degradation pathway and therefore, 635M06 (OH-sulphonamide) was a major degradation product for the phenyl-label of tritosulfuron. Aminotriazine (AMTT), as the corresponding metabolite for the triazine-label of tritosulfuron, was also detected, but only as an intermediate and a fast further degradation leads to a cluster of very polar degradation products.

In bean plants, a different degradation pathway was observed to be the preferred. The triazine ring was cleaved first and afterwards, a step by step further degradation leading to the metabolites 635M01, 635M03, 635M18 and 635M02. This degradation pathway appeared to be also a major one in the soil. Therefore, the metabolites could also have been translocated from the soil into the plant. This could be the reason for slightly higher residue levels after longer plant back intervals.

Wheat grain appeared to have the degradation pathway as described for beans. The intermediate degradation products (635M01, 635M03) were not detected in larger quantities. The major metabolites in wheat grain, was 635M18 for the phenyl-label and the polar peak cluster for the triazine-label. Wheat straw showed almost the whole range of different metabolites including 635M01 as a major one.

Figure B.7.9-1: Metabolic pathway in rotational crops



B.7.9.3 Storage stability

Samples were stored up to two years and no major changes in the metabolite pattern and in distribution of radioactive residues were observed.

B.7.9.4 Conclusion

The confined rotational crop study was conducted with phenyl and triazine labelled ^{14}C-tritosulfuron. The soil was treated with an application rate of 60 g as/ha (GAP: 50 g as/ha) and aged for 30, 120 and 365 days.

In the edible parts of succeeding crops destined for human consumption, the total radioactive residues were low for carrot root (≤ 0.011 mg/kg), green beans (≤ 0.005 mg/kg), lettuce head (≤ 0.022 mg/kg) and wheat grain (≤ 0.019 mg/kg) after all 3 plant back intervals. The concentration of parent tritosulfuron was ≤ 0.001 mg/kg for carrot root samples and ≤ 0.006 mg/kg for lettuce head samples. No tritosulfuron was detected in wheat grain samples. In carrot foliage and bean plant samples at time of harvest parent was found in concentrations of ≤ 0.016 mg/kg and ≤ 0.008 mg/kg for wheat straw.

The metabolite AMTT (635M04) was detected in almost all samples of the triazine label but mostly at low absolute concentrations. Only after plant back intervals of 30 days amounts above 0.01 mg/kg were found with highest amounts in wheat straw (0.029 mg/kg).

Besides parent, 635M06 (OH-sulphonamide) and 635M02 (sulphonamide) were detected as major metabolites in carrot foliage, carrot root and lettuce samples of the phenyl label. In the corresponding samples of the triazine label a range of very polar peaks, AMTT (635M04, aminotriazine) in very low concentrations and a sugar conjugate of the parent compound (635M13) were detected.

The dominant degradation products in bean plants were 635M01 (long guanidine) and 635M03 (short guanidine) after longer plant back intervals. A further degradation lead to the metabolite 635M18, which was the major degradation product in wheat grain. Wheat straw showed almost the whole range of different metabolites including 635M01 as a major one.

B.7.9.5 Field trials

Due to the low concentration of tritosulfuron and its degradation products in the edible parts of the succeeding crops, no field trials are required.

B.7.10 Proposed pre-harvest intervals for envisaged uses, or withholding periods, in the case of post-harvest uses (Annex IIA 6.8; Annex IIIA 8.7)

Products containing tritosulfuron will be used as post-emergence herbicides at the latest timing at stage BBCH 39 for cereals and at stage BBCH 17 for maize. The results of the supervised residue trials show that residues of tritosulfuron were not found in grain (cereal and maize) at time of harvest.

The PHI for cereal grain and maize grain is covered by the normal vegetation period between application and harvest.

B.7.11 Community MRLs and MRLs in EU Member States (Annex IIIA 12.2)

Tritosulfuron is a new active substance which is not authorised in any EU Member State and no MRL has been set in the EU yet.

B.7.12 Proposed EU MRLs and justification for the acceptability of those residues (Annex IIA 6.7; Annex IIIA 8.6)

B.7.12.1 MRL proposal for plants

In cereals, residue trials up to harvest were conducted with different formulations covering both the North and the South of EU in winter barley, spring barley, winter wheat, spring wheat and durum wheat. In maize, residue trials also covered both the North and the South of EU.

No residues of tritosulfuron in cereal and maize grain were found above the limit of quantitation of the method used (0.001 mg/kg).The MRL proposal is therefore

0.01 mg/kg for cereal and maize grain and other food of plant origin.

The MRL value proposed corresponds to the limit of quantitation of the enforcement method submitted.

B.7.12.2 MRL proposal for animal products

The calculation in B.7.8 shows that no residues in products of animal origin above the LOQ are to be expected.

Therefore, no MRL for products of animal origin is proposed.

B.7.13 Proposed EU Import tolerances and justification for the acceptability of those residues

No import tolerances have been proposed in the EU or applied for in any EU Member State.

B.7.14 Basis for differences, if any, in conclusion reached having regard to established or proposed Codex MRLs

Not applicable since no Codex MRLs have been established yet.

B.7.15 Estimates of potential and actual dietary exposure through diet and other means (Annex IIA 6.9; Annex IIIA 8.8)

Due to the toxicological properties of the metabolite AMTT an **ADI value of 0.5 mg/kg bw/d** was proposed for **tritosulfuron with a maximum content of 0.02 % AMTT.** The Theoretical Maximum Daily Intake (TMDI) was calculated using the total diet of food of plant origin based on both the German and the WHO diet. Since after treatment of cereals or maize no quantifiable residues of tritosulfuron are to be expected in edible plant parts, the MRL for all food of plant origin is proposed at the LOQ of 0.01 mg/kg.

Both calculations lead to very low TMDI values. The contribution to the proposed ADI of 0.5 mg/kg bw/d is for tritosulfuron (max. 0.02 % AMTT) 0.07 % and 0.04 % according to the German and the WHO calculation model, respectively (see Table B.7.15-1 and Table B.7.15-2).

Table B.7.15-1: TMDI calculation of tritosulfuron (max. 0.02 % AMTT) German model

Food	Raw	Processed	Whole	MRL mg/kg	Intake mg/kg bw
Mean food consumption (g/d) of a 4 to 6 year old girl					
Food of plant origin	105.8	386.2	492.0	0.01	0.00036444
Intake whole (mg/kg bw):					**0.0004**
Percent of ADI (%)					**0.07**
Mean food consumption (g/d) of a 36 to 50 years old woman					
Wine grapes (wine)		97.6	97.6	0.01	0.00001627
Tea		1.1	1.1	0.01	0.00000018
Hops		4.9	4.9	0.01	0.00000082
Coffee beans		26.5	26.5	0.01	0.00000442
Intake whole (mg/kg bw):					**0.00002**
Percent of ADI (%)					**0.00**

Table B.7.15-2: TMDI calculation of tritosulfuron (max. 0.02 % AMTT) WHO model (European diet 1998)

Food	Consumption g/day	MRL mg/kg	Intake mg/kg bw
Food of plant origin	1253.4	0.01	0.000209
Intake whole (mg/kg bw):			**0.0002**
Percent of ADI (%)			**0.04**

B.7.16 Summary and evaluation of residue behaviour (Annex IIA 6.10; Annex IIIA 8.9)

B.7.16.1 Metabolism in plants

The metabolism and distribution of tritosulfuron was investigated in maize using [phenyl-U-^{14}C]-tritosulfuron and [triazine-2,4-^{14}C]-tritosulfuron with an exaggerated application rate of 180 g as/ha. The plants were treated at growth stage BBCH 14/15.

Tritosulfuron was metabolised by the following key transformation steps:
- Hydroxylation of the phenyl ring system followed by glucosylation yielding to the metabolites 635M17 and 635M13,
- cleavage of the triazine ring system yielding to the metabolite 635M01,
- cleavage of the sulfonyl urea bridge yielding to the metabolites 635M06 and 635M07.

In most samples tritosulfuron was the main component. In addition, a range of metabolites were detected. With one exception (forage 30 DAT, 635M13) all metabolites identified or unidentified were clearly below 0.05 mg/kg or 0.01 mg/kg in grain, respectively. The metabolite AMTT (635M04) was not detected in the maize metabolism study. Therefore, parent only is included in the residue definition.

Residue definition plant: parent tritosulfuron

B.7.16.2 Metabolism in livestock

The metabolism of tritosulfuron has been investigated in lactating goats and laying hens using two labelled forms (^{14}C-label in the phenyl ring and in the triazine ring).

After administration of an exaggerated dose residues were found at very low levels consisting of unchanged parent compound and three major metabolites (635M02, 635M04, 635M09). As expected the molecule is cleaved at the sulfonylurea bridge. Breakdown products were found containing either the phenyl or the triazine moiety according to the labelling position.

Since the total radioactive residue level in edible matrices of the goat and hen metabolism studies was below 0.05 mg/kg in most of the cases and since these residue levels resulted from overdosing the goats and hens compared to realistic feeding levels obtained according to GAP, the criteria for the designation of a relevant metabolite are not met. With focus on the metabolite 635M04 (AMTT), it can be assumed that this compound would be present in animal matrices at levels below 0.001 mg/kg after feed up-take with realistic residues and therefore, it would not be detected by any residue analytical method.

The parent compound was detected at significant proportions in all matrices, even though it occurred at very little absolute residue levels.

Based on these facts, the following definition of relevant residues is proposed for products of animal origin for monitoring purposes:

Residue definition animal products: parent tritosulfuron

B.7.16.3 Residues in cereals and maize, maximum residue levels and pre-harvest interval

A sufficient number of trials was presented to support the GAP´s of tritosulfuron in cereals and maize for North and South Europe. The residue results from wheat and barley are considered equally applicable to other cereal crops. In all cases the residues of tritosulfuron in grain were below 0.001 mg/kg at harvest.

The MRL proposal is therefore 0.01 mg/kg for cereal and maize grain and other food of plant origin.

The PHI for cereal grain and maize grain is covered by the normal vegetation period between application and harvest.

B.7.16.4 Stability of residues prior to analysis

The storage trials showed that tritosulfuron was stable over a period of 3 years in frozen maize and wheat samples. In all residue trials, tritosulfuron was analysed within this period and obtained data can therefore be regarded as valid.

Storage trials with AMTT had only be conducted to a maximum of 12 months until reporting and trials are still ongoing. AMTT was stable during the interval investigated and it can be expected that it will be stable for longer periods. Thus, the results obtained in the residue trials, with intervals between sampling and analysis of 6 – 14 months, are regarded as valid.

B.7.16.5 Residues in succeeding crops

The confined rotational crop study was conducted with phenyl and triazine labelled ^{14}C-tritosulfuron. The soil was treated with an application rate of 60 g as/ha (GAP: 50 g as/ha) and aged for 30, 120 and 365 days.

In the edible parts of succeeding crops destined for human consumption, the total radioactive residues were low for carrot root (≤ 0.011 mg/kg), green beans (≤ 0.005 mg/kg), lettuce head (≤ 0.022 mg/kg) and wheat grain (≤ 0.019 mg/kg) after all 3 plant back intervals.

The concentration of parent tritosulfuron was ≤ 0.001 mg/kg for carrot root samples and ≤ 0.006 mg/kg for lettuce head samples. No tritosulfuron was detected in wheat grain samples. In carrot foliage and bean plants only few samples showed residues of tritosulfuron slightly above 0.01 mg/kg.

The metabolite AMTT (635M04) was detected in almost all investigated samples of the triazine label but mostly at low absolute concentrations. Only after plant back intervals of 30 days and for early growth stages AMTT was found at higher percentages. Highest concentration was found in wheat straw (0.029 mg/kg) after a plant back interval of 30 days.

Besides parent, major metabolites in the investigated samples were sulphonamide (635M02) and OH-sulphonamide (635M06) as well as long and short guanidine (635M01, 635M03).

B.7.16.6 Estimate of dietary exposure to tritosulfuron

Due to the toxicological properties of the metabolite AMTT an ADI value of 0.5 mg/kg bw/d was proposed for tritosulfuron with a maximum content of 0.02 % AMTT. The Theoretical

Maximum Daily Intake (TMDI) was calculated using the German and the WHO diet and the proposed MRL value of 0.01 mg/kg.

There appears to be no chronic dietary consumer risk for tritosulfuron with a maximum content of 0.02 % AMTT (German diet: 0.07 %, WHO European diet: 0.04 %).

B.7.17 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.0	Jordan J.	2001	Storage stability of AMTT (BH 635-5) in wheat matrices and radish root. 2001/5001046 GLP, unpublished RIP2001-611	Y	BAS
AIIA-6.0	Stewart J.M.	2001	Storage stability of BAS 635 H in plant matrices. 2001/5001045 GLP, unpublished RIP2001-610	Y	BAS
AIIA-6.1	Hofmann M.	1997	Plant uptake study with BAS 635 H (triazin-2,4-14C) and maize use rate: 180 g a.i./ha. 97/10843 GLP, unpublished RIP2001-588	Y	BAS
AIIA-6.1	Hofmann M.	1997	Plant uptake study with BAS 635 H (triazin-2,4-14C) and maize use rate: 120 g a.i./ha. 97/10838 GLP, unpublished RIP2001-587	Y	BAS
AIIA-6.1	Hofmann M.	1997	Plant uptake study with 14C-BAS 635 H (Phenyl-U-14C) and maize use rate: 180 g a.i./ha. 97/10844 GLP, unpublished RIP2001-586	Y	BAS
AIIA-6.1	Hofmann M.	1997	Plant uptake with 14C-BAS 635 H (phenyl-U-14C) and maize use rate: 120 g a.i./ha. 97/10837 GLP, unpublished RIP2001-585	Y	BAS

[6] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.1	Hofmann M.	1998	Plant uptake study with 14C-BAS 635H and maize use rate: 180 g a.i./ha [phenyl-U-14C and triazine-2,4-14C]. 98/10630 GLP, unpublished RIP2001-584	Y	BAS
AIIA-6.1	Reinhard K.	1998	Metabolism of 14C-BAS 635 H in corn. 98/11379 GLP, unpublished RIP2001-589	Y	BAS
AIIA-6.2	Kohl W.	1999	The metabolism of 14C-BAS 635 H (14C-Reg. No. 271272) in laying hens. 99/10272 GLP, unpublished RIP2001-594	Y	BAS
AIIA-6.2	Kohl W.	2000	The metabolism of 14C-BAS 635 H (14C-Reg. No. 271272) in lactating goats. 2000/1013502 GLP, unpublished RIP2001-591	Y	BAS
AIIA-6.2	Leibold E.	1997	Amendment No. 1 to the report: 14C-BAS 635 H- Study of the absorption, distribution and excretion after repeated oral administration in laying hens. 97/11241 GLP, unpublished RIP2001-593	Y	BAS
AIIA-6.2	Leibold E., Hoffmann, H. D., Hildebrand, B.	1997	14C-BAS 635 H- Study of the absorption, distribution and excretion after repeated oral administration in lactating goats. 97/11172 GLP, unpublished RIP2001-590	Y	BAS
AIIA-6.2	Leibold E., Hoffmann H. D., Hildebrand, B.	1997	14C-BAS 635 H - Study of the absorption, distribution and excretion after repeated oral abministration in laying hens. 97/11170 GLP, unpublished RIP2001-592	Y	BAS
AIIA-6.3	Beck J., Bross, M., Mackenroth, C,	2000	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 641 00 H under field conditions in Belgium, France, Germany, Great Britain , Spain, Sweden and the Netherlands, 1998. 2000/1012391 GLP, unpublished RIP2001-602	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.3	Beck J., Bross, M., Mackenroth, C.	2000	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 641 00 H under field conditions in France, Germany, Great Britain, Spain and Sweden, 1997. 2000/1014843 GLP, unpublished RIP2001-600	Y	BAS
AIIA-6.3	Meumann H., Bross, M., Mackenroth, C.	2000	Study on the residue behaviour of BAS 635 H after application of BAS 635 01 H and BAS 635 GJH in maize under field conditions in Germany, France and Sweden, 1998. 2000/1012399 GLP, unpublished RIP2001-609	Y	BAS
AIIA-6.3	Meumann H., Bross, M., Mackenroth, C.	2000	Study on the residue behaviour of BAS 639 00 H and BAS 635 01 H in maize under field conditions in Belgium, France, Germany, Great Britain and Spain, 1997. 2000/1012389 GLP, unpublished RIP2001-607	Y	BAS
AIIA-6.3	Meumann H., Bross, M., Mackenroth, C.	2000	Study on the residue behaviour of BAS 639 00 H in maize under field conditions in Germany, the Netherlands and Spain, 1996. 2000/1012388 GLP, unpublished RIP2001-606	Y	BAS
AIIA-6.3	Raunft E., Benz, A., Mackenroth, C.	2001	Study on the residue behaviour of BAS 615 H and BAS 635 H in cereals after treatment with BAS 635 00 H and BAS 641 01 H under field conditions in Denmark, Spain and Great Britain, 2000. 2000/1014857 GLP, unpublished RIP2001-598	Y	BAS
AIIA-6.3	Schulz H.	2001	Determination of the residues of BAS 641 H and BAS 635 H in wheat and barley following treatment with BAS 641 01 H, BAS 635 00 H and BAS 152 00 S under field conditions in Italy and France 2000. 2000/1014884 GLP, unpublished RIP2001-597	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.3	Schulz H.	2001	Determination of the residues of Reg.-No. 271 272 and Bentazone in maize following treatment with BAS 635 00 H, BAS 351 40 H and BAS 152 00 S under field conditions in France 1999. 2001/1000919 GLP, unpublished RIP2001-604	Y	BAS
AIIA-6.3	Schulz H.	2000	Determination of the residues of BAS 635 H in maize following treatment of BAS 639 00 H and BAS 635 01 H under field conditions in Italy 1997. 2000/1012398 GLP, unpublished RIP2001-608	Y	BAS
AIIA-6.3	Schulz H.	2001	Determination of the residues of BAS 655 H in wheat and barley following treatment with BAS 655 00 H and BAS 152 00 S under field conditions in Italy and France 2000. 2000/1014888 GLP, unpublished RIP2001-599	Y	BAS
AIIA-6.3	Schulz H.	2001	Determination of the residues of BAS 655 H in wheat and barley following treatment with BAS 655 00 H and BAS 152 00 S under field conditions in Italy and France 1999. 2001/1000922 GLP, unpublished RIP2001-596	Y	BAS
AIIA-6.3	Schulz H.	2001	Determination of the residues of BAS 641 H in wheat and barley following treatment with BAS 641 01 H and BAS 152 00 S under field conditions in Germany and France 1999. 2001/1000920 GLP, unpublished RIP2001-595	Y	BAS
AIIA-6.3	Treiber S.	2001	Determination of the residues of BAS 635 H in maize following treatment with BAS 635 00 H under field conditions in Germany, Denmark, France, Great Britain, the Netherlands and Spain, 2000. 2000/1014858 GLP, unpublished RIP2001-605	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.3	Treiber S.	2000	Study on the residue behaviour of BAS 635 H in maize after treatment with BAS 635 00 H under field conditions in Germany and Spain, 1999. 2000/1012406 GLP, unpublished RIP2001-603	Y	BAS
AIIA-6.5.1	Goetz A.J.	1996	Hydrolysis of 14C-BAS 635 H at 100 °C and pH5. 96/5200 GLP, unpublished RIP2001-612	Y	BAS
AIIA-6.6	Hofmann M.	1998	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 365 Tage. 98/10633 GLP, unpublished RIP2001-617	Y	BAS
AIIA-6.6	Hofmann M.	1998	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 120 Tage. 98/10634 GLP, unpublished RIP2001-619	Y	BAS
AIIA-6.6	Hofmann M.	1998	Nachbaustudie mit 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 365 Tage. 98/10631 GLP, unpublished RIP2001-621	Y	BAS
AIIA-6.6	Hofmann M.	1998	Nachbaustudie mir 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 120 Tage. 98/10632 GLP, unpublished RIP2001-623	Y	BAS
AIIA-6.6	Hofmann M.	1998	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 365 days. 2000/1014898 GLP, unpublished RIP2001-624	Y	BAS
AIIA-6.6	Hofmann M.	1998	Crop rotation study with 14C-271272 (phenyl-U-14C) BAS 635 H - Aging: 365 days. 2000/1014900 GLP, unpublished RIP2001-622	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[6]
AIIA-6.6	Hofmann M.	1998	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 120 days. 2000/1014897 GLP, unpublished RIP2001-620	Y	BAS
AIIA-6.6	Hofmann M.	1998	Crop rotation study with 14C-271272 (phenyl-U-14C) BAS 635 H - Aging: 120 days. 2000/1014899 GLP, unpublished RIP2001-618	Y	BAS
AIIA-6.6	Hofmann M.	1996	Nachbaustudie mit 14C-271272 (triazin-2,4-14C) BAS 635 H - Alterung: 30 Tage. 96/10170 GLP, unpublished RIP2001-615	Y	BAS
AIIA-6.6	Hofmann M.	1996	Crop rotation study with 14C-271272 (triazin-2,4-14C) BAS 635 H - Aging: 30 days. 2000/1014896 GLP, unpublished RIP2001-616	Y	BAS
AIIA-6.6	Hofmann M.	1996	Crop rotation study with 14C-271272 (Phenyl-U-14C) BAS 635 H - Aging: 30 days. 2000/1014894 GLP, unpublished RIP2001-614	Y	BAS
AIIA-6.6	Hofmann M.	1996	Nachbaustudie mit 14C-271272 (phenyl-U-14C) BAS 635 H - Alterung: 30 Tage. 96/10165 GLP, unpublished RIP2001-613	Y	BAS
AIIA-6.6	Veit P.	2001	Quantification and identification of radioactive residues in rotantional crop after treatment with 14C-BAS 635 H (14C-271272). 2001/1000995 GLP, unpublished RIP2001-625	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-8: Environmental fate and behaviour

B.8 Environmental fate and behaviour

B.8.1 Route and rate of degradation in soil (Annex IIA 7.1.1; Annex IIIA 9.1.1)

B.8.1.1 Route of degradation

B.8.1.1.1 Aerobic degradation

Kellner, O. (1998a): The aerobic soil metabolism of BAS 635 H (^{14}C-phenyl). BASF RegDoc# 1998/10619; BOD 2001-484

Kellner, O. (1997): The aerobic soil metabolism of BAS 635 H (^{14}C-triazine). BASF RegDoc# 1997/11242; BOD 2001-486

Guidelines: BBA IV, 4-1; USA-EPA, Subdivision N, 162-1

GLP: yes

Test system:
The aerobic soil metabolism of ^{14}C-tritosulfuron was investigated using [^{14}C-U-phenyl = ph] and [^{14}C-2,4-triazine = tr] labelled acitve substance (radiochemical purity > 99 % and > 99 %; chemical purity 99.3 and 98.7 %, specific activity 9.6 MBq/mg and 9.26 MBq/mg), respectively. The soil parameters are listed in Table B.8.1-1. The initial concentration in the soil was 0.065 mg as/kg dry soil, which is equivalent to a field application rate of 50 g as/ha (5 cm layer, bulk density of 1.5 kg/l). Some additional soil samples were treated with 1, 5 or 10 mg as/kg dry soil to facilitate identification of occuring metabolites. Incubation conditions were: aerobic by continous flow of air, in the dark, temperature maintained 20 ± 1 °C and a soil moisture of 40 % maximum water holding capacity (MWHC). The moisture content was checked periodically by weighing and readjusted if necessary. A single soil sample was analysed on each sampling date. Samples with phenyl labelled tritosulfuron was collected on day 0, 3, 7, 14, 28, 58, 91, 113, 126, 183, 272 and 358 after application, soil containing triazine labelled tritosulfuron was assayed at day 0, 3, 7, 14, 28, 62, 90, 181, 272 and 358 after treatment. Volatiles were trappd by continously washing the effluent gas with 0.5 m NaOH, H_2O, ethylene glycole and 0.5 M H_2SO_4. At each sampling date aliquots of soil samples were combusted and the amount of the total radioactive residues (TRR) was determined by LSC. The soil samples were extracted consecutively three times with each of the solvents: dichloromethane, methanol and methanol/water 1:1 by volume. Samples were centrifuged after each extraction and the extraction solution was decanted or filtrated from the soil. The relevant fractions were pooled and the radioactivity of the extracts was determined by LSC. The extracts were concentrated, redissolved and analysed by TLC and HPLC. The soil residues were combusted and the evolved $^{14}CO_2$ was determined by LSC. Some extracted soil samples (^{14}C-phenyl: day 28 - 358, ^{14}C-triazine: day 62 - 358) were selected for further characterisation of soil radioactivity which remained in bound to the humic and fulvic acids and the humin fraction (soil extraction with 0.5 N NaOH, acidification of the extract).

Table B.8.1-1: Aerobic soil metabolism of ^{14}C-tritosulfuron: Characterisation of the soils used

	^{14}C-Phenyl	^{14}C-Triazine
Soil,	Li 35 b	
Origin	Limburgerhof, Germany	
Characterisation (DIN classification, Germany)	loamy sand	
Characterisation (USDA)	sandy loam	
% sand (0.063 – 2 mm)	76	77
% silt (0.002 – 0.063 mm)	11	13
% clay (< 0.002 mm)	13	10
pH value ($CaCl_2$)	6.3	6.5
% organic carbon	0.7	0.9
Maximum water holding capacity [g H_2O/100g dry soil]	31	33
Field capacity [g H_2O/100g dry soil], 330 hPa	7.6	7.8
Cation exchange capacity [meq / 100 g]	5.7	4.4
Microbial biomass - beginning of study [mg C / 100 g soil]	17.3	23.1
Microbial biomass - end of study [mg C / 100 g soil]	5.0	6.6

Findings:
The distribution of the radioactivity and the amounts of tritosulfuron and metabolites are given in Table B.8.1-2. Metabolites < 3 % TAR (< 0.002 mg/kg) are not given in the table. The total recoveries for individual incubation ranged from 103.1 % on day 7 to 70.8 % on day 91 and 88.7 % of the applied radioactivity (TAR) on day 358 for the phenyl label. The mass balance of the triazine label ranged from 100 % (day 0) to 81.6 % (day 358). The mineralisation rates of tritosulfuron to CO_2 after 358 days were different for both labels and reached 2.6 % TAR for the phenyl label and 20.7 % TAR for the triazine label.
Non-extractable residues (bound residues) increased to 46 % TAR after 272 days with the phenyl label and to 34 % TAR after 181 days with the triazine label. The bound residues lightly decreased towards the end of the study: 43.1 % (ph) and 28.1 % TAR (tr), respectively. In both studies about halb of the bound radioactivity could be extracted by NaOH. Further work-up steps revealed that the major part was associated with the fulvic acid fraction. Following HPLC analysis showed no active ingredient but the presence of the metabolites 635M01, 635M02 and 635M03. The distribution of the radioactivity bound in the fulvic and humic acid fraction and the amounts of metabolites detected in the fulvic acid fractions are given in Table B.8.1-3.
The amount of tritosulfuron decreased from 100 % (ph) and 97.8 % (tr) on day 0 to 0.0 (ph) and 1.0 (tr) % TAR during the incubation of 358 days. As major metabolites 635M01, 635M03 and 635M02 are formed in maximum amounts of 40.9 % (day 90), 14 % (day 358) and 11.1 % TAR (day 113), respectively.
It is assumed that the first degradation step is the demethylation at the triazine ring to the corresponding hydroxy triazine (= metabolite 635M19, not detected in the study, but during anaerobic degradation), followed by a cleavage of the triazine ring, which results in the formation of the metabolite 635M01. Further degradation steps (hydrolysis) lead to the formation of the metabolites 635M03, 635M02 (“sulfonamide”). As an alternative a direct hydrolysis of tritosulfuron or 635M01 to 635M02 or a direct hydrolysis of tritosulfuron to 635M04 (AMTT) could not be excluded.

Table B.8.1-2: Aerobic soil metabolism of ^{14}C-tritosulfuron: Recovery of radioactivity and distribution of active substance and metabolites [% of applied radioactivity], determined by HPLC analysis

DAT	$^{14}CO_2$	tritosulfuron	635M02	635M03	635M01	635M04 (AMTT)	bound residues	total
phenyl-label								
0	0.0	100.0	0.0	0.0	0.0	-	0.0	100.0
3	0.0	97.5	0.0	0.0	2.1	-	0.0	101.5
7	0.0	94.4	0.0	0.0	5.0	-	1.5	103.1
14	0.0	73.9	4.1	0.0	15.5	-	3.1	101.5
28	0.0	48.7	7.3	1.1	27.2	-	9.2	98.5
58	0.0	19.2	7.5	2.2	34.4	-	16.9	81.5
91	0.0	4.8	5.9	3.8	37.8	-	18.5	70.8
113	0.0	2.8	11.1	8.0	40.3	-	35.4	98.5
126	0.0	1.8	9.8	5.6	33.2	-	33.8	89.2
183	1.5	0.0	10.0	9.2	24.2	-	32.3	78.5
272	1.5	0.0	10.7	12.0	20.9	-	46.2	92.3
358	2.6	0.0	10.5	13.9	17.3	-	43.1	88.7
triazine-label								
0	0.0	97.8	-	0.0	0.0	0.0	0.0	100.0
3	0.0	88.1	-	0.0	1.6	1.4	1.6	98.4
7	0.0	85.5	-	0.0	4.5	0.0	1.6	93.8
14	0.0	67.5	-	0.0	11.8	2.4	3.1	89.1
28	0.0	58.9	-	0.0	20.2	3.5	6.3	95.3
62	2.3	24.0	-	1.2·2*	37.9	5.5	12.5	89.8
90	4.7	17.4	-	2.4·2*	40.9	6.3	17.2	92.2
181	9.4	2.5	-	4.2·2*	28.0	2.5	34.4	90.6
272	15.6	1.5	-	5.6·2*	22.6	2.0	32.8	85.9
358	20.7	1.0	-	7.0·2*	19.2	2.2	28.1	81.6

* The percent of applied radioactivity must be duplicated for the calculation of the amount of 635M03

Table B.8.1-3: Aerobic soil metabolism of ^{14}C-tritosulfuron: Distribution of the radioactivity in the non-extractable residues fractions and the amounts of metabolites in the fulvic acid fraction [% of applied radioactivity], determined by HPLC analysis

DAT	Fulvic acid	Metabolites in the fulvic acid fraction				humin acids
		635M02	635M03	635M01	635M04 (AMTT)	
phenyl-label						
28	3.1	n.a.	n.a.	n.a.	-	0.0
58	6.2	n.a.	n.a.	n.a.	-	1.5
91	9.2	1.3	0.5	3.9	-	1.5
113	15.4	3.1	0.8	6.3	-	1.5
126	20.0	1.5	1.1	9.1	-	1.5
183	15.4	1.4	1.1	6.2	-	3.1
272	16.9	2.8	1.9	7.8	-	3.1
358	18.5	2.7	2.0	7.7	-	3.1
triazine-label*						
62	6.3	-	< 0.5	< 3.1	< 0.5	1.6
90	7.8	-	< 0.5	< 3.1	< 0.5	1.6
181	12.5	-	< 0.5	< 6.3	< 0.5	1.6
272	12.5	-	< 0.5	< 4.7	< 0.5	1.6
358	14.1	-	< 0.5	< 4.7	< 0.5	3.1

* exact values for the metabolites are not given in the report, but the statement, that all metabolites were < 0.5 % TAR, except metabolite 635M01 which accounted for > 80 % of the radioactivity extractable by ethylacetate. In the table the amounts of the radioactivity found in the ethylacetate fraction were given as maximum amounts of 635M01.

Comment:
The study is acceptable.

Staudenmaier, H. and Lehmann, C. (1999): Degradation behaviour of BAS 635 H in lysimeter soil. BASF RegDoc# 1999/11823; BOD 2001-485

Guidelines: BBA IV, 4-1; SETAC Europe; Dutch guideline (Regeling uitvoering milieutoelatingseisen bestrijdingsmiddelen, Annex I)

GLP: yes

Test system:
The aerobic soil metabolism of ^{14}C-tritosulfuron was investigated using [^{14}C-U-phenyl] labeled acitve substance (radiochemical purity 99.2 %; chemical purity 98.2 %, specific activity 9.6 MBq/mg). The soil was sieved, air dried and passed through a 2 mm sieve prior use. The soil parameters are listed in Table B.8.1-4. This soil is equivalent to the soil, which was used for the lysimeter study. The initial concentration in the soil was 0.067 mg as/kg dry soil, which corresponds roughly to a field application rate of 50 g as/ha (5 cm layer, bulk density of 1.5 kg/l). Incubation conditions were: aerobic by continous flow of air, in the dark, temperature maintained 20 ± 2 °C and a soil moisture of 40 % maximum water holding capacity (MWHC). The moisture content was checked periodically by weighing and

readjusted if necessary. A single soil sample was analysed on each sampling date: 0, 3, 7, 14, 31, 60, 90 and 122 days after treatment. Volatiles were trappd by continously washing the effluent gas with 0.5 m NaOH, H_2O, ethylene glycole and 0.5 M H_2SO_4. The soil samples were extracted consecutively three times with each of the solvents: methanole and methanole/water (1 : 1). Samples were centrifuged after each extraction and the extraction solution was filtrated from the soil. The radioactivity of the extracts was determined by LSC. Then the fractions were pooled, concentrated, redissolved and analysed by HPLC. The soil residues were combusted and the evolved $^{14}CO_2$ was determined by LSC.

Table B.8.1-4: Aerobic soil metabolism of [^{14}C-U-phenyl] tritosulfuron: Characterisation of the soil used

Soil,	Speyerer Wald
Origin	Schifferstadt, Germany
Characterisation (DIN classification, Germany)	clayed sand
Characterisation (USDA)	loamy sand
% sand (0.063 – 2 mm)	82
% silt (0.002 – 0.063 mm)	14
% clay (< 0.002 mm)	4
pH value ($CaCl_2$)	5.4
% organic carbon	0.8
Maximum water holding capacity [g H_2O/100g dry soil]	24
Field capacity [g H_2O/100g dry soil], 330 hPa	10
Cation exchange capacity [meq / 100 g]	8
Microbial biomass - beginning of study [mg C / 100 g soil]	13.1$^+$
Microbial biomass - end of study [mg C / 100 g soil]	not determined

$^+$ No information is available, when the micobial biomass was investigated

Findings:

The distribution of the radioactivity and the amounts of tritosulfuron and metabolites are given in Table B.8.1-5. The total recoveries for individual incubation ranged from 102.3 % on day 14 to 98.0 % on day 3 and 99.4 % of the applied radioactivity on day 122. There was no mineralisation of tritosulfuron to CO_2 or the formation of other volatile compounds during the incubation period. The non-extractable residues (bound residues) increased to 28.4 % TAR after 122 days.

The amount of tritosulfuron decreased from 94 % on day 0 to 1.4 % TAR during the incubation of 122 days. As major metabolites 635M01 and 635M02 are formed in maximum amounts of 56.4 % (day 60) and 13.7 % TAR (day 122), respectively.

Table B.8.1-5: Aerobic soil metabolism of [^{14}C-U-phenyl]-tritosulfuron: Recovery of radioactivity and distribution of active substance and metabolites [% of applied radioactivity], determined by HPLC analysis

DAT	tritosulfuron	635M01	635M02	635M03	others	bound residues	total
0	94.0	0.0	2.0	0.0	3.5	1.5	101.0
3	85.4	4.3	1.8	0.0	3.7	2.7	98.0
7	78.0	7.2	2.2	0.0	6.6	5.7	99.7
14	66.0	16.7	4.2	0.0	4.1	8.1	99.0
31	29.9	46.7	9.0	0.4	4.0	12.2	102.3
60	8.6	56.4	11.6	1.3	2.0	21.3	101.2
90	3.2	55.3	13.2	2.6	1.1	25.2	100.6
122	1.4	50.3	13.7	4.4	1.3	28.4	99.4

Comment:
The study is acceptable. The microbial activity of the soil was not checked at the end of the study.

Kellner, O. (1998c): Soil degradation rates of ^{14}C-BAS 635 H (including metabolites BH 635-2,-3,-4) under laboratory conditions. BASF RegDoc# 1998/10687; BOD 2001-487

Guidelines: BBA IV, 4-1; SETAC Europe 03/95

GLP: yes

Test system:
The aerobic soil metabolism of ^{14}C-tritosulfuron was investigated using [^{14}C-U-phenyl] labeled acitve substance (radiochemical purity 99.2 %; chemical purity 98.2 %, specific activity 9.6 MBq/mg) and four soils. The soils were sieved, air dried and passed through a 2 mm sieve prior use. The soil parameters are listed in Table B.8.1-6.
The initial concentration in the soil was 0.06 mg as/kg dry soil, which corresponds roughly to a field application rate of 50 g as/ha (5 cm layer, bulk density of 1.5 kg/l). Incubation conditions were: aerobic under static conditions, in the dark, temperature maintained 20 °C and a soil moisture of 40 % maximum water holding capacity (MWHC). Additionally, soil C was incubated under sterile conditions (20 °C, 40 % MWHC). The degradation rate of tritosulfuron was further investigated using soil C and following temperature and water content combinations: 20 °C and 20 % MWHC, 5 and 30 °C and 40 % MWHC. The moisture content was checked periodically by weighing and readjusted if necessary. A single soil sample was analysed on each sampling date: 0, 3, 7 or 8, 14, 28 or 29, 57 or 62 or 64, 90 or 91 or 92 and 118 or 121 days after treatment. Volatile compounds were not trapped and the amounts of bound residues were not determined. The soil samples were extracted consecutively three times with each of the solvents: dichloromethane, methanole and methanole/water (1 : 1). Samples were centrifuged after each extraction and the extraction solution was filtrated or decanted from the soil. The radioactivity of the extracts was determined by LSC. Then the fractions were pooled, concentrated, redissolved and analysed by HPLC.

Table B.8.1-6: Aerobic soil metabolism of [^{14}C-U-phenyl] tritosulfuron: Characterisation of the soils used

Soil,	Soil A	Soil B	Soil C	Soil D
Origin	Speyer, Germany	US soil	Limburgerh. Germany	Canadian soil
Characterisation (DIN classification, Germany)	clayed sand	clayed sand	loamy sand	not given
Characterisation (USDA)	sandy loam	sandy loam	sandy loam	sandy loam
% sand (0.063 – 2 mm)	76	80	53	44*
% silt (0.002 – 0.063 mm)	13	7	31	36*
% clay (< 0.002 mm)	11	12	16	20*
pH value ($CaCl_2$)	5.8	4.9	7.6	8.1
% organic carbon	1.8	0.6	2.0	3.9
MWHC [g H_2O/100g dry soil]	41	29	31	49
FC [g H_2O/100g dry soil], 330 hPa	15.4	9.2	22.2	43.2
CEC [meq / 100 g]	12.1	2.5	16.5	36.7
Microbial biomass - beginning of study [mg C / 100 g soil]	52.8^{+}	18.2^{+}	45.3/50.5^{+}	32^{+}
Microbial biomass - end of study [mg C / 100 g soil]	not determined	not determined	not determined	not determined

* USDA scheme (sand: 50 - 2000 µm, silt: 2 - 50 µm, clay: < 2 µm)
$^{+}$ No information is available, when the micobial biomass was investigated

Findings:
The amounts of tritosulfuron and metabolites [% of applied radioactivity] determined in the studies under 20 °C and 40 % MWHC are given in Table B.8.1-7. The tritosulfuron content in the soil decreased from 94.8 - 99.3 % on day 0 to 0.4 - 50.7 % TAR during the incubation of 118 - 120 days. As major metabolites the following compounds were formed in amounts > 10 %: 635M01 (6.4 - 55.4 % TAR, day 62 - 120), 635M03 (0.6 - 14.8 % TAR, day 118 - 120) and 635M02 (6.0 - 23.1 % TAR, day 90 - 120).
The results of the additional studies (sterile conditions, incubation conditions ≠ 20 °C and 40 % MWHC) are listed in Table B.8.1-8. The result under sterile conditions (Soil C) showed a clearly reduced degradation of tritosulfuron in comparison to the degradation under non-sterile conditions. After 120 days 85.5 % of the active substance remained in the sterile system but 10.3 % could be detected in the activated soil. The incubation temperature has a strong influence on the degradation rate tritosulfuron. Comparing the studies using the same water content (40 % MWHC), but different temperatures (5, 20 and 30 °C) the amount of active substance detected at the end of the studies was different: 5 °C: 85.3 % TAR, 20 C: 10.3 % TAR and 30 °C: 2.2 % TAR. Dry conditions (20 % MWHC) seemed to reduce the degradation of tritosulfuron. In this study 52.6 % TAR could be identified as tritosulforin after 121 days, while 10.3 % (day 120) could be detected in the study under 40 % MWHC.
The material balance or the amounts of CO_2 or volatile compounds formed are not given, because an open incubation system was used. The amounts of bound residues were not determined.

Table B.8.1-7: Aerobic soil metabolism of [^{14}C-U-phenyl]-tritosulfuron: Amounts of extractable radioactivity and of active substance and metabolites [% of applied radioactivity] in the studies at 20 °C and 40 % MWHC, determined by HPLC analysis

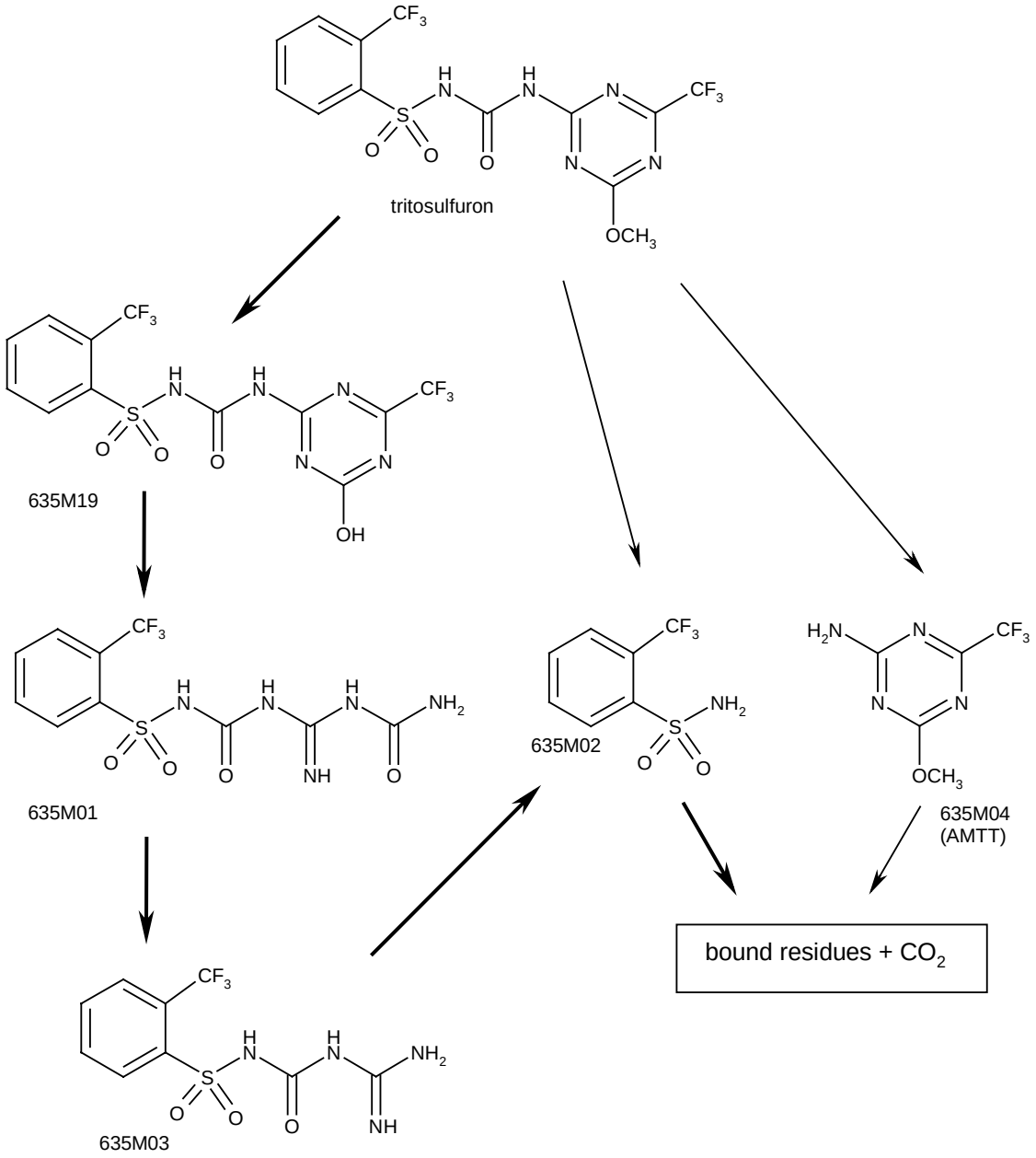
	DAT	tritosulfuron	635M01	635M02	635M03	sum extractables
Soil A	0	99.3	0.7	0.0	0.0	100.0
	3	88.3	5.1	0.0	0.0	93.4
	7	72.9	13.9	3.1	0.0	91.8
	14	51.7	27.8	6.8	0.5	86.9
	31	28.6	42.0	10.5	1.0	83.6
	63	5.8	47.5	14.2	2.3	70.5
	90	3.9	47.6	16.4	2.6	70.5
	119	0.4	42.7	17.6	4.5	65.6
Soil B	0	94.8	0.1	0.0	0.0	100.0
	3	85.9	5.4	1.9	0.0	94.8
	7	78.6	11.9	5.2	0.3	96.6
	14	50.3	28.4	8.1	0.3	91.4
	28	19.3	50.9	16.2	0.0	87.9
	62	2.3	55.4	20.0	0.9	81.0
	87	0.6	46.8	22.8	1.6	72.4
	118	0.4	43.1	23.1	2.4	69.0
Soil C	0	98.2	0.0	0.0	0.0	100.0
	3	91.8	0.9	0.6	0.0	94.9
	8	91.4	2.3	0.0	0.0	96.6
	14	79.8	3.9	1.2	0.0	88.1
	28	60.0	15.2	8.2	0.9	89.8
	64	31.6	22.9	15.5	6.3	81.4
	90	21.8	15.3	16.4	10.9	67.8
	121	10.3	19.3	9.2	14.8	62.7
Soil D	0	97.1	0.2	0.0	0.0	100.0
	7	81.2	0.6	0.0	0.0	86.0
	14	74.1	1.0	0.9	0.0	78.9
	28	68.9	1.7	1.9	0.0	73.7
	57	60.5	3.0	2.7	0.2	68.4
	90	51.8	5.3	4.4	0.3	63.2
	120	50.7	6.4	6.0	0.6	64.9

Table B.8.1-8: Aerobic soil metabolism of [^{14}C-U-phenyl]-tritosulfuron: Amounts of extractable radioactivity and of active substance and metabolites [% of applied radioactivity] in the studies under sterile conditions or ≠ 20 °C and 40 % MWHC, determined by HPLC analysis

	DAT	tritosulfuron	635M01	635M02	635M03	sum extractables
Soil C sterile	0	96.2	0.0	0.0	0.0	100.0
	3	92.0	0.0	0.0	2.2	98.2
	7	99.6	0.6	0.0	0.0	105.4
	14	101.7	1.8	0.0	0.0	107.1
	28	91.8	3.5	0.0	0.0	100.0
	57	85.5	6.3	0.0	0.5	96.4
	91	77.6	6.3	2.3	1.2	92.9
	118	85.5	6.7	1.2	2.4	101.8
Soil C 20 °C 20 % MWHC	0	100.0	0.0	0.0	0.0	100.0
	3	105.9	0.0	0.0	0.0	107.4
	8	107.3	0.5	0.0	0.0	109.3
	14	94.9	2.0	1.9	0.0	101.9
	28	90.3	2.6	2.6	0.5	100.0
	64	83.6	4.8	4.4	0.8	96.3
	90	46.9	11.4	6.3	4.0	81.5
	121	52.6	5.3	4.2	2.2	66.7
Soil C 5 °C 40 % MWHC	0	98.4	0.0	0.0	0.0	100.0
	3	88.7	0.0	1.6	0.0	94.5
	7	96.9	0.0	1.2	0.0	100.0
	14	96.7	0.0	0.9	0.0	100.0
	29	96.5	1.2	0.9	0.0	101.8
	62	91.7	1.9	1.0	0.0	100.0
	92	83.4	2.6	0.0	0.0	92.7
	121	85.3	3.9	0.8	0.7	98.2
Soil C 30 °C 40 % MWHC	0	98.4	0.0	0.0	0.0	100.0
	3	92.7	1.9	2.1	0.0	101.8
	7	83.3	5.3	1.8	1.0	98.2
	14	64.1	11.3	3.7	2.3	94.5
	29	51.2	12.6	7.8	6.1	87.3
	62	12.7	11.0	9.3	22.3	61.8
	92	4.1	5.8	12.8	27.7	54.5
	121	2.2	4.1	12.4	28.9	50.9

Comment:
The study is acceptable. The microbial activity of the soil was not checked at the end of the study.

Figure B.8.1-1: Proposed degradation pathway of tritosulfuron in soil under aerobic conditions



B.8.1.1.2 Soil photolysis

Venkatesh, K. and Trollinger, J. (1996a): Photolysis of ^{14}C-BAS 635 H (phenyl label) on soil. BASF RegDoc# 1996/5209; BOD 2001-488

Venkatesh, K. and Trollinger, J. (1996b): Photolysis of ^{14}C-BAS 635 H (triazin label) on soil. BASF RegDoc# 1996/5226; BOD 2001-489

Guidelines: US-EPA, Subdivision N, 161-3

GLP: yes

Test system:
The photolysis of ^{14}C-tritosulfuron in soil was investigated using [^{14}C-U-phenyl = ph] and [^{14}C-2,4-triazine = tr] labeled acitve substance (radiochemical purity 99.2 % and 99.4 %; chemical purity 98.2 and 98.3 %, specific activity 9.6 MBq/mg and 9.26 MBq/mg), respectively. The soil parameters are listed in Table B.8.1-9. The soil was sieved (2 mm) and 0.335 mg as/kg dry soil was applicated, which is equivalent to a field application rate of 50 g as/ha (1 cm layer, bulk density of 1.5 kg/l). The soil was weighed in aluminium dishes (0.01 x 0.08 m) forming a thin layer of 2 mm. Incubation conditions were: aerobic by continous flow of air, continuous irrigation in a Hanau Suntest CPU Model with a xenon lamp (> 290 nm, 765 W/m^3), temperature maintained 22 ± 1 °C and a soil moisture of 75 % field capacity (FC). The moisture content was checked daily by weighing and readjusted if necessary. Additionally, samples were kept in the dark at 22 ± 1 °C and a soil moisture of 75 % field capacity (FC). A single soil sample was analysed on each sampling date: 0, 3, 7, 10 and 15 days after treatment. Volatiles were trappd by continously washing the effluent gas with 2.0 M NaOH, ethylene glycole and 0.1 N H_2SO_4. At each sampling date aliquots of soil samples were combusted and the amount of the total radioactive residues was determined by LSC. The soil samples were extracted consecutively three times with each of the solvents: dichloromethane, methanol and methanol/water 1:1 by volume. Samples were centrifuged after each extraction and the extraction solution was decanted or filtrated from the soil. The radioactivity of the fractions were determined by LSC, then the relevant fractions were pooled. The extracts were concentrated, redissolved and analysed by TLC and HPLC. The remaining soil residues were combusted and the evolved $^{14}CO_2$ was determined by LSC. No further analysis was done on the bound residues since the % TAR remaining in the soil after extraction were less than 4.2 and 5.8 % in irradiated soil and 3 and 4.3 % in dark control soils in the studies with phenyl and triazine labelled substance, respectively.

Table B.8.1-9: Soil photolysis of [^{14}C-U-phenyl] and [^{14}C-2,4-triazine] tritosulfuron: Characterisation of the soil used

Soil,	Li 35 b
Origin	Limburgerhof, Germany
Characterisation (DIN classification, Germany)	loamy sand
Characterisation (USDA)	sand
% sand (0.063 – 2 mm)	88
% silt (0.002 – 0.063 mm)	7
% clay (< 0.002 mm)	5
pH value ($CaCl_2$)	6.4
% organic carbon	0.8
Maximum water holding capacity [g H_2O/100g dry soil]	27
Field capacity [g H_2O/100g dry soil], 330 hPa	8.6
Cation exchange capacity [meq / 100 g]	5.3
Microbial biomass - beginning of study [mg C / 100 g soil]	19.8$^+$
Microbial biomass - end of study [mg C / 100 g soil]	not determined

$^+$ Micobial biomass was determined two month before the study was started

Findings:
The distribution of the radioactivity and the amounts of tritosulfuron and metabolites are given in Table B.8.1-10 and Table B.8.1-11 determined in the studies with phenyl and triazine labelled substance, respectively.

The total recoveries for individual incubation ranged from 102.4 % on day 0 to 92.6 % on day 10 of the applied radioactivity (TAR) for the irradiated soil samples, treated with phenyl labelled substance. The dark control samples showed recoveries between 108.4 % TAR on 7 and 96.0 % TAR on day 10. The mass balance of the triazine label study ranged from 104.3 % (day 3) to 89.1 % (day 7) in the irradiated soil. The recoveries in the dark control samples laid between 101.0 % TAR (day 0) and 98.3 % TAR (day 10).
The mineralisation rates of tritosulfuron to CO_2 after 15 days were low for both labels and under irradiated and dark conditions (< 1 %). The formation of bound residues was comparable with and without irradiation. The maximum was between 2.9 and 5.8 %.
The degradation of tritosulfuron was only slightly accelerated in the studies under irradiation in comparison to the dark control studies. In the study with phenyl labelled substance 78 % TAR remained on day 15 as active substance, while 88.2 % TAR could be determined in the dark control study. Using triazine labelled substance the tritosulfuron amount on day 15 was 80.8 % determined under irradiation and 86.7 % TAR in dark control samples. The amounts and the structure of the metabolites formed are comparable in the studies under irradiation and in the dark. in the irradiated soil, the same metabolites were found as in the aerobic soil metabolism study or in the dark control samples of this study. No metabolite exceeded 6 % TAR a any sampling time.
These results indicate that tritosulfuron is photolytically stable and therefore, photolysis is not a major degradation pathway for the metabolism of tritosulfuron in the soil.

Table B.8.1-10: Soil photolysis of ^{14}C[Phenyl] tritosulfuron: Recovery of radioactivity and distribution of active substance and metabolites [% of applied radioactivity], determined by HPLC analysis

DAT	CO_2	tritosulfuron	635M01	635M02	others	bound residues	total
irradiation							
0	0.0	98.7	0.4	1.1	1.7	0.5	102.4
3	0.2	90.8	0.3	2.1	2.1	2.9	98.4
7	0.3	80.3	1.1	2.8	4.4	4.1	93.0
10	0.5	79.5	1.1	3.7	4.8	3.0	92.6
15	0.6	78.0	3.2	3.2	7.6	2.9	95.7
dark control							
0	0.0	98.7	0.4	1.1	1.7	0.5	102.4
3	0.0	92.6	1.5	2.0	4.5	1.2	101.7
7	0.1	98.4	0.9	1.9	4.4	2.6	108.4
10	0.1	87.4	1.7	1.4	3.1	2.3	96.0
15	0.0	88.2	1.9	2.8	4.2	2.9	100.1

Table B.8.1-11: Soil photolysis of ^{14}C[Triazine]-tritosulfuron: Recovery of radioactivity and distribution of active substance and metabolites [% of applied radioactivity], determined by HPLC analysis

DAT	CO_2	tritosulfuron	635M01	635M04 (AMTT)	others	bound residues	total
irradiation							
0	0.0	94.4	0.3	2.3	3.5	0.4	101.0
3	0.0	86.7	0.8	5.1	5.8	5.8	104.3
7	0.0	77.0	1.0	5.8	3.9	1.3	89.1
10	0.1	87.9	0.2	4.6	1.0	3.2	96.9
15	0.0	80.6	1.1	4.6	4.0	4.9	95.2
dark control							
0	0.0	94.4	0.3	2.3	3.5	0.4	101.0
3	0.3	88.9	1.0	2.6	3.8	2.0	98.7
7	0.1	89.0	1.3	2.4	2.6	4.3	99.6
10	0.1	87.4	1.3	2.6	4.3	2.7	98.3
15	0.1	86.7	1.4	2.4	4.8	3.3	98.6

Comment:
The study is acceptable.

B.8.1.1.3 Anaerobic degradation

Kellner, O. (1998d): The anaerobic soil metabolism of BAS 635 H (^{14}C-phenyl). BASF RegDoc# 1998/10891; BOD 2001-490

Kellner, O. (1998e): The anaerobic soil metabolism of BAS 635 H (^{14}C-triazine). BASF RegDoc# 1998/10893; BOD 2001-491

Guidelines: BBA IV, 4-1; SETAC Europe

GLP: yes

Test system:
The degradation of ^{14}C-tritosulfuron in soil under anaerobic conditions was investigated using [^{14}C-U-phenyl = ph] and [^{14}C-2,4-triazine = tr] labeled acitve substance (radiochemical purity 99.2 % and 99.2 %; chemical purity 98.2 % and 99.9 %, specific activity 9.6 MBq/mg and 2.55 MBq/mg), respectively. The soil parameters are listed in Table B.8.1-12. The soil was sieved (2 mm) and a water content of 75 % FC was established in the soil samples. The soil was flooded with water (50 ml water on 100 g soil) preincubated for 28 days under anaerobic conditions. The incubator was continuously purged with moistened nitrogen and then 0.1 mg as/kg dry soil was applicated, which is equivalent to a field application rate of 75 g as/ha (5 cm layer, bulk density of 1.5 kg/l). The samples were kept in the dark at 20 ± 1 °C. Volatiles were trappd by continuously washing the effluent gas with 0.5 M NaOH, ethylene glycole and 0.5 M H_2SO_4. A single soil sample was analysed on each sampling date: 0, 7, 14, 28, 62, 90 or 92 and 120 days after treatment. The soil samples were extracted consecutively three times with each of the solvents: acetonitrile/water (1 : 1, v/v), and acetonitrile. The extraction solution was decanted or filtrated from the soil. The radioactivity of the fractions

were determined by LSC, then the relevant fractions were pooled. The extracts were concentrated, redissolved and analysed by TLC and HPLC. The remaining soil residues were combusted and the evolved $^{14}CO_2$ was determined by LSC. No further analysis was done on the bound residues since the % TAR remaining in the soil after extraction were less than 10 % TAR.

Table B.8.1-12: Anaerobic degradation of ^{14}C-tritosulfuron in soil: Characterisation of the soils used

	^{14}C-Phenyl	^{14}C-Triazine
Soil,	Li 35 b	
Origin	Limburgerhof, Germany	
Characterisation (DIN classification, Germany)	loamy sand	
Characterisation (USDA)	loamy sand	
% sand (0.063 – 2 mm)	84	82
% silt (0.002 – 0.063 mm)	8	10
% clay (< 0.002 mm)	8	8
pH value ($CaCl_2$)	6.5	6.5
% organic carbon	0.9	1.0
Maximum water holding capacity [g H_2O/100g dry soil]	31	30
Field capacity [g H_2O/100 g dry soil], 330 hPa	7.9	9.5
Cation exchange capacity [meq / 100 g]	6.0	3.6
Microbial biomass - beginning of study [mg C / 100 g soil]	14.4	32.0
Microbial biomass - end of study [mg C / 100 g soil]	20.1	18.2

Findings:
The distribution of the radioactivity and the amounts of tritosulfuron and metabolites are given in Table B.8.1-13. The total recoveries for individual incubation ranged from 102.1 % on day 14, 28 and 90 to 97.9 % on day 62 and 99.0 % of the applied radioactivity (TAR) on day 120 for the phenyl label. The mass balance of the triazine label ranged from 100 % (day 0 and 14) to 91.9 % (day 62) and 97 % TAR on day 120. There was no mineralisation of tritosulfuron to CO_2 during the 120 days of incubation (ph and tr label). Non-extractable residues (bound residues) increased to 6.2 and 6.1 % TAR with the phenyl label and triazine label, respectively.
The amount of tritosulfuron decreased from 98.7 % (ph) and 88.3 % (tr) on day 0 to 32.5 (ph) and 23.8 (tr) % TAR during the incubation of 120 days. Two major metabolites are formed: 635M01 in maximum amounts of 37.3 % TAR (ph) and 52.7 % TAR (tr) on day 120 and 635M19 in maximum amounts of 12.9 % (ph, day 120) and 16.0 % TAR (tr, day 26). Metabolite 635M02 was only detectable in the study with phenyl labelled substance and reached maximum amounts of 5.6 % TAR on day 120. The sum of non-identified degradation productions reached 6.9 % TAR (day 28) and 10.1 % TAR (day 92) in the phenyl and triazine study, respectively.
It is assumed that the first degradation step is the demethylation at the triazine ring to the corresponding hydroxy triazine (= metabolite 635M19), followed by a cleavage of the triazine ring, which results in the formation of the metabolite 635M01. Further degradation steps (hydrolysis) lead to the formation of 635M02 (“sulfonamide”).
The results indicate that tritosulfuron is anaerobically degradable, but the mineralisation under anaerobic conditions is negligible.

Table B.8.1-13: Anaerobic soil metabolism of [^{14}C-U-phenyl] and [^{14}C-2,4-triazine]-tritosulfuron: Recovery of radioactivity and distribution of active substance and metabolites [% of applied radioactivity], determined by HPLC analysis

DAT	CO_2	tritosulfuron	635M19	635M01	635M02	others	bound residues	total
phenyl-label								
0	0.0	98.7	0.0	0.0	1.3	0.0	0.0	100.0
7	0.0	97.3	0.0	0.0	1.6	0.1	1.0	101.0
14	0.0	96.3	3.7	0.0	0.0	0.0	1.0	102.1
28	0.0	84.6	3.2	2.5	1.8	6.9	2.1	102.1
62	0.0	71.1	8.6	12.5	2.4	1.3	2.1	97.9
90	0.0	58.4	9.1	24.6	3.3	2.5	3.1	102.1
120	0.0	32.5	12.9	37.3	5.6	3.5	6.2	99.0
triazine label								
0	0.0	88.3	9.7	0.0	-	0.0	1.0	100.0
7	0.0	78.5	11.5	1.0	-	1.9	2.0	96.0
14	0.0	79.7	7.2	1.7	-	6.3	4.0	100.0
28	0.0	69.1	16.0	5.5	-	4.3	3.0	99.0
62	0.0	59.7	11.3	17.9	-	0.0	3.0	91.9
92	0.0	26.9	13.7	39.2	-	10.1	4.0	93.9
120	0.0	23.8	13.4	52.7	-	0.0	6.1	97.0

Comment:
The study is acceptable.

B.8.1.2 Rate of degradation

B.8.1.2.1 Laboratory studies

The test systems for these studies are already described under section B.8.1.1. Tritosulfuron was applied to soils and incubated for periods up to 358 days. Additionally to the common study under 20 °C and 40 % MWHC, one soil type Bruch West (study: Kellner, O. (1998c), BASF RegDoc# 1998/10687) was incubated at lower and higher temperature (5 °C, 30 °C), at a lower soil moisture (20 % MWHC) and after soil sterilisation. Because the acknowledged stand of technology for the calculation of degradation rates changed after termination of the studies, some degradation rates for tritosulfuron were recalculated in additional reports. The tools used for calculation were basically the standard methods by Timme&Frehse. Additionally, the TOPFIT pharmacokinetic analysis system (G. Heinzel et al.: TOPFIT Version 2.0; Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC, Gustav Fischer Verlag, Stuttgart-Jena-New York 1993) or ModelMaker (Version 3, Cherwell Scientific Publishing Ltd. Oxford, United Kingdom; Andrew Walker) were used. In the respective tables the mathematical models are indicated.
In the following, details are given about the models used for the calculation reported in the studies mentioned above. A summary of the DT_{50} and DT_{90} values of tritosulfuron and metabolites calculated from the laboratory studie are given in Table B.8.1-14 and Table B.8.1-15, respectively.

Kellner, O. (1998a): The aerobic soil metabolism of BAS 635 H (^{14}C-phenyl). BASF RegDoc# 1998/10619; BOD 2001-484

Kellner, O. (1997): The aerobic soil metabolism of BAS 635 H (^{14}C-triazine). BASF RegDoc# 1997/11242; BOD 2001-486

Kellner, O. (1998b): Estimation of the transformation coefficients of BAS 635 H, BH 635-2, BH 635-3, BH 635-4 and BH 635-5 during aerobic soil metabolism of ^{14}C-BAS 635 H (phenyl and triazine label). BASF RegDoc# 1998/10662; BOD 2001-495

Gottesbüren, B. and Platz, K. (1998): Estimation of the transformation coefficients of BAS 635 H during aerobic metabolism in soil. BASF RegDoc# 1998/10617; BOD 2001-494

Guidelines: BBA IV, 4-1; USA-EPA, Subdivision, 162-1

GLP: yes

Test system:
The test systems of the degradation study with phenyl and triazine labeled tritosulfuron were described in B.8.1.1.1.
The DT_{50} values of the active substance (phenyl and triazine label) were calculated by using the Timme & Frehse program (Kellner, O., 1998a and 1997). The transformation coefficients of tritosulfuron and the metabolites (phenyl and triazine label) were estimated by using the program TOPFIT, version 2.0 (Kellner, O., 1998b). A multi compartment was used to describe the degradation pathways, considering 1st order kinetics. In this model tritosulfuron (triazine label) was degradaded to 635M01 or 635M04. 635M01 reacts to 635M03. The data of the study conducted with phenyl labeled substance was described by a compartment model considering the degradation of tritosufuron to 635M01. This metabolite could form 635M03 or 635M02. Metabolite 635M03 could form 635M02. In both compartment models the active substance and all metabolites mentioned could form the compartment "others". A further calculation of the transformations coefficients using the data of the study with triazine labelled substance was conducted with the program Modelmaker, version 3.03 (Gottesbüren, B. and Platz, K., 1998). The compartment model used was comparable with the TOPFIT model, which was built for the study with triazine labeled substance.

Findings:
DT_{50} and DT_{90} values of tritosulfuron and metabolites are given in Table B.8.1-14 and Table B.8.1-15, respectively.

Comment:
The studies are acceptable, except the DT_{50} value calculation of metabolite 635M03 of the degradation studie with [^{14}C-triazine] labeled tritosulfuron. In the calculations of Gottesbüren, and Platz (1998) it was not considered, that the amount of 635M03 in % of applied radioactivity have to be multiplicated by factor 2 to obtain the total amount of this metabolite.

Staudenmaier, H. and Lehmann, C. (1999): Degradation behaviour of BAS 635 H in lysimeter soil. BASF RegDoc# 1999/11823; BOD 2001-485

Guidelines: BBA IV, 4-1; SETAC Europe

GLP: yes

Test system:
The test system of the degradation study with phenyl labeled tritosulfuron in one soil (Speyerer Wald) was described in B.8.1.1.1.
The determination of the transformations coefficients of tritosulfuron and metabolite 635M01 were conducted with the program Modelmaker, version 3.03. A multi compartment was used to describe the degradation pathways, considering 1st order kinetics. In the compartment model tritosulfuron was degraded to an intermediate compartment and directly to an elimination compartment. Metabolite 635M01 was formed from the intermediate compartment and degraded into the elimination compartment.

Findings:
DT_{50} and DT_{90} values of tritosulfuron and metabolite 635M01 are given in Table B.8.1-14 and Table B.8.1-15, respectively.

Comment:
The study is acceptable.

Kellner, O. (1998c): Soil degradation rates of ^{14}C-BAS 635 H (including metabolites BH 635-2,-3,-4) under laboratory conditions. BASF RegDoc# 1998/10687; BOD 2001-487

Kellner, O. (2001c): Amendment No. 1 fo final report: Soil degradation rates of ^{14}C-BAS 635 H (including metabolites BH 635-2,-3,-4) under laboratory conditions. BASF RegDoc# 2001/1008970; BOD 2001-487

Guidelines: BBA IV, 4-1; SETAC Europe

GLP: yes

Test system:
The test system of the degradation study with phenyl labeled tritosulfuron in four soils, including the degradation in one soil under different temperatures and water contents was described in B.8.1.1.1.
The DT_{50} values of the active substance (phenyl label) were calculated by using the Timme & Frehse program (Kellner, O., 1998c and 2000c). The degradation rates of tritosulfuron and metabolites (635M01, 635M02 and 635M03) were estimated with TOPFIT. A multi compartment was used to describe the degradation pathways, considering 1st order kinetics. In this model tritosufuron was degraded to 635M01. This metabolite could form 635M02 or 635M03. Metabolite 635M03 could form 635M02. The active substance and all metabolites mentioned could form the compartment “others”.

Findings:
DT_{50} and DT_{90} values of tritosulfuron and metabolites are given in Table B.8.1-14 and Table B.8.1-15 , respectively.

Comment:
The studies are acceptable.

Gottesbüren, B. (2001): Calculation of the DT_{50}-values of BAS 635 H at 10°C derived from DT_{50}-values at 20°C. BASF RegDoc# 2001/1008965; BOD 2001-499

Guidelines: None

GLP: No, not subject of GLP regulations

Test system:
The DT_{50} values at 20 °C obtained from the laboratory studies with tritosulfuron were used to extrapolate the degradation behaviour of the active substance at 10 °C. Additionally, the results of field studies were considered to calculate DT_{50} values at 10 °C. In a first step the degradation curves of the field studies were used to derive DT_{50} values under standard conditions (20 °C), see chapter B.8.1.2.2.
The Arrhenius law was used to calculate the DT_{50} values at 10 °C. An activation energy of 54 kJ mol^{-1} (= Q_{10}-value of 2.2) was used for the calculations.

Findings:
The DT_{50}-values for tritosulfuron under standard incubation conditions in the European soils (20 °C, 40 % MWC) were in the range of 13 – 56 days (see Table B.8.1-14), calculated by using the TOPFIT pharmacokinetic analysis system (G. Heinzel et al.: TOPFIT Version 2.0; Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC, Gustav Fischer Verlag, Stuttgart-Jena-New York 1993) or Modelmaker (Version 3, Cherwell Scientific Publishing Ltd. Oxford, United Kingdom; Andrew Walker). The half-life values of tritosulfuron obtained from field studies and recalculated to a reference temperature of 20 °C range from 2.6 to 32.7 days.
Taken the laboratory studies the derived half life values of tritosulfuron at 10 °C range from 41.6 to 271.4 days, with a median value of 58.4 d. Using the standardised values from the field studies the derived half life values of tritosulfuron at 10 °C range from 5.7 to 71.6 days, with an arithmetic mean and a median value of 30.9 d and of 18.4 d, respectively.

Comment:
The calculation is acceptable.

<u>Anaerobic degradation studies</u>
Kellner, O. (1998d): The anaerobic soil metabolism of BAS 635 H (^{14}C-phenyl). BASF RegDoc# 1998/10891; BOD 2001-490

Kellner, O. (1998e): The anaerobic soil metabolism of BAS 635 H (^{14}C-triazine). BASF RegDoc# 1998/10893; BOD 2001-491

Kellner, O. (2001b): Amendment No. 1 to final report: The anaerobic soil metabolism of BAS 635 H (^{14}C-phenyl). BASF RegDoc# 2001/1008969; BOD 2001-490

Kellner, O. (2001a): Amendment No. 1 to final report: The anaerobic soil metabolism of BAS 635 H (^{14}C-triazine). BASF RegDoc# 2001/1008968; BOD 2001-491

Guidelines: BBA IV, 4-1; SETAC

GLP: yes

Test system:
The test system of the degradation study with phenyl and triazine labeled tritosulfuron in one soil was described in B.8.1.1.1.
The DT_{50} values of the active substance were calculated by using the Timme & Frehse program.

Findings:
The best fit for the Timme & Frehse evaluation was a first order calculation with a DT_{50} of 61 and 82 days for [^{14}C-triazine] and [^{14}C-phenyl] tritosulfuron, respectively.

Comment:
The studies are acceptable.

Summary of the dissipation studies in the laboratory
Tritosulfuron
The degradation rates for tritosulfuron in various soils and under different incubation conditions are shown in Table B.8.1-14.
The DT_{50}-values for tritosulfuron under standard incubation conditions (20 °C, 40 % MWHC) were in the range of 16 – 56 days, in one soil the DT_{50} was 124 days. Lower soil moisture decreased the degradation rate, whereas elevated temperature increased it. At cold temperatures (5 °C) and under sterile conditions, almost no degradation took place, most likely due to the reduced soil microbial activity under these conditions. Photolysis does not have a strong influence on the disappearance time. Because the incubation lasted only for 15 days, the degradation rates were not calculated from these experiments.
DT_{50}-values of tritosulfuron at 10 °C were deducted from available half-lives at 20 °C from laboratory studies and from field studies (half-lives standardised to 20 °C) using the Arrhenius-approach as recommended by FOCUS workgroups.
Taken the laboratory studies the derived half life values of tritosulfuron at 10 °C range from 41.6 to 271.4 days, with a median value of 58.4 d.
Even under anaerobic soil conditions the degradation of tritosulfuron showed moderate values with 61 and 82 days.
Soil photolysis is no significant degradation pathway, therefore, the degradation rates were not calculated from these experiments.

Metabolites
The DT_{50}-values of the metabolites are calculated from data obtained from the studies with the active substance. They are shown in Table B.8.1-15.
For metabolite 635M01 DT_{50} values (20 °C/40 % MWHC) between 23 and 184 days have been calculated from studies with tritosulfuron. Metabolite 365M02 showed half-life values 28 and 96 days under standard conditions. The degradation rates of metabolite 635M03

estimated from studies with triosulfuron showed a wide range (32 - 347 days). The DT_{50} value of Metabolite 635M04 (AMTT) could only be determined in one study with tritosulfuron. The calculated half-life was 98 days.

Table B.8.1-14: DT_{50}/DT_{90}-values (1st order kinetic) for tritosulfuron in laboratory soil studies. The r^2 value (if available) is given in brackets

BASF DocID	label	soil	incu-bation [days]	temp. [°C]	moisture [% MWC]	DT_{50} TF [days]	DT_{90} TF [days]	DT_{50} MM [days]	DT_{90} MM [days]	DT_{50} TOP [days]
aerobic soil metabolism										
1998/10619 (1998/10662)	phenyl	Li35b	358	20	40	21 (0.982)	69	-	-	31 (0.992)
1997/11242 (1998/10662) (1998/10617)	triazine	Li35b	358	20	40	50 (0.912)	166	34	114	32 (0.997)
aerobic soil degradation										
1998/10687	phenyl	Lufa 2.2	119	20	40	16 (0.997)	53	-	-	20 (0.993)
		US-soil	118	20	40	13 (0.969)	45	-	-	19 (0.979)
		Bruch West	120	20	40	38 (0.994)	126	-	-	56 (0.984)
		Canadian	120	20	40	141 (0.857)	n.c.	-	-	124 (0.970)
		Bruch West	121	20	**20**	108 (0.881)	n.c.	-	-	168 (0.988)
			121	**30**	40	21 (0.985)	70	-	-	33 (0.986)
1999/11823	phenyl	Speyerer W.	122	20	40	-	-	20	66	
anaerobic soil metabolism										
1998/10891	phenyl	Li35b	120	20	flooded	82	273	-	-	-
1998/10893	triazine	Li35b	120	20	flooded	61	204	-	-	-

n.c. not calculated (degradation time > twofold of study duration)
TF = calculated with Timme & Frehse , 1. Order
TOP = calculated with TOPFIT
MM = calculated with Modelmaker

Table B.8.1-15: DT_{50}/DT_{90} values (1st order kinetic) of tritosulfuron soil metabolites in laboratory studies (incubation conditions 20 °C and 40 % MWHC if not stated otherwise). The r^2 value (if available) is given in brackets

metabolite	BASF RegDoc#	study	label	soil	maximum % TAR	DT_{50} MM [days]	DT_{90} MM [days]	DT_{50} TOP [days]
635M01	1998/10687	Rate study	Phenyl	LUFA 2.2	47.6	-	-	65 (0.979)
				US-soil	55.4	-	-	59 (0.979)
				Bruch West	22.9	-	-	23 (0.886)
				Canadian	6.4	-	-	44 (0.922)
				LUFA 2.2; 20 % MWHC	11.4	-	-	20 (0.797)
				LUFA 2.2; 30 °C	12.6	-	-	13 (0.979)
	1999/11823	Rate study with lysimeter soil	Phenyl	Speyerer soil	56.4	115	n.c.	-
	1998/10619 1998/10662	Aerobic soil metabolism	Phenyl	Li35b	40.3	-	-	110 (0.980)
	1997/11242 1998/10662 1998/10617	Aerobic soil metabolism	Triazine	Li35b	40.9	174	577	184 (0.987)

metabolite	BASF RegDoc#	study	label	soil	maximum % TAR	DT_{50} MM [days]	DT_{90} MM [days]	DT_{50} TOP [days]
635M02	1998/10687	Rate study	Phenyl	LUFA 2.2	17.6	-	-	37 (0.951)
				US-soil	23.1	-	-	44 (0.924)
				Bruch West	16.4	-	-	28 (0.932)
				Canadian	6.0	-	-	n.c.
				LUFA 2.2; 20 % MWHC	6.3	-	-	22 (0.940)
				LUFA 2.2; 30 °C	12.8	-	-	70 (0.962)
	1998/10619 1998/10662	Aerobic soil metabolism	Phenyl	Li35b	11.1	-	-	96 (0.900)
635M03	1998/10687	Rate study	Phenyl	LUFA 2.2	4.5	-	-	203 (0.976)
				US-soil	2.4	-	-	32 (0.893)
				Bruch West	14.8	-	-	n.c.
				Canadian	0.6	-	-	n.c.
				LUFA 2.2; 20 % MWHC	4.0	-	-	63 (0.819)
				LUFA 2.2; 30 °C	28.9	-	-	n.c.
	1998/10619 1998/10662	Aerobic soil metabolism	Phenyl	Li35b	13.9	-	-	347* (0.977)
	1997/11242 1998/10662 1998/10617	Aerobic soil metabolism	Triazine	Li35b	14.0	737*	-	n.c.
635M04 (AMTT)	1997/11242 1998/10662 1998/10617	Aerobic soil metabolism	Triazine	Li35b	6.3	97	323	98 (0.962)

* DT_{50} values calculated exceeded two times of the study period, these values are uncertain
MWHC maximum water holding capacity
n.c. not calculated, no parameter estimation possible
TAR total applied radioactivity
TOP calculated with TOPFIT
MM calculated with Modelmaker

B.8.1.2.2 Field studies

Kellner, O. and Keller, W. (1998): Examination of soil dissipation of BAS 635 H (271 272) under field conditions after treatment with formulation BAS 639 00 H. BASF RegDoc# 1998/11244; BOD 2001-500

Kellner, O. and Richter, T. (1998): Field soil dissipation of BAS 635 H (271 272) in formulation BAS 639 00 H. BASF RegDoc# 2000/1013301; BOD 2001-501

Guidelines: BBA IV, 4-1, SETAC Europe, IVA-Guideline for residue chemistry

GLP: yes

Test system:
Two field soil dissipation studies have been performed in Europe to investigate the degradation and dissipation of tritosulfuron in soil and to determine the concentrations of the metabolites 635M01, 635M02, 635M03 and 635M04 (= AMTT). 635M04 (= AMTT) was only analysed in 3 trials (Spain and Sweden). In total, 6 trials were conducted: 3 trials at locations in Germany, 2 trials in Spain and 1 trial in Sweden. The six locations were distributed over Northern, Central and Southern Europe. A range of soils with organic carbon

contents from 0.6 to 1.6 % with a pH range from 5.0 to 7.7 was covered. The geographical distribution of the trial locations and the soil parameters of the fields are given in Table B.8.1-16.

The trials were performed using the formulated product BAS 639 00 H, which contain tritosulfuron and bentazone. It was applied as a homogenous spray mixture with a single nominal application rate of 100 g tritosulfuron/ha. This application rate was about twice the recommended application rate for the use in crops. The formulated product was always broadcast sprayed onto non-cropped (bare) soil with knapsack sprayers and an attached sprayboom. Recoveries were determined by using the tritosulfuron concentration found in soil cores sampled directly after the application. Additionally, in the studies in year 1997, petri dishes filled with 50 g soil were placed on the field before the application. Immediately after application the dishes were closed and analysed. Samples (soil cores) were taken up to about 1 year after application with 7 samplings.

The soil cores were analysed with various BASF methods. The trials starting in 1996 were first analysed with BASF method no. 390, a common moiety method for tritosulfuron. In method 390 soil was extracted with water : methanole (1 : 1). The extracts are reduced to aqueous phases and acidified up to a H_2SO_4 concentration of 0.5 mol/l. These solutions are then refluxed for 30 min. At this hydrolysis step tritosulfuron and its metabolites metabolites split off metabolite 635M02, which was extracted by DCM-ethyl acetate and determined by GC. All samples with detectable residues were thereafter analysed with BASF method 406, a specific method for tritosulfuron and the metabolites 635M01, 635M02 and 635M03. In this method soil was extracted with acetonitrile : water (8 : 2), then the extract was filtered and reduced to the aqueous phase. A pH of 6 was adjusted and the extracts were measured by HPLC/MS/MS. For the determination of 635M02 aqueous extracts are phased partitioned into dichloromethane, concentrated, cleaned (silica gel column) and analysed by GC/MS. The trials starting in 1997 were analysed with BASF method 406 as described above and, additionally, with BAS method 988 to determine residues of the soil metabolite 635M04 (AMTT). In method 988 soil was extracted with acetonitrile : water (8 : 2), then the extract was filtered, reduced to the aqueous phase and analysed by HPLC/MS/MS. Although the standard storage time for 635M04 (AMTT) was exceeded it can be concluded that 635M04 (AMTT) was stable for the time period of storage (see chapter B.8.1.2.3).

DT_{50} values of tritosulfuron and metabolites were calculated by using different compartment models which were established with the program Modelmaker. Additionally, the DT_{50} values of tritosulfuron in two field studies in Germany were calculated with the Timme & Frehse program (best fit: 1st order kinetics).

Table B.8.1-16: Characterisation of fields in field soil dissipation studies with tritosulfuron in Europe

Reference BASF DocID#	trial no.	location (postal code)	soil type	soil properties % C_{org}	pH
1998/11244	D05/04/96	Germany, Großharrie (24625)	loamy sand	1.1	6.2
1998/11244	DU2/06/96	Germany, Niederhofen (74193)	silty loamy sand	1.2	5.0
1998/11244	DU3/02/96	Germany, Meckenheim (67149)	loamy sand	0.6	5.6
2000/1013301	ALO/11/97	Spain, Manzanilla (21890)	loamy sand	0.6	7.7
2000/1013301	ALO/12/97	Spain, Utrera (41710)	loamy sand	0.5	7.7
2000/1013301	HUS/11/97	Sweden, Bjärred (23791)	silty sand	1.6	5.6

Findings:
The applied product, the nominal application rates and the verified recoveries are given in Table B.8.1-17. When excluding trial D05/04/96 (recovery 40 %), the mean recovery value is 84 %.
All trials show that tritosulfuron degrades fast. Furthermore, tritosulfuron does not show a significant tendency to move into deeper layers of soil in amounts measurable by the soil method. It was mostly detected in the top 10 cm soil layer. In all trials the tritosulfuron concentration were lower than the detection limit of 1 µg/kg in the soil layer 25 - 50 cm or deeper, with the exception of one sampling date in trial in Spain (ALO/12/27): a concentration of 1.0 µg/kg was detected 30 days after application in the 25 - 50 soil layer. The concentrations of tritosulfuron and metabolites determined in the soils of the trials are given in Table B.8.1-18 - Table B.8.1-23.
635M03 was found in all trials only in minor amounts and sporadically. Therefore no degradation rate could be calculated. 635M01 and 635M02 were the major metabolites in soil and show that the major degradation pathway in soil is the opening of the triazine ring. The presence of 635M04 (AMTT) indicates that the breaking of the sulfonylurea bridge between the triazine and the phenylring is a minor pathway. The concentrations of 635M04 (AMTT) were low.
The transformation parameters of tritosulfuron and metabolites presented here were estimated with the mathematical program Modelmaker (A. Walker, N. Crout 1997: Modelmaker User Manual, Version 3.03/3.0.4, Cherwell Scientifc Publishing Limited, Oxford). The DT_{50} and DT_{90}-values were determined by the use of compartment models. They are summarised in Table B.8.1-24. The residue values of trial D05/04/96 (Germany, Großharrie) could not be calculated, because the results of the first samples fluctuated too much. Nevertheless, tritosulfuron could only be detected up to 105 days in this trial.
The DT_{50}-values of tritosulfuron were consistently between 11 and 21 days and the DT_{90}-values were between 37 and 77 days. The residue values of trial D05/04/96 could not be calculated, because the results of the first samples fluctuated too much. Nevertheless, tritosulfuron could only be detected up to 105 days in this trial. Therefore, the degradation behaviour of tritosulfuron is sufficiently characterised by the field soil dissipation studies. No additional soil accumulation studies are required. The metabolites 635M01 and 635M02 were significantly more stable than the as tritosulfuron. For 635M03 no calculation was possible, because it was only found sporadically in very low amounts. For 635M04 (AMTT) only in 2 trials values could be calculated. The values varied much between the 2 trials.

Table B.8.1-17: Application rate verification for tritosulfuron in field soil dissipation studies

Reference BASF Reg.Doc.#	trial no.	formulation	target rate [g as/ha]	recovery [% of applied amount]
1998/11244	D05/04/96	BAS 639 00 H	100	40
1998/11244	DU2/06/96	BAS 639 00 H	100	80
1998/11244	DU3/02/96	BAS 639 00 H	100	84
2000/1013301	ALO/11/97	BAS 639 00 H	100	91
2000/1013301	ALO/12/97	BAS 639 00 H	100	92
2000/1013301	HUS/11/97	BAS 639 00 H	100	74

Table B.8.1-18: Field soil dissipation results from trial in Germany (trial D05/04/96): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M01	635M02	635M03	635M04
0 – 10	0	0.0263	0.0016	0.0052	0.0063	n. a.
0 – 10	14	0.0220	0.002	0.0064	0.0066	n. a.
0 – 10	30	0.0255	0.0061	0.0084	0.0085	n. a.
10 – 25	30	0.0068	0.0018	0.0045	0.0072	n. a.
0 – 10	64	0.0047	0.0094	0.0106	0.0073	n. a.
10 – 25	64	< d. l.	0.0028	0.0054	0.0079	n. a.
0 – 10	105	0.0015	0.0102	0.0091	< d. l.	n. a.
10 – 25	105	< d. l.	0.0019	0.0013	< d. l.	n. a.
0 – 10	177	< d. l.	0.0102	0.0076	< d. l.	n. a.
0 – 10	352	< d. l.	0.0054	0.0027	< d. l.	n. a.
10 – 25	352	< d. l.	0.0036	0.0026	< d. l.	n. a.
25 – 50	352	< d. l.	< d. l.	< d. l.	< d. l.	n. a.

Table B.8.1-19: Field soil dissipation results from trial in Germany (trial DU2/06/96): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M02	635M03	635M01	635M04
0 – 10	0	0.0532	0.0019	< d. l.	0.0032	n. a.
10 – 25	0	0.0011	< d. l.	< d. l.	< d. l.	n. a.
0 – 10	14	0.0251	0.0081	0.0012	0.0085	n. a.
0 – 10	32	0.0119	0.0087	0.0010	0.0124	n. a.
10 – 25	32	0.0019	< d. l.	< d. l.	< d. l.	n. a.
0 – 10	62	0.0014	0.0101	0.0016	0.0167	n. a.
10 – 25	62	< d. l.	< d. l.	< d. l.	0.0028	n. a.
0 – 10	95	< d. l.	0.0069	0.0011	0.0142	n. a.
10 – 25	95	< d. l.	< d. l.	< d. l.	0.0027	n. a.
0 – 10	176	< d. l.	0.0043	0.0012	0.0087	n. a.
10 – 25	176	< d. l.	< d. l.	< d. l.	0.0020	n. a.
0 – 10	354	< d. l.	< d. l.	< d. l.	0.0014	n. a.
10 – 25	354	< d. l.	0.0015	< d. l.	0.0062	n. a.
25 – 50	354	< d. l.	< d. l.	< d. l.	< d. l.	n. a.

Table B.8.1-20: Field soil dissipation results from trial in Germany (trial DU3/02/96): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M02	635M03	635M01	635M04
0 – 10	0	0.0546	< d. l.	< d. l.	< d. l.	n. a.
10 – 25	0	0.0016	< d. l.	< d. l.	< d. l.	n. a.
0 – 10	14	0.0328	0.0016	< d. l.	0.0039	n. a.
10 – 25	14	0.0013	< d. l.	< d. l.	< d. l.	n. a.
0 – 10	29	0.0090	0.0017	< d. l.	0.0029	n. a.
10 – 25	29	0.0100	< d. l.	< d. l.	0.0012	n. a.
25 - 50	29	< d. l.	< d. l.	< d. l.	< d. l.	n. a.
0 – 10	63	0.0017	0.0020	0.0010	0.0040	n. a.
10 – 25	63	0.0027	0.0019	< d. l.	0.0044	n. a.
0 – 10	99	< d. l.	0.0017	< d. l.	0.0035	n. a.
10 – 25	99	< d. l.	0.0011	< d. l.	0.0051	n. a.
0 – 10	174	< d. l.	0.0020	0.0010	0.0034	n. a.
10 – 25	174	< d. l.	0.0012	< d. l.	0.0052	n. a.
0 – 10	357	< d. l.	< d. l.	< d. l.	0.0020	n. a.
10 – 25	357	< d. l.	0.0011	< d. l.	0.0054	n. a.
25 – 50	357	< d. l.	< d. l.	< d. l.	< d. l.	n. a.

Table B.8.1-21: Field soil dissipation results from trial in Spain (trial ALO/11/97): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M02	635M03	635M01	635M04
0 – 10	0	0.055	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	0	0.005	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	15	0.020	0.003	< d. l.	0.003	0.001
10 – 25	15	0.004	< d. l.	< d. l.	< d. l.	0.001
0 – 10	29	0.005	0.002	< d. l.	< d. l.	0.001
10 – 25	29	0.002	0.002	< d. l.	< d. l.	< d. l.
25 - 50	29	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	62	< d. l.	0.003	< d. l.	0.002	0.002
10 – 25	62	0.001	< d. l.	< d. l.	< d. l.	< d. l.
25 - 50	62	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	104	< d. l.	0.002	0.001	0.002	0.002
10 – 25	104	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	104	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	182	< d. l.	0.002	0.001	0.001	0.002
10 – 25	182	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	182	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	356	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	356	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	356	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.

Table B.8.1-22: Field soil dissipation results from trial in Spain (trial ALO/12/97): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M02	635M03	635M01	635M04
0 – 10	0	0.039	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	0	0.013	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	14	0.005	0.002	< d. l.	< d. l.	< d. l.
10 – 25	14	0.009	< d. l.	< d. l.	0.001	< d. l.
0 – 10	30	0.003	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	30	0.006	0.001	< d. l.	0.002	< d. l.
25 - 50	30	0.001	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	61	< d. l.	0.001	< d. l.	< d. l.	< d. l.
10 – 25	61	0.002	< d. l.	< d. l.	0.001	< d. l.
25 - 50	61	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	100	<0.001	0.002	< d. l.	< d. l.	< d. l.
10 – 25	100	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	100	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	180	< d. l.	0.001	< d. l.	< d. l.	< d. l.
10 – 25	180	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	180	< d. l.	< d. l.	< d. l.	< d. l.	0.001
0 – 10	362	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	362	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	362	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.

Table B.8.1-23: Field soil dissipation results from trial in Sweden (trial HUS/11/97): Summary results of the residues in soil (mg/kg)

soil depth [cm]	DAT	tritosulfuron	635M02	635M03	635M01	635M04
0 – 10	0	0.045	< d. l.	< d. l.	< d. l.	< d. l.
10 – 25	0	0.001	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	14	0.021	0.003	< d. l.	0.008	0.002
10 – 25	14	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	34	0.012	0.005	< d. l.	0.011	0.002
10 – 25	34	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 - 50	34	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	67	< d. l.	0.002	< d. l.	0.008	< d. l.
10 – 25	67	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 - 50	67	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	102	< d. l.	0.002	< d. l.	0.006	< d. l.
10 – 25	102	< d. l.	< d. l.	< d. l.	0.001	< d. l.
25 – 50	102	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	186	< d. l.	< d. l.	< d. l.	0.004	< d. l.
10 – 25	186	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
25 – 50	186	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.
0 – 10	368	< d. l.	< d. l.	< d. l.	0.004	< d. l.
10 – 25	368	< d. l.	0.001	< d. l.	0.003	< d. l.
25 – 50	368	< d. l.	< d. l.	< d. l.	< d. l.	< d. l.

Table B.8.1-24: Degradation rates (1st order kinetic) of tritosulfuron and metabolites in field soil dissipation studies in Europe

	Germany				Spain				Sweden	
	DU2/06/96		DU3/02/96		ALO/11/97		ALO/12/97		HUS/11/97	
	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]	DT_{50} [days]	DT_{90} [days]
tritosulfuron	15	49	21	70	11	37	12	39	15	77
635M01	336	nc	nc	nc	130*	430*	30*	99*	nc	nc
635M02	50	168	216	nc	63	210	nc	nc	36	120
635M04 (AMTT)	na	na	na	na	133*	442*	nc	nc	11*	37*

* degradation rate with a high standard deviation
nc: no meaningful calculation possible
na: not analysed

Comment:
The studies are acceptable.

Jackson, S., Smith, K. and McDonell, J. (2001): Field dissipation of BAS 635..H in terrestrial use pattern. BASF RegDoc# 2000/5285; BOD 2001-731

Guidelines: USA-EPA, Subdivision N, 164-1

GLP: yes

Test system:
The 4 trials were conducted in areas representative of major field/row crop growing regions of the United States, that were South Dakota, California, Indiana and Texas. The geographical distribution and some soil parameters of the fields are given in Table B.8.1-25. A range of soils with organic matter contents from 0.8 to 4.0 with a pH range from 5.1 to 7.9 was covered.
The trials were performed using the formulated product BAS 635 00 H, a typical formulation for the end use product of tritosulfuron in cereals and corn. It is a WG formulation with a concentration of 73 %. In addition, a crop oil concentrate and a liquid fertilizer were added to the spray tank. All applications were broadcast sprayed directly on the soil surface using ground rig spray equipment (tractor mounted, flat boom sprayers). The nominal application rates were 73 g tritosulfuron/ha. Recoveries were determined by using petri dishes filled with 10 g soil which were placed on the field before the application. The treated plots were scheduled to be sampled before the application and 1, 2, 3, 5, 7, 10, 14, 21, 30, 60, 90, 120, 180, 300, 360, 450 and 540 days after application. A sampling variance of +/-2 days was acceptable after thirty days. The temperatures and the volumetric water contents of the soils were determined continuously measured by TDR on the field plots.
After collection the soil cores were divided into layers and extracted by suing acetonitrile and water (8 : 2) or pure acetonitrile. In some case the extracts were additionally cleaned up on an amino-propyl SPE column. Quantification was performed using HPLC MS/MS for parent and transformation products 635M01, 635M02, 635M03 and 635M04 (AMTT).
DT_{50} values of tritosulfuron and metabolites were calculated by using the non-linear Gustafson Holden model. DT_{50} and DT_{75} were calculated. The half-lives of metabolites were calculated by starting the calculation with the highest concentration measured.

Table B.8.1-25: Characterisation of fields in the field soil dissipation study with tritosulfuron in the United States

trial No.	state	location	soil type	soil properties	
				% C_{org}	pH
RCN97009	South Dakota	Britton, Marshall County	Loam	2.3	7.9
RCN97010	California	Porterville, Tulare County	Sandy loam	0.5	7.8
RCN97011	Indiana	Noblesville, Hamiliton County	Loam	2.1	6.3
RCN97012	Texas	Brookshire, Waller County	Sandy loam	0.7	5.1

Findings:
The verified recoveries with an application verification method (Petri dishes) were 80 %, 70 %, 35 % and 90 % for the South Dakota, California, Indiana and Texas sites respectively. The low recovery at the Indiana site was due to mishandling in the laboratory.

The DT_{50} of tritosulfuron is short in all trials, whereas the major metabolites 635M01 and 635M02 are significantly more stable in soil. 635M03 was only found in 3 trials in minor amounts. Metabolite 635M04 (AMTT) is degraded in most cases with a short half live. A summary of the DT_{50} and DT_{75} values calculated by using the non-linear Gustafson Holden model is given in Table B.8.1-26.

Table B.8.1-26: Maximum concentrations (% of parent concentration) and degradation rates of tritosulfuron and metabolites in the US field soil dissipation study using Gustafson Holden model

	South Dakota			California			Indiana			Texas		
	max [%]	DT_{50} [d]	DT_{75} [d]	max [%]	DT_{50} [d]	DT_{75} [d]	max [%]	DT_{50} [d]	DT_{75} [d]	max [%]	DT_{50} [d]	DT_{75} [d]
tritosulfuron	-	14	40	-	15	34	-	4	8	-	3	6
635M01	5.7	> 621	> 621	9.2	93	187	20.7	90	332	11.8	65	158
635M02	3.6	> 614	> 614	6.7	363	> 417	16.4	85	172	9.6	76	191
635M03	1.2	nd	nd	8.0	> 417	> 417	2.1	81	> 439	0.9	53	322
635M04 (AMTT)	5.9	69	170	4.2	5	23	10.0	14	33	7.4	7	14

nd : not detected

Comment:
The study is acceptable.

Dressel, J. and Beigel, C. (2001): Estimation of standardized transformation rates of BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 from field dissipation studies. BASF RegDoc# 2000/1018554; BOD 2001-502

Guidelines: None, calculation

GLP: No, not subject of GLP regulations

Test system:
Seven (4 US, 2 Spain, 1 Sweden) of the ten field trials were used for the estimation of the degradation parameters for tritosulfuron and the metabolites, as the concentrations of the metabolites did allow a reliable estimation of the kinetic parameters of all metabolites.
Mathematical compartment models were developed using Modelmaker V.4.0, based on the proposed route of dissipation of tritosulfuron. These processes can be described using first-order reactions. The objective was to describe the observed field data and to calculate the half-life values of tritosulfuron and soil metabolites that were standardized to reference soil temperature and reference soil moisture of 20 °C and of pF 2, respectively. The degradation rate constants in the compartment models can be corrected for differences between the actual soil temperature and the actual soil moisture by using the correction factor recommended by FOCUS (Q_{10} value of 2.2, B-exponent of 0.7). The temperature correction was modified in comparison with the FOCUS approach, because, it was assumed that no degradation takes place below 0 °C and the temperature correction between 0 and 5 °C was done by a linear correction. A correction of the degradation was done in the US trials by using measured soil temperature and volumetric water content in the soil. In the European studies a temperature correction was considered only.
Modelmaker was used to optimize the initial concentration of the parent, and the rate constants of tritosulfuron and metabolites, by solving differential equations simultaneously. Modelmaker is sensitive to the initial input values of the parameters to be optimized. As a result, the parameters to be optimized were first adjusted manually by repeated integration steps in Modelmaker, to provide initial values that allowed to roughly describe the measured data. These initial values were then optimized with Modelmaker for a better fit and statistical analysis. To describe the metabolism fluxes between the different substances their different molar weights had to be accounted for. To ease the parameter estimation process the residue concentrations were therefore expressed in molar units instead of mass units.
The three field trials conducted in Germany could be used in a validation step to check the predictability of the field dissipation of tritosulfuron based on the degradation parameters obtained from the four US trials and the three EU field trials in Spain and Sweden. The comparability of the trials in the USA with European soil and weather conditions was shown by the notifier (see Table B.8.1-27).

Table B.8.1-27: Climatic conditions at the US field dissipation sites and at corresponding EU sites

US Site yearly average temp. / accu-mulated natural rainfall	Corresponding EU site 1 yearly average temp. / accumulated natural rainfall	Corresponding EU site 2 yearly average temp. / accumulated natural rainfall
California (USA) 16.3 °C / 188 mm	Almeria (Spain) 18.4 °C / 215 mm	Heraklion (Greece) 18.4 °C / 501 mm
Texas (USA) 20.3 °C / 548 mm	Trapani (Italy) 17.5 °C / 489 mm	Athens (Greece) 17.7 °C / 377 mm
Indiana (USA) 12.7 °C / 536 mm	Marseille (France) 14.5 °C / 534 mm	Karlsruhe (Germany) 10.3 °C / 770 mm
South Dakota (USA) 16.2 °C / 260 mm	Valladolid (Spain) 16.4 °C / 228 mm	Paris (France) 14.6 °C / 388 mm

Findings:
The significance (95 % probability level) of each parameter in each individual field trial of the compartment model in modelmaker was checked. In Table B.8.1-28 DT_{50} values were given, where the 95 % probability level of the degradation rater were reached.
The standardised half-lives (20 °C, pF 2) of tritosulfuron obtained from the field studies range from 2.6 d (Texas) to 32.7 d (California), reflecting the variability of the biological/chemical degradation rates in different soils, as the rates were standardised for the temperature and the soil moisture. The half-lives obtained from the European studies were 5.9, 8.4 and 11.0 d in 'Utrera', 'Bjärred' and 'Manzanilla'. The average standardised half-lives (20 °C, pF 2) for metabolites 635M01, 635M02, and 635M04 (AMTT) are 69.9 d, 64.4 d and 9.7 d. A mean DT_{50} value of 67.7 d was calculated for metabolite 635M03. Because of the presence of two DT_{50} values only, which differ strongly (9.5 and 126 days), the calculation of a mean value of metabolite 635M03 is not useful. In Table B. 8.1-29 the fitted molar fractions of the metabolites formed throughout each field study, the highest and the arithmetic mean values were given.
Three field trials conducted in Germany (study DE/HA/042/96) were not taken for the parameter estimation, and therefore they could be used in a validation excercise to check the predictability of the field dissipation of tritosulfuron in Europe based on the average standardised half-life of 14.1 d (20 °C). The measured residues of tritosulfuron in soil in all trials could be described very well with the average standardised degradation rate of tritosulfuron considering the actual temperatures during the studies. A "validation" of the DT_{50} values at reference conditions of the metabolites was not conducted.

Table B.8.1-28: Standardised half-lives (20 °C, pF 2) for tritosulfuron, 635M01, 635M02, 635M03 and 635M04 (AMTT) estimated from different field studies

	South Dakota	California	Indiana	Texas	Manzanilla	Utrera	Bjärred	Arithmetic mean
	Half-life [d]	Half-life [d]	Half-life [d]	Half-life [d]	Half-life [d]	Half-life [d]	Half-life [d]	Half-life [d]
tritosulfuron	32.5	32.7	5.4	2.6	11.0	5.9	8.4	14.1
635M01	-	62.4	90.0	57.3	-	-	-	69.9
635M02	-	115.5	47.2	74.5	66.0	-	18.6	64.4
635M03	-	126.0	9.5	-	-	-	-	67.7*
635M04 (AMTT)	4.1	5.6	23.1	2.5	-	-	13.0	9.7

* the mean value calculation of two values is not useful

Table B. 8.1-29: Maximum molar fraction formed throughout each field study, the highest and arithmetric mean values

	South Dakota	California	Indiana	Texas	Manzanilla	Utrera	Bjärred	Highest fraction	Mean fraction
	[%]	[%]	[%]	[%]	[%]	[%]	[%]	[%]	[%]
635M01	9.6	16.7	21.8	14.8	4.0	4.6	29.6	29.6	14.4
635M02	8.1	12.6	27.0	17.6	13.5	7.2	19.4	27.0	15.0
635M03	1.1	15.8	2.0	2.0	1.6	-	-	15.8	4.5
635M04 (AMTT)	11.4	7.2	19.2	15.9	7.7	-	12.0	19.2	12.2

Comment:
The estimation of degradation rates of tritosulfuron and the standardisation (20 °C, pF 2) is acceptable for tritosulfuron. A validation of the DT_{50} of the metabolites values by predicting the degradation on field sites, which were not used for the estimation, was not performed. Therefore, the estimated and standardised DT_{50} values (20 °C, pF 2) of the metabolites 635M01, 635M02, 635M03 and 635M04 (AMTT) should be used as additional information.

B.8.1.2.3 Storage stability of soil residues

Keller, W. (1998b): Storage stability of BAS 635 H (271 272) residues in soil. BASF RegDoc# 1998/10899; BOD 2001-516

Richter, T. (2001d): Evaluation of residue stability of BAS 635 H (271 272) and the following metabolites 335184, 335182, 292564 in soil samples under usual storage conditions. BASF RegDoc# 2000/1013302; BOD 2001-517

Guidelines: US-EPA, Subdivision O, 171-4(e), IVA-Guideline for residue chemistry part II

South, N.L. and Smith, K. (2001): Freezer storage stability study with BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in sediment. BASF RegDoc# 2000/5279; BOD 2001-518

Guidelines: Canadian Guidelines T-1-255

GLP: yes

Test system:
Soil samples from field soil dissipation studies were stored generally at less than – 18 °C in a freezer. Two studies were performed to determine the storage stability of tritosulfuron and metabolite residues in deep frozen (< –18 °C) soil and a third study was used to evaluate the residue stability in sediment at <= - 5 °C. In the first two studies soil samples were fortified with tritosulfuron and its major soil metabolites 635M01, 635M02 and 635M03. The third study investigated the stability of as and the above mentioned metabolites, but additionally included 635M04 (AMTT).

Findings:
In the first study, the stability of total residues of tritosulfuron in fortified and frozen soil samples was shown for up to 24 months. For analysis, a common moiety method was used.
In the second study, the stability of tritosulfuron and its soil metabolites 635M01, 635M02 and 635M03 was checked over a time period of 35 months. The compounds were determined individually. They were stable.
The third study demonstrated the stability of tritosulfuron, 635M01, 635M02, 635M03 and 635M04 (AMTT) in sediment over a time period of 33 months. Even at temperatures <= -5 °C, all compounds are proved to be stable.
Therefore it can be assumed, that 635M04 (AMTT) is expected to be stable over a time period of about 48 months especially at storage temperatures below –18 °C (with respect to study BASF RegDoc# 2000/1013301 where samples were stored up to almost 48 months from sampling until 635M04 (AMTT) analysis). Additionally, a storage stability study with 635M04 (AMTT) in soil at about –18 °C with fortified control samples is in progress and also indicates the stability of 635M04 (AMTT) over a long time period.

Comment:
The studys are acceptable

B.8.2 Adsorption, desorption and mobility in soil (Annex IIA 7.1.2, 7.1.3; Annex IIIA 9.1.2)

Sorption behaviour of tritosulfuron

Seher, A. (1996a): Soil adsorption/desorption study of 271 272 (BAS 635 H). BASF RegDoc# 1996/10455; BOD 2001-505

Seher, A. (1996b): Soil adsorption/desorption study of 271 272 (BAS 635 H). Addendum No. 1 to BASF RegDoc# 1996/10455; BASF RegDoc# 1996/10748; BOD 2001-506

Seher, A. (1997): Soil adsorption/desorption study of 271 272 (BAS 635 H). Addendum No. 2 to BASF RegDoc# 1996/10455; BASF RegDoc# 1997/11062, BOD 2001-507

Guidelines: OECD Guideline No. 106

GLP: yes

Test system:
The adsorption and desorption behaviour of [triazine-2,4-^{14}C]-labeled tritosulfuron (radiochemical purity: > 99 %, specific radioactivity: 9.26 MBq/mg) was investigated in four German and two US soils. The characteristics of the soils used are given in Table B.8.2-1. The soils were air dried, sieved (2 mm mesh) and sterilized by γ-irradiation. An adsorption equilibrium test was conducted over 24 h with a soil solution ratio of 1 : 5. In three soil the highest amounts adsorbed were measured after 24 h. The other soils show no significant increase of the adsorption after 8 hours. The Freundlich adsorption and desorption isotherm were determined by using 10 g soil and 20 g solution containing 0.01 M $CaCl_2$ and 0.032, 0.23, 1.03 and 5.03 mg tritosulfuron per liter. The test was carried out at the equilibrium time of 6 hours. The test temperature was 22 °C. The soil/solution system was centrifuged and the supernatant was removed. Then the desorption test was conducted by adding 20 ml of $CaCl_2$ solution and shaking the mixture for 16 h. Then the supernatant was remove, the solute retained in the soil was measured by weighing and a second desorption step was repeated as described before. After all adsorption and desorption steps the radioactivity in the solutions were determined by LCS.

Table B.8.2-1: Characteristics of soils used for adsorption/desorption of [triazine-2,4-^{14}C] labeled tritosulfuron

Soil	LUFA 2.1	LUFA 2.2	LUFA 2.3	Bruch Ost	USA 538-30-5	USA 538-31-2
Origin	Speyer	Speyer	Speyer	Limb.	USA	USA
Characterisation (DIN classification, Germany)	clayey sand	clayey sand	loamy sand	loamy sand	n.d.	n.d.
Characterisation (USDA)	loamy sand	sandy loam	sandy loam	loamy sand	loamy sand	silty loam
% sand (0.063 – 2 mm)	84	79	66	38	82*	22*
% silt (0.002 – 0.063 mm)	3	7	19	25	13*	57*
% clay (< 0.002 mm)	13	14	15	37	5*	11*
pH value ($CaCl_2$)	5.7	6.0	6.5	7.8	6.7	5.4
% organic carbon	0.7	2.6	1.5	3.3	0.4	0.4
MWHC [g H_2O/100g soil]	23	36	31	40	n.d	n.d.
FC [g H_2O/100g soil], 330 hPa	4.5	10.2	12.9	25.1	7.2	16.7
CEC [meq / 100 g]	4.3	11.5	11.4	11.2	3.1	10.2

* USDA scheme (sand: 50 - 2000 µm, silt: 2 - 50 µm, clay: < 2 µm)
n.d. not determined

Findings:
A summary of the Freundlich adsorption and desorption coefficients is given in Table B.8.2-2. The adsorption constants K_F calculated from the Freundlich isotherms for the six test soils range from 0.035 and 0.158 l/kg and the exponent ranged from 0.761 to 0.980. K_{oc}-values of 2 – 11 were obtained. There seemed to be an influence of the pH value of the soils on the adsorption. The lower the pH value of the soil**,** the more adsorption of tritosulfuron on the soil occurs.
A subsequent determination of the desorption in two steps with 0.01 M $CaCl_2$-solution resulted for six soils in K_{FdesI}-values from 1.1 to 1.91 ml/g and in K_{FdesII} values from 0.12 to 2.55 ml/g.

Table B.8.2-2: Adsorption and desorption behaviour of [triazine-2,4^{14}C] tritosulfuron

Soil	textural class [DIN]	adsorption			desorption I	desorption II
		K_F [ml/g]	1/n	K_{oc} [ml/g]	K_F [ml/g]	K_F [ml/g]
LUFA 2.1	clayey sand	0.069	0.955	9.8	1.61	1.19
LUFA 2.2	clayey sand	0.158	0.945	6.1	1.86	2.55
LUFA 2.3	loamy sand	0.062	0.980	4.1	1.10	1.46
Bruch Ost	loamy sand	0.066	0.860	2.0	1.91	0.61
USA 538-30-5	n.d.	0.038	0.961	10.8	1.76	0.12
USA 538-31-2	n.d.	0.035	0.761	10.1	1.40	0.17

Comment:
The study is acceptable. Because of the short equilibrium time of 6 hours, the adsorption coefficients reported seemed to be an conservative estimation of the sorption behaviour of tritosulfuron.

Sorption behaviour of tritosulfuron and metabolites

Seher, A. (1999b): Adsorption/desorption - Study of 271 272 (BAS 635 H), 292 564 (BH 635-2), 335 182 (BH 635-3), 335 184 (BH 635-4) and 231 700 (BH 635-5) on a lysimeter soil. BASF RegDoc# 1999/10085; BOD 2001-508

Guidelines: OECD Guideline No. 106; US-EPA, Subdivision N, 163-1

GLP: yes

Test system:
The adsorption and desorption behaviour of [triazine-2,4-^{14}C]-labeled tritosulfuron and several metabolites (635M01, 635M02, 635M03 and 635M04) were investigated in one soil. Label position, specific radioactivity, and purity of the test substances are listed in Table B.8.2-3. The characteristics of the soil, which is comparable with the soil used for the lysimeter studies, are given in Table B.8.2-4. The soil was air dried, sieved (2 mm mesh) and sterilized by γ-irradiation. An adsorption equilibrium test was conducted over 24 h with a soil solution ratio of 1 : 2. In the soil the highest amounts of tritosulfuron and the metabolites adsorbed were measured after 16 - 24 h. The Freundlich adsorption and desorption isotherm were determined by using 10 g soil and 20 g solution containing 0.01 M $CaCl_2$ and nominal 0.04, 0.2, 1.0 and 5.0 mg of the test substances (tritosulfuron, 635M01, 635M02, 635M03 and 635M04, respectively) per liter. The test was carried out at the equilibrium time of 16 hours. The test temperature was 20 °C. The soil/solution system was centrifuged and the supernatant was removed. Then the desorption test was conducted by adding 20 ml of $CaCl_2$ solution and shaking the mixture for 16 h. Then the supernatant was remove, the solute retained in the soil was measured by weighing and a second desorption step was repeated as described before. After all adsorption and desorption steps the radioactivity in the solutions were determined by LCS.

Table B.8.2-3: Properties of test substances used for adsorption/desorption test in a lysimeter soil

Test substance	Reg.No.	Label	Spec. activity [MBq/mg]	radioch. Purity	Water solubility
Tritosulfuron	271272	Triazine	4.18	> 99 %	44 mg/l
635M02	292564	Phenyl	3.44	> 95 %	300 mg/l
635M03	335182	Phenyl	3.47	> 95 %	173 mg/l
635M01	335184	Phenyl	2.23	> 95 %	12 mg/l
635M04 (AMTT)	231700	Triazine	4.68	> 99 %	1.255 g/l

Table B.8.2-4: Lysimeter soil used to investigate adsorption and desorption of [triazine-2,4^{14}C] labeled tritosulfuron and metabolites

Soil	Speyerer Wald (98/1287)
Origin	Speyer, RP, Germany
Characterisation (DIN classification, Germany)	clayey sand/loamy sand
Characterisation (USDA)	loamy sand
% sand (0.063 – 2 mm)	85
% silt (0.002 – 0.063 mm)	8
% clay (< 0.002 mm)	7
pH value ($CaCl_2$)	6.0
% organic carbon	0.7
MWHC [g H_2O/100g soil]	26
FC [g H_2O/100g soil], 330 hPa	8.7
CEC [meq / 100 g]	5

Findings:
A summary of the Freundlich adsorption and desorption coefficients is given in Table B.8.2-5.

Table B.8.2-5: Adsorption and desorption behaviour of tritosulfuron and metabolites in a lysimeter soil

Soil	Reg.No.	adsorption			desorption 1	desorption 2
		K_F [ml/g]	1/n	K_{oc} [ml/g]	K_F [ml/g]	K_F [ml/g]
Tritusulfuron	271272	0.0635	0.9274	9	1.74	5.45
635M01	335184	0.5205	0.9363	74	5.62	4.37
635M02	292564	0.2545	0.9721	36	6.01	3.54
635M03	335182	0.2320	0.9695	33	6.70	3.83
635M04 (AMTT)	231700	0.1075	0.9815	15	1.70	1.95

Comment:
The study is acceptable.

Sorption behaviour of metabolites 635M01, 635M02 and 635M03

Seher, A. (1998b): Soil adsorption/desorption study of 292 564 (BH 635-2). BASF RegDoc# 1998/10713; BOD 2001-509

Seher, A. (1998c): Soil adsorption/desorption study of 335 182 (BH 635-3). BASF RegDoc# 1998/10714; BOD 2001-510

Seher, A. (1998a): Soil adsorption/desorption study of 335 184 (BH 635-4). BASF RegDoc# 1998/10612; BOD 2001-511

Guidelines: OECD Guideline No. 106; US-EPA, Subdivision N, 163-1

GLP: yes

Test system:
The adsorption and desorption behaviour of the metabolites 635M01, 635M02 and 635M03 were investigated in four German and two US soils. The characteristics of the soils used are given in Table B.8.2-6. Label position, specific radioactivity, and purity of the test substances are listed in Table B.8.2-3. The soils were air dried, sieved (2 mm mesh) and sterilized by γ-irradiation. An adsorption equilibrium test was conducted over 24 h with a soil solution ratio of 1 : 2. The Freundlich adsorption and desorption isotherm were determined by using 10 g soil and 20 g solution containing 0.01 M $CaCl_2$ and nominal concentrations of 0.04, 0.2, 1.0 and 5.0 mg test substance per liter. The tests were carried out at the equilibrium times, which were determined in the pre-tests (they range between 16 and 24 hours). The test temperature was 22 °C. The soil/solution system was centrifuged and the supernatant was removed. Then the desorption test was conducted by adding 20 ml of $CaCl_2$ solution and shaking the mixture for 16 h. Then the supernatant was remove, the solute retained in the soil was measured by weighing and a second desorption step was repeated as described before. After all adsorption and desorption steps the radioactivity in the solutions were determined by LCS.

Table B.8.2-6: Soils used to investigate adsorption and desorption of ^{14}C-labeled metabolites 635M01, 635M02 and 635M03

Soil	LUFA 2.1	LUFA 2.2	LUFA 2.3	Bruch West	USA 538-30-5	USA 538-31-2
Origin	Speyer	Speyer	Speyer	Limb.	USA	USA
Characterisation (DIN classification, Germany)	clayey sand	clayey sand	loamy sand	loamy sand	n.d.	n.d.
Characterisation (USDA)	loamy sand	sandy loam	sandy loam	sandy loam	loamy sand	silty loam
% sand (0.063 – 2 mm)	82	76	66	50	82*	22*
% silt (0.002 – 0.063 mm)	7	13	20	33	13*	67*
% clay (< 0.002 mm)	11	11	14	17	5*	11*
pH value ($CaCl_2$)	5.8	5.8	6.5	7.5	6.7	5.4
% organic carbon	0.5	1.8	1.0	1.8	0.4	0.4
MWHC [g H_2O/100g soil]	25	41	31	38	n.d	n.d.
FC [g H_2O/100g soil], 330 hPa	5.9	15.4	14.8	22.7	7.2	16.7
CEC [meq / 100 g]	3.1	12.1	7.7	16.0	3.1	10.2

* USDA scheme (sand: 50 - 2000 µm, silt: 2 - 50 µm, clay: < 2 µm)
n.d. not determined

Findings:
A summary of the Freundlich adsorption and desorption coefficients is given in Table B.8.2-7. There seemed to be an influence of the pH value of the soils on the adsorption. The lower the pH value of the soil**,** the more adsorption of tritosulfuron and its metabolites 635M01, 635M02 and 635M03 on the soil occurs.

Table B.8.2-7: Adsorption and desorption behaviour of metabolites 635M01, 635M02 and 635M03 in different soils

test substance	soil	adsorption			desorption 1	desorption 2
		K_F [ml/g]	1/n	K_{oc} [ml/g]	K_F [ml/g]	K_F [ml/g]
635M01	LUFA 2.1	0.443	0.916	89	1.83	2.23
(335184)	LUFA 2.2	1.466	0.940	81	4.05	5.04
	LUFA 2.3	0.609	0.901	61	5.55	5.52
	Bruch West	0.319	0.958	18	5.77	5.57
	US 538-30-5	0.407	0.899	116	3.36	2.92
	US 538-31-2	0.642	0.914	184	9.56	5.33
635M02	LUFA 2.1	0.195	0.978	39	1.74	3.52
(292564)	LUFA 2.2	0.517	0.943	29	1.62	2.49
	LUFA 2.3	0.332	0.921	33	3.17	3.99
	Bruch West	0.291	0.942	16	3.30	2.70
	US 538-30-5	0.179	0.964	51	5.87	5.40
	US 538-31-2	0.278	0.980	79	3.98	7.63
635M03	LUFA 2.1	0.114	0.910	23	0.13	-[1)]
(335182)	LUFA 2.2	0.421	0.935	23	1.52	1.52
	LUFA 2.3	0.228	0.897	29	4.93	2.25
	Bruch West	0.323	0.927	18	9.12	2.29
	US 538-30-5	0.119	0.854	34	0.53	0.45
	US 538-31-2	0.177	0.892	51	1.50	0.24

[1)] measured values were not reliable

Comment:
The study is acceptable.

Sorption behaviour of metabolites 635M04 (AMTT)

Seher, A. (1998d): Soil adsorption/desorption study of 231 700 (BH 635-5). BASF RegDoc# 1998/11370; BOD 2001-512

Seher, A. (1999a): Soil adsorption/desorption study of 231 700 (BH 635-5). Addendum No. 1 to BASF RegDoc# 1998/11370; BASF RegDoc# 1998/11413; BOD 2001-513

Guidelines: OECD Guideline No. 106; ; US-EPA, Subdivision N, 163-1

GLP: yes

Test system:
The adsorption and desorption behaviour of [triazine-2,4-^{14}C]-labeled 635M04 (AMTT) (radiochemical purity: > 99 %, specific radioactivity: 4.68 MBq/mg) was investigated in four German and two US soils. The characteristics of the soils used are given in Table B.8.2-8. The soils were air dried, sieved (2 mm mesh) and sterilized by γ-irradiation. An adsorption equilibrium test was conducted over 24 h with a soil solution ratio of 1 : 2. The Freundlich adsorption and desorption isotherm were determined by using 10 g soil and 20 g solution containing 0.01 M $CaCl_2$ and nominal concentrations of 0.04, 0.2, 1.0 and 5.0 mg test substance per liter. The tests were carried out at the equilibrium time of 16 hours, which was

determined in a pre-test. The test temperature was 22 °C. The soil/solution system was centrifuged and the supernatant was removed. Then the desorption test was conducted by adding 20 ml of $CaCl_2$ solution and shaking the mixture for 16 h. Then the supernatant was remove, the solute retained in the soil was measured by weighing and a second desorption step was repeated as described before. After all adsorption and desorption steps the radioactivity in the solutions were determined by LCS.

Table B.8.2-8: Soils used to investigate adsorption and desorption of ^{14}C-labeled metabolite 635M04 (AMTT)

Soil	LUFA 2.1	LUFA 2.2	LUFA 2.3	Bruch West	USA 538-30-5	USA 538-31-2
Origin	Speyer	Speyer	Speyer	Limb.	USA	USA
Characterisation (DIN classification, Germany)	sand	sand/loamy sand	loamy sand	loamy sand	loamy sand	silty loamy sand
Characterisation (USDA)	sand	loamy sand	sandy loam	sandy loam	loamy sand	loam
% sand (0.063 – 2 mm)	89	85	71	72	81	40
% silt (0.002 – 0.063 mm)	7	10	17	18	11	47
% clay (< 0.002 mm)	4	5	12	10	8	13
pH value ($CaCl_2$)	5.8	5.8	6.8	7.5	5.8	5.2
% organic carbon	0.7	2.5	1.0	1.5	0.4	0.5
MWHC [g H_2O/100g soil]	24	43	33	40	22	31
FC [g H_2O/100g soil], 330 hPa	5.8	14.7	13.1	16.3	7.3	19.6
CEC [meq / 100 g]	2.6	11.2	8.3	12.1	4	10

Findings:
A summary of the Freundlich adsorption and desorption coefficients of metabolite 635M04 (AMTT) is given in Table B.8.2-9. The adsorption constants K_F calculated from the Freundlich isotherms for the six test soils range from 0.092 and 0.29 l/kg and the exponent ranged from 0.898 to 0.971. K_{oc}-values of 8 – 57 were obtained. There seemed to be an influence of the pH value of the soils on the adsorption. The lower the pH value of the soil**,** the more adsorption of metabolite 635M04 (AMTT) on the soil occurs.
A subsequent determination of the desorption in two steps with 0.01 M $CaCl_2$-solution resulted for six soils in K_{FdesI}-values from 0.86 to 3.77 ml/g and in K_{FdesII} values from 1.27 to 3.12 ml/g.

Table B.8.2-9: Adsorption and desorption behaviour of metabolites 635M04 (AMTT) in different soils

test substance	soil	adsorption			desorption I	desorption II
		K_F [ml/g]	1/n	K_{oc} [ml/g]	K_F [ml/g]	K_F [ml/g]
635M04	LUFA 2.1	0.0919	0.9000	13	0.86	1.36
(231700)	LUFA 2.2	0.2485	0.9508	10	1.64	1.92
	LUFA 2.3	0.1800	0.8977	18	1.21	1.27
	Bruch West	0.1232	0.9325	8	3.01	3.12
	US 538-30-5	0.0941	0.9097	24	3.77	2.42
	US 538-31-2	0.2870	0.9708	57	1.06	1.98

Comment:
The study is acceptable.

B.8.2.1 Mobility in soil

B.8.2.1.1 Column leaching studies

Keller, W. (1994): Leaching behaviour of ^{14}C-271 272 without soil ageing and after aerobic ageing for 30 days. BASF RegDoc# 1994/10924; BOD 2001-514

Guidelines: BBA IV, 4-2

GLP: yes

Test system:
The leaching characteristics of [triazine-2,4-^{14}C] labeled tritosulfuron (chemical purity: > 99 %, radiochemical purity: > 99 %, specific radioactivity: 2.55 MBq/mg) was studied in a clayey sand soil LUFA 2.1. The characteristics of the soil are given in Table B.8.2-10. Air-dried soil, sieved to particle size < 2 mm was filled into glass columns (column dimensions: length 30 cm, segmented into 5 x 6 cm, internal diameter 5 cm). The packed soil columns were infiltrated from the bottom with 0.01 M calcium chloride solution until the liquid level reached the soil surface. The soil columns were kept in the dark by wrapping an aluminium foil around the column. Then the soil was treated with [triazine-2,4-^{14}C]-labeled tritosulfuron reaching a concentration of 0.1 mg/kg (dry weight). 100 g (dry weight) of the treated soil was applied onto the top of each of the two soil columns. The columns were eluted within two days with 393 ml (= 200 mm precipitation) of 0.01 M aqueous calcium chloride solution. Four eluate fractions of approx. 100 ml each were collected. The different leachate fractions and the individual soil segments were analysed for [^{14}C]-residues.
Aliquots of the soil samples were combusted and the radioactivity was determined by LSC. The soil samples were extracted three times with methanole followed by one extraction with methanole : water (1 : 1). The combined extracts were evaporated to dryness and dissolved in methanole. Aliquots of the extracts were radioassayed by LSC and analyzed by TLC. To determine the non-extractable radioactivity in soil aliquots of the extracted soil were combusted and LSC-analysed. The amounts of leachate water were measured and analysed by LSC. The eluates were acidified with HCL and extracted three times with dichloromethane. The extracts were evaporated to dryness and dissolved in methanole. Aliquots were analysed by LCS and TLC.

Table B.8.2-10: Characteristics of the soil used for column leaching

Soil	LUFA 2.1
Origin	Speyer, Germany
Characterisation (DIN classification, Germany)	clayey sand
Characterisation (USDA)	sandy loam / loamy sand
% sand (0.063 – 2 mm)	84
% silt (0.002 – 0.063 mm)	3
% clay (< 0.002 mm)	13
pH value ($CaCl_2$)	5.7
% organic carbon	0.7
MWHC [g H_2O/100g soil]	23
FC [g H_2O/100g soil], 330 hPa	4.5
CEC [meq / 100 g]	4.3

Findings:
The distribution of the radioactivity two days after application is given in Table B.8.2-11. The recovery of the radioactivity was 85.5 and 89.6 % of the applied radioactivity in the two soil columns, respectively.
The results clearly showed that under non-aged conditions, most of the radioactivity applied on top of the soil column was found in the leachate after two days. Only small amounts of radioactivity remained in the soil segments (< 2 % of the applied radioactivity). TLC-analysis revealed that the radioactivity found in the leachate consists mainly of unchanged parent.

Table B.8.2-11: Leaching behaviour of ^{14}C-labeled tritosulfuron under non-aged conditions [% of applied radioactivity]

replicates	non-aged	
	1	2
soil segment 0-6 cm	< 2	< 2
soil segment 6-12 cm	< 2	< 2
soil segment 12-18 cm	< 2	< 2
soil segment 18-24 cm	< 2	< 2
soil segment 24-30 cm	< 2	< 2
quartz sand	3.1	< 2
soil total	3.1	< 2
leachate (total, in 393 ml)	86.5	85.5
soil + leachate	89.6	85.5

Comment:
The study is acceptable.

B.8.2.1.2 Aged residue column leaching

Keller, W. (1994): Leaching behaviour of ^{14}C-271 272 without soil ageing and after aerobic ageing for 30 days. BASF RegDoc# 1994/10924; BOD 2001-514

Guidelines: BBA IV, 4-2

GLP: yes

Test system:
The leaching characteristics of [triazine-2,4-^{14}C]-labeled tritosulfuron (chemical purity: > 99 %, radiochemical purity: > 99 %, specific radioactivity: 2.55 MBq/mg) was studied in a clayey sand soil LUFA 2.1. The characteristics of the soil are given in Table B.8.2-10. Air-dried soil, sieved to particle size < 2 mm was filled into glass columns (column dimensions: length 30 cm, segmented into 5 x 6 cm, internal diameter 5 cm). The packed soil columns were infiltrated from the bottom with 0.01 M calcium chloride solution until the liquid level reached the soil surface. The soil columns were kept in the dark by wrapping an aluminium foil around the column. 500 g soil (dry weight) was treated with [triazine-2,4-^{14}C]-labeled tritosulfuron reaching a concentration of 0.1 mg/kg and incubated under standard conditions (20 °C and 40 % MWC) for 30 days. Volatile compounds formed during the incubation were trapped in ethylene glycol, NaOH and H_2SO_4, respectively. And then, 100 g portions of the aged soil were applied on top of each of the two soil columns. The columns were eluted within two days with 393 ml (= 200 mm precipitation) of 0.01 M aqueous calcium chloride solution. Four eluate fractions of approx. 100 ml each were collected. The different leachate fractions and the individual soil segments were analysed for [^{14}C]-residues.
Aliquots of the soil samples were combusted and the radioactivity was determined by LSC. The soil samples were extracted three times with methanole followed by one extraction with methanole : water (1 : 1). The combined extracts were evaporated to dryness and dissolved in methanole. Aliquots of the extracts were radioassayed by LSC and analyzed by TLC. To determine the non-extractable radioactivity in soil aliquots of the extracted soil were combusted and LSC-analysed. The amounts of leachate water were measured and analysed by LSC. The eluates were acidified with HCL and extracted three times with dichloromethane. The extracts were evaporated to dryness and dissolved in methanole. Aliquots were analysed by LCS and TLC.

Findings:
The distribution of the radioactivity two days after application is given in Table B.8.2-12. The recovery of the radioactivity was 108.1 and 101.1 % of the applied radioactivity in the two soil columns, respectively.
Under aged conditions, the amount of radioactivity in the leachate was considerably reduced if compared with the non-aged column leaching study, but still reached about 40 % of the applied radioactivity. TLC-analysis of top soil layer extracts showed unchanged parent. TLC-analysis of the leachate showed also mostly unchanged parent, however, also some polar metabolites could be found. An identification of the polar compounds was not possible because of to low substance amounts.

Table B.8.2-12: Leaching behaviour of ^{14}C-labeled tritosulfuron under aged conditions [% of applied radioactivity]

replicates	aged	
	1	2
soil segment 0-6 cm	28.2	25.9
soil segment 6-12 cm	7.6	7.4
soil segment 12-18 cm	8.9	7.2
soil segment 18-24 cm	9.0	9.0
soil segment 24-30 cm	9.7	7.8
quartz sand	3.8	4.0
soil total	67.2	61.3
leachate (total, in 393 ml)	40.9	39.8
soil + leachate	108.1	101.1

Comment:
The study is acceptable.

B.8.2.1.3 Lysimeter studies

Becker-Arnold, R. and Lehmann, C. (1998): Outdoor lysimeter study with ^{14}C-BAS 635 H. BASF RegDoc# 1998/11268; BOD 2001-515

Guidelines: BBA IV, 4-3

GLP: yes

Richter, T. (2001c): Determination of residues of BH 635-5 in several lysimeter leachates. BASF RegDoc# 2000/1013300; BOD 2001-504

Guidelines: IVA guidelines for residue chemistry, part IV, 1992

GLP: yes

Test system:
The leaching behaviour of [^{14}C-phenyl] tritosulfuron (radiochemical purity: > 99 %, specific radioactivity: 9.63 MBq/mg) and its metabolites was investigated in two outdoor lysimeters (lysimeter 5 and 6). The study was conducted for two years with a single application in the first year. The lysimeter vessels (1 m^2 surface and 1.2 m depth each) were filled with soil monoliths from the plot "Speyerer Wald" at Schifferstadt, Rhineland-Palatinate, Germany. The lysimeters and their surrounding area of about 3.3 m x 3.6 m (for each lysimeter) was planted with the same crops in order to establish ideal micro climatic conditions. The soil was characterised as a poorly developed "Parabraunerde" according to the German nomenclature and fulfilled the BBA criteria for lysimeter soils (> 70 % sand, ≤ 1.5 % organic C, ≤ 10 % clay). The soil characteristics are listed in Table B.8.2-13.
The applications were done on spring wheat on growth stage 25 (28 April, 1994). The nominal application rate was 50 g as/ha (= 5 mg as/m^2) for each treatment (see Table B.8.2-14). The treatment was done with [phenyl-U-^{14}C] labeled tritosulfuron in the blank

formulations LAB 271 272 WP 92 000 (wettable powder). The cultivation of the lysimeters (crops, sowing and harvest dates) are given in Table B.8.2-15.
In the study, the total amount of precipitation (incl. additional irrigation) was 807.5 mm in the first year and 834.9 mm in the second year. The total precipitation was 1642.4 mm for this two year study (see Table B.8.2-16). This represents realistic worst case field conditions to assess the potential groundwater contamination according to the BBA guideline.
Leachate and soil extracts were analysed by LSC and radio-HPLC. Soil and plant samples were combusted and analysed by LSC. Samples of the top soil layer were taken in the first experimental year after harvest of the spring wheat, and in the second experimental year after harvest of the winter barley. The two lysimeters (No. 5 and 6) were disassembled by cutting into 10 cm soil layers after two years in May 1996. The soil layers containing significant amounts of radioactivity were extracted with MeOH + MeOH/H_2O. The extracts were analysed by HPLC. The soil samples of the end of the study were also extracted three times with NaOH. For further distribution of the NaOH-soluble humic substances into fulvic- and humic acids, hydrochloric acid was added. The leachate was pre-cleaned over a (SPE Solid Phase Extraction)-NH_2 column. Then the leachate was evaporated to dryness. The residues were dissolved in methanole/acetonitrile and analysed by HPLC. Identification of metabolites was done by comparison of their retention times with those of co-chromatographed reference compounds except for metabolite 635M17, which was identified by mass spectrometry.
The determination limit of tritosulfuron and metabolites 635M01, 635M02, 635M03 and 635M17 was 0.01 µg/l in the leachate. The determination limit of tritosulfuron in the soil was 0.02 µg/kg; no information is given about the metabolites.
Since it was not possible to detect metabolite 635M04 (AMTT) in the lysimeter study due to the labeling position of the radiolabeled test substance, this compound was analysed for in lysimeter leachate samples using the water residue method. Final determination with this method is done by GC/MS; the LOQ for 635M04 (AMTT) is 0.05 µg/kg.

Table B.8.2-13: Characteristics of the soils used for the outdoor lysimeter studies with [^{14}C-phenyl] tritosulfuron

Horizon	Sand [%]	Silt [%]	Clay [%]	Org. C [%]	pH
Ap 0-35 cm	75.8	16.6	7.7	0.9	5.7
B 35-60 cm	76.3	14.1	9.7	0.4	6.3
Cv 60-80 cm	87.5	5.3	7.3	0.1	6.5
C 80-100 cm	90.1	6.3	3.6	0.2	6.8

Table B.8.2-14: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Application pattern

	Lysimeter 5	Lysimeter 6
Date of application	28.04.94	28.04.94
Application rate	50 g as/ha	50 g as/ha

Table B.8.2-15: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Cultivation

	Crop	Sowing	Harvest
1st crop	spring wheat	03.03.94	22.07.94
2nd crop	winter barley	21.09.94	06.07.95
3nd crop	winter rape	13.09.95	29.04.96

Table B.8.2-16: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Precipitation and irrigation

	period	Precipitaion [mm]	Irrigation [mm]	Sum [mm]
1st year	04.94-03.95	482.5	325	807.5
2nd year	04.94-03.96	669.9	165	834.9
total	1994/1996	1152.4	490	1642.4

Findings:
The results of the two individual lysimeters were very similar. The total amount of leachate was in the range of 199 – 271 l in the first year and 454 – 487 l in the second year (see Table B.8.2-17). The mean total radioactive residues (^{14}C-tritosulfuron-equivalents) in the leachate water are summarised in Table B.8.2-18. The yearly mean radioactivity in the leachate laid between 0.62 and 1.44 µg tritosulfuron equivalent per liter. The sum of radioactivity found in the leachate after two years was 14.1 and 22.4 % of applied for lysimeter 6 and 5, respectively. The highest radioactivity detected in a single leachate sample in one experimental year laid between 0.91 and 2.1 µg tritosulfuron equivalents.
The results of leachate analysis are shown in Table B.8.2-19 (yearly mean concentration) and Table B.8.2-20 (highest concentrations in a sample). The active substance tritosulfuron was detectable in low concentrations (yearly average < 0.05 µg as/l, maximum 0.042 µg/l) in all lysimeters. The concentration of tritosulfuron was below 0.1 µg/l in all individual leachate samples (maximum 0.072 µg/l). The annual average concentration of metabolites 635M01 and 635M03 exceeded 0.1 µg/l. The yearly mean concentrations of 635M01 were 0.12 and 0.22 µg/l in the 1st year and 0.39 and 0.54 µg/l in the 2nd year in lysimeter 6 and 5, respectively. The yearly mean concentrations of 635M03 were 0.05 and 0.09 µg/l in the 1st year but 0.20 and 0.26 µg/l in the 2nd year in lysimeter 6 and 5, respectively. The yearly mean concentration of metabolite 636M02 never exceeded 0.1 µg/l (maximum 0.088 µg/l), but individual samples showed maximum concentrations up to 0.18 µg/l. The yearly mean concentration of 635M17 was equal or lower than 0.05 µg/l. Maximum concentrations in individual leachate samples were 0.161 µg/l. 635M17 could possibly originate from decaying roots, because it is known to be a plant metabolite but was not detected in soil metabolism studies. Those leachate samples in which the highest concentrations of 635M04 (AMTT) were expected were selected for analysis. A total of 6 leachate samples (three samples of lysimeter 5 and 6, respectively) were analysed to determine the 635M04 (AMTT) concentration. The concentration of 635M04 (AMTT) in all samples were < 0.05 µg/l (limit of quantification). Neither in lysimeter 5 nor in lysimeter 6 ^{14}C-CO_2 could be detected in the leachate, with the exception of one sample of lysimeter 6. On Decembre 25, 1996 0.03 µg/l were analysed. The yearly mean concentration of not identified radioactivity (NIR) in leachate was > 0.1 µg/l in lysimeter 5 and 6 in both years (maximum 0.416 µg/l).
At the end of the study there was still 43.6 % (lysimeter 5) and 61.6 % (lysimeter 6) of the applied radioactivity in the whole soil profiles, most of it being found in the top soil layers

down to a depth of 30 cm. Radioactive residues found below a depth of 40 cm are for both lysimeters <0.001 mg/kg. 26.4 % (lysimeter 5) and 30.7 % (lysimeter 6) of the applied radioactivity had been incorporated into the humic substance matrix as bound residues after 2 years and could no longer be extracted with organic solvents. The two upper layers were extracted and analysed. Tritosulfuron and the metabolites 635M01, 635M02, 635M03 and 635M17 could be detected in the top soil layers (0 - 10 cm and 10 - 20 cm) in small amounts. The values of tritosulfuron at the first sampling (27 July 1994) were below 0.8 µg/kg (0 - 10 cm) and 1.5 µg/kg (10 - 20 cm). The concentration found for the metabolites ranged from 0.4 to 5.9 µg/kg (0 -10 cm) and 0.07 to 2.6 µg/kg (10 - 20 cm) in the soil layer. At the second sampling date (26 July 1995) tritosulfuron could only be found in a concentration of 0.02 µg/kg in a mixed sampling of the upper 0 - 20 cm soil layer and the concentrations of the metabolites ranged from 0.05 to 0.33 µg/kg. The concentrations of metabolites in the soil at the end of the study are shown in Table B.8.2-21.
The radioactivity in the plant after harvest of the 1st and 2nd year is given in Table B.8.2-22. The mass balance of the radioactivity at the end of the study is shown in Table B.8.2-23.

Table B.8.2-17: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Amounts of leachate

Study period	Lysimeter 5 [l]	Lysimeter 6 [l]
1st year	271.2	199.4
2nd year	486.6	453.9
total	757.8	653.3

Table B.8.2-18: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Radioactivity in leachate [^{14}C-tritosulfuron - equivalents]

Study period	Lys. No.	Mean total radioactive residues [µg/l]	% of the radioactivity applied	Maximum concentration [µg/l]
1st year	5 6	1.08 0.62	6.6 2.6	1.601 0.907
2nd year	5 6	1.44 1.22	15.8 11.5	2.120 1.833
total	5 6	1.31 1.04	22.4 14.1	- -

Table B.8.2-19: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Yearly mean concentration of tritosulfuron and metabolites in leachate

Study period	Lys. No.	tritosulfuron		635M02		635M03		635M01		635M17		NIR
		µg/l	%	µg/l	%	µg/l	%	µg/l	%	µg/l	%	µg/l
1st year	5	0.042	0.25	0.09	0.53	0.09	0.57	0.22	1.36	0.05	0.31	0.416
	6	0.022	0.09	0.02	0.08	0.05	0.21	0.12	0.50	0.02	0.07	0.322
2nd year	5	0.019	0.20	0.08	0.83	0.26	2.82	0.54	5.89	0.01	0.13	0.217
	6	0.014	0.13	0.09	0.83	0.20	1.91	0.39	3.68	0.01	0.09	0.236
total	5	0.027	0.46	0.08	1.36	0.20	3.39	0.43	7.25	0.03	0.43	0.288
	6	0.017	0.23	0.07	0.91	0.16	2.12	0.31	4.18	0.01	0.15	0.262

Table B.8.2-20: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Maximum concentration in leachate

Study period	Lys. No.	tritosulfuron		635M02		635M03		635M01		635M17	
		µg/l	%	µg/l	%	µg/l	%	µg/l	%	µg/l	%
1st year	5	0.072	0.06	0.183	0.19	0.184	0.19	0.484	0.28	0.161	0.14
	6	0.049	0.05	0.037	0.04	0.108	0.10	0.259	0.23	0.040	0.04
2nd year	5	0.053	0.06	0.152	0.15	0.369	0.39	0.839	0.92	0.130	0.13
	6	0.030	0.05	0.145	0.16	0.299	0.28	0.144	0.63	0.027	0.04

Table B.8.2-21: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Metabolites radioactivity in soil (end of study)

Study layers (cm)	Lys. No.	Tritosulfuron		635M02		635M03		635M01		635M17	
		µg/kg	%	µg/kg	%	µg/kg	%	µg/kg	%	µg/kg	%
0-10	5	nd	nd	0.054	0.26	0.115	0.55	0.194	0.94	0.030	0.14
	6	nd	nd	0.064	0.26	0.114	0.46	0.272	1.90	0.027	0.11
10-20	5	nd	nd	0.052	0.16	0.084	0.26	0.278	0.87	n.dt.	n.dt.
	6	nd	nd	0.071	0.26	0.105	0.38	0.374	1.35	n.dt.	n.dt.

n.dt. not determinable

Table B.8.2-22: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Radioactivity in plants

Period of study	Crop	Total uptake by the plants in % of the radioactivity applied	
		Lysimeter 5	Lysimeter 6
1st year	Spring wheat	1.06	0.92
2nd year	Winter barley	0.40	0.27

Table B.8.2-23: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Total balance in % of the applied radioactivity

	Lysimeter 5	Lysimeter 6
Leachate	22.4	14.1
Soil	43.6	61.6
Plant	1.46	1.19
Mineralization[1)]	32.5	23.1

[1)] determination by calculating the difference

Comment:
The study is acceptable.

Staudenmaier, H. (2001): Outdoor lysimeter study with ^{14}C-BAS 635 H. BASF RegDoc# 2000/1013297; BOD 2001-503

Guidelines: BBA IV, 4-3

GLP: yes

Richter, T. (2001c): Determination of residues of BH 635-5 in several lysimeter leachates. BASF RegDoc# 2000/1013300; BOD 2001-504

Guidelines: IVA guidelines for residue chemistry, part IV, 1992

GLP: yes

Test system:
The leaching behaviour of [^{14}C-Phenyl] tritosulfuron (radiochemical purity: > 99 %, specific radioactivity: 9.63 MBq/mg) and its metabolites was investigated in three outdoor lysimeters (lysimeters 16, 17 and 18). The study was conducted for three years including a second application on one of the lysimeters in the second experimental year. The lysimeter vessels (1 m^2 surface and 1.2 m depth each) were filled with soil monoliths from the plot "Speyerer Wald" at Schifferstadt, Rhineland-Palatinate, Germany. The lysimeters and their surrounding area of about 3.3 m x 3.6 m (for each lysimeter) was planted with the same crops in order to establish ideal micro climatic conditions. The soil was characterised as a poorly developed "Parabraunerde" according to the German nomenclature and fulfilled the BBA criteria for lysimeter soils (> 70 % sand, ≤ 1.5 % organic C, ≤ 10 % clay). The soil characteristics are listed in Table B.8.2-24.
The applications in the first experimental year were done on spring wheat on growth stage 31 (20 May, 1996). In the second vegetation period, the test substance was applied only on lysimeter 18, whereas the other lysimeters remained untreated. This second application was done on winter barley at growth stage 31 (03 April, 1997), see Table B.8.2-25. The nominal application rate was 50 g as/ha (= 5 mg as/m^2) for each treatment. The treatment was done with [phenyl-U-^{14}C] labeled tritosulfuron in the blank formulations BAS 635 DA H WP 92 001 (wettable powder). The cultivation of the lysimeters (crops, sowing and harvest dates) are given in Table B.8.2-26.
In the study, the total amount of precipitation (incl. additional irrigation) was 802.2 mm in the first year, 806.9 mm in the second year and 835.6 mm in the third year. The total precipitation was 2444.7 mm for this three year study (see Table B.8.2-27). This represents realistic worst case field conditions to assess the potential groundwater contamination according to the BBA guideline.
Samples of the top soil layer were taken in the first experimental year after harvest of the spring wheat, and in the second experimental year after harvest of the winter barley. Lysimeter 16 was disassembled after two years in June 1998. Lysimeter 17 (treated only in the first year) and lysimeter 18 (treated in first and second year) were disassembled by cutting into 10 cm soil layers after three years in June 1999. The methods for the analysis of tritosulfuron and metabolites in soil and leachate are described in study Becker-Arnold et al. (1998), BASF RegDoc# 1998/11268.
The determination limit of tritosulfuron and metabolites 635M01, 635M02, 635M03 and 635M17 was 0.01 µg/l in the leachate. The determination limit of tritosulfuron in the soil was 0.02 µg/kg; no information is given about the metabolites.

Since it was not possible to detect metabolite 635M04 (AMTT) in the lysimeter study due to the labeling position of the radiolabeled test substance, this compound was analysed for in lysimeter leachate samples using the water residue method. Final determination with this method is done by GC/MS; the LOQ for 635M04 (AMTT) is 0.05 µg/kg.

Table B.8.2-24: Characteristics of the soils used for the outdoor lysimeter studies with [^{14}C-phenyl] tritosulfuron

Horizon	Sand [%]	Silt [%]	Clay [%]	Orgn. C [%]	pH
Ap 0-35 cm	74.1	21.8	4.3	0.9	5.7
B 35-57 cm	79.6	18.6	1.9	0.2	5.9
Cv 57-75 cm	92.6	6.6	0.75	0.1	6.2
C 75-100 cm	95.2	3.9	0.85	0.1	6.2

Table B.8.2-25: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Application pattern

	Lysimeter 16	Lysimeter 17	Lysimeter 18
Date of application	20.05.96	20.05.96	20.05.96 03.04.97
Application rate	50 g as/ha	50 g as/ha	50 g as/ha

Table B.8.2-26: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Cultivation

	Crop	Sowing	Harvest
1st crop	spring wheat	19.03.96	07.08.96
2nd crop	winter barley	09.09.96	11.07.97
3nd crop	winter rape	16.09.97	01.07.98
4th crop	winter rye	27.10.98	20.05.99

Table B.8.2-27: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Precipitation and irrigation

	period	Precipitaion [mm]	Irrigation [mm]	Sum [mm]
1st year	1996/1997	485.2	317.0	802.2
2nd year	1997/1998	521.9	285.0	806.9
3nd year	1998/1999	520.6	315.0	835.6
1st+2nd year	1996-1998	1007.1	602.0	1609.1
1st-3nd year	1996-1999	1527.7	917.0	2444.7

Findings:
The results of the two individual lysimeters were very similar. The amounts of leachate were 207 – 241 l in the first year, 272 – 299 l in the second year and 415 – 423 l in the third year (see Table B.8.2-28). The mean total radioactive residues (^{14}C-tritosulfuron - equivalents) in the leachate water are summarised in Table B.8.2-29. The yearly mean radioactivity in the leachate laid between 0.66 and 2.5 µg tritosulfuron equivalent per liter. The sum of

radioactivity found in the leachate after three years was 6.5, 17.6 and 19.4 % of applied for lysimeter 16, 17 and 18, respectively. The highest radioactivity detected in a single leachate sample in one experimental year laid between 0.73 and 3.12 µg tritosulfuron equivalents.
The results of leachate analysis is shown in
Table B.8.2-30 (yearly mean concentration) and Table B.8.2-31 (highest concentration in a sample). The active substance tritosulfuron was detectable in low concentrations (yearly average < 0.04 µg as/l) in all lysimeters. The concentration of tritosulfuron was below 0.1 µg/l in all individual leachate samples even in the double treated lysimeter 18 (maximum 0.067 µg/l). The annual average concentration of metabolites 635M01, 635M02 and 635M03 exceeded 0.1 µg/l.
The yearly mean concentrations of 635M01 were 0.01, 0.05 and 0.03 µg/l in the 1st year, but 0.096, 0.33 and 0.41 µg/l in the 2nd year in lysimeter 16, 17 and 18, respectively. In the 3rd year the yearly mean concentration of 635M01 were 0.36 and 1.04 in lysimeter 17 and 18, respectively. The yearly mean concentrations of 635M02 were 0.02, 0.04 and 0.04 µg/l in the 1st year, but 0.02, 0.06 and 0.10 µg/l in the 2nd year in lysimeter 16, 17 and 18, respectively. In the 3rd year the yearly mean concentration of 635M02 were 0.03 and 0.11 in lysimeter 17 and 18, respectively. The yearly mean concentrations of 635M03 were 0.03, 0.05 and 0.04 µg/l in the 1st year, but 0.07, 0.22 and 0.30 µg/l in the 2nd year in lysimeter 16, 17 and 18, respectively. In the 3rd year the yearly mean concentration of 635M03 were 0.20 and 0.57 in lysimeter 17 and 18, respectively. The yearly mean concentration of 635M17 was equal or lower than 0.08 µg/l. The yearly mean concentration of not identified radioactivity (NIR) exceeded 0.1 µg/l in each year and in each lysimeter, except in lysimeter 17 in the 3rd year. The maximum yearly concentration of NIR in leachate was 0.675 µg/l.
Maximum concentrations in individual leachate samples were 0.17 µg/l. 635M17 could possibly originate from decaying roots, because it is known to be a plant metabolite but was not detected in soil metabolism studies. Those leachate samples in which the highest concentrations of 635M04 (AMTT) were expected were selected for analysis. A total of 20 leachate samples were analysed covering single (6 samples lysimeter 16, 7 samples of lysimeter 17) and double treated lysimeters (7 samples of lysimeter 18). Only one out of 20 lysimeter leachate samples contained residues of 635M04 (AMTT) above the LOQ of 0.05 µg/kg. The concentration found in this sample was 0.085 µg/kg. The amounts of ^{14}C-CO_2 in leachate were low (maximum 0.002 µg/l in individual samples).
At the end of the study there was still 54.3 % (lysimeter 16, disassembled after 2 years), 39.0 % (lysimeter 17) and 45.4 % (lysimeter 18) of the applied radioactivity in the whole soil profiles, most of it being found in the top soil layers down to a depth of 30 cm. Radioactive residues found below a depth of 40 cm are for all lysimeters < 0.001 mg/kg. 20.8 % (lysimeter 16), 9.7 % (lysimeter 17) and 9.5 % (lysimeter 18) of the applied radioactivity had been incorporated into the humic substance matrix as bound residues after 2 or 3 years and could no longer be extracted with organic solvents. The two upper layers were extracted and analysed. Tritosulfuron and the metabolites 635M01, 635M02, 635M03 and 635M17 could be detected in the top soil layers (0 - 10 cm and 10 - 20 cm) in small amounts. The values of tritosulfuron at the first sampling (13 August 1996) were below 0.22 µg/kg (0 - 10 cm) and 0.17 µg/kg (10 - 20 cm). The concentration found for the metabolites ranged from 0.34 to 3.6 µg/kg (0 - 10 cm) and 0.17 to 4.4 µg/kg (10 - 20 cm) in the soil layer. At the second sampling date (11 July 1997) tritosulfuron could only be found in lysimeter 18 in a concentration of 0.21 µg/kg in a mixed sampling of the upper 0 - 20 cm soil layer and the concentrations of the metabolites ranged from 0.03 to 0.86 µg/kg. The concentrations of metabolites in the soil at the end of the study are shown in Table B.8.2-32.

The radioactivity in the plant after harvest of the 1st, 2nd and 3rd year is given in Table B.8.2-33. The mass balance of the radioactivity at the end of the study is shown in Table B.8.2-34.

Table B.8.2-28: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Amounts of leachate

period	Lysimeter 16 [l]	Lysimeter 17 [l]	Lysimeter 18 [l]
1996/1997	206.46	227.63	240.61
1997/1998	272.06	289.80	282.54
1998/1999	-	415.15	423.04
sum	478.52	932.58	946.19

Table B.8.2-29: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Radioactivity in leachate [^{14}C-tritosulfuron - equivalents]

Study period	Lys. No.	Mean total radioactive residues [µg/l]	% of the radioactivity applied	Maximum concentration [µg/l]
1st year	16	0.746	2.98	1.091
	17	0.901	4.02	1.376
	18	0.931	4.30	1.490
2nd year	16	0.660	3.47	0.732
	17	1.126	6.40	1.240
	18	1.882	5.04	2.394
3nd year	16	-	-	-
	17	0.886	7.21	1.231
	18	2.501	10.04	3.118
total	16	0.697	6.46	
	17	0.964	17.63	
	18	1.917	19.38	

Table B.8.2-30: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Yearly mean concentration of tritosulfuron and metabolites in leachate

Study	Lys.	tritosulfuron		635M02		635M03		635M01		635M17		NIR
period	No.	µg/l	%	µg/l	%	µg/l	%	µg/l	%	µg/l	%	%
1st year	16	0.023	0.09	0.015	0.11	0.032	0.18	0.013	0.06	0.048	0.18	0.585
	17	0.020	0.09	0.042	0.37	0.052	0.34	0.053	0.30	0.031	0.13	0.642
	18	0.014	0.07	0.036	0.33	0.041	0.27	0.030	0.17	0.076	0.34	0.675
2nd year	16	0.009	0.05	0.023	0.24	0.073	0.55	0.096	0.64	0.010	0.05	0.371
	17	0.012	0.07	0.056	0.63	0.222	1.81	0.331	2.37	nd	0.00	0.267
	18	0.036	0.10	0.105	0.56	0.302	1.16	0.411	1.39	0.077	0.20	0.612
3nd year	16	-	-	-	-	-	-	-	-	-	-	-
	17	nd	0.00	0.34	0.54	0.198	2.31	0.359	3.68	nd	0.00	0.083
	18	nd	0.00	0.107	0.85	0.567	3.27	1.041	5.27	nd	0.00	0.163
total	16	0.015	0.14	0.019	0.35	0.055	0.73	0.060	0.70	0.027	0.24	0.464
	17	0.009	0.16	0.043	1.54	0.170	4.46	0.276	6.35	0.008	0.13	0.272
	18	0.014	0.16	0.088	1.74	0.354	4.70	0.771	6.83	0.042	0.54	0.427

Table B.8.2-31: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Maximum concentration in leachate

Study period	Lys. No.	tritosulfuron		635M02		635M03		635M01		635M17	
		µg/l	%	µg/l	%	µg/l	%	µg/l	%	µg/l	%
1st year	16	0.047	0.04	0.028	0.04	0.066	0.07	0.026	0.03	0.098	0.07
	17	0.040	0.03	0.076	0.12	0.127	0.14	0.113	0.11	0.065	0.06
	18	0.037	0.04	0.081	0.13	0.103	0.12	0.088	0.09	0.138	0.13
2nd year	16	0.021	0.02	0.058	0.05	0.164	0.18	0.139	0.15	0.037	0.02
	17	0.036	0.03	0.103	0.19	0.270	0.30	0.402	0.46	nd	0.00
	18	0.067	0.03	0.145	0.11	0.475	0.32	0.708	0.42	0.169	0.07
3rd year	16	-	-	-	-	-	-	-	-	-	-
	17	nd	0.00	0.044	0.10	0.341	0.52	0.481	0.65	nd	0.00
	18	nd	0.00	0.167	0.18	0.907	0.62	1.236	0.85	nd	0.00

Table B.8.2-32: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Metabolites radioactivity in soil (end of study)

Study layers (cm)	Lys. No.	tritosulfuron		635M02		635M03		635M01		635M17	
		µg/kg	%	µg/kg	%	µg/kg	%	µg/kg	%	µg/kg	%
0-10	16	nd	nd	0.04	0.18	0.27	1.03	0.49	1.61	nd	0.00
	17	nd	nd	0.06	0.19	0.22	0.56	0.10	0.23	nd	0.00
	18	nd	nd	0.07	0.16	0.24	0.42	0.33	0.50	nd	0.00
10-20	16	nd	nd	0.09	0.52	0.46	1.87	1.17	4.16	nd	0.00
	17	nd	nd	0.03	0.23	0.18	0.85	0.27	1.14	nd	0.00
	18	nd	nd	0.04	0.09	0.27	0.47	0.42	0.64	nd	0.00
20-30	16	nd	nd	0.06	0.32	0.26	1.01	1.09	3.68	nd	0.00
	17	nd	nd	0.03	0.21	0.17	0.86	0.60	2.60	nd	0.00
	18	nd	nd	0.10	0.30	0.45	1.04	1.36	2.74	nd	0.00

nd not determinable

Table B.8.2-33: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Radioactivity in plants

Period of study	Crop	Total uptake by the plants in % of the radioactivity applied		
		Lysimeter 16	Lysimeter 17	Lysimeter 18
1st year	spring wheat	2.87	1.63	2.07
2nd year	winter barley	0.25	0.26	0.70
3rd year	winter rape	0.15*	0.18	0.28

* harvested as green matter

Table B.8.2-34: Lysimeter study with [^{14}C-phenyl] tritosulfuron: Total balance in % of the applied radioactivity

	Lysimeter 16	Lysimeter 17	Lysimeter 18
Leachate	6.46	17.63	19.38
Soil	54.30	38.98	45.41
Plant	3.26	2.12	3.29
Mineralization[1)]	35.98	41.27	31.92

[1)] determination by calculating the difference

Comment:
The study is acceptable.

B.8.3 Predicted environmental concentrations in soil (Annex IIIA 9.1.3)

Hauck, T. (2001): Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in soil. BASF RegDoc# 2000/1017054; BOD 2001-519

Guidelines: None; calculation

GLP: No, not subject of GLP regulations

The intended application time is in spring for cereals and maize (early growth stages). For worst case considerations it was assumed that 100 % of the applied amount (50 g as/ha) reaches the soil in a single application. The PEC-values of tritosulfuron and its metabolites 635M01, 635M02, 635M03 and 635M04 (AMTT) in soil (PEC_s) are calculated on the basis of standardised field half-lives (see Chapter B.8.1.2.2, Table B.8.1-28 and Table B.8.3-1). For the short term exposure assessment, the worst case values were selected and standardised to a temperature of 15 °C by using the Arrhenius equation and a Q_{10} value of 2.2 (see Table B.8.3-1). The PEC values in soil are indicated as substance mass per soil mass (mg/kg). Therefore, the units of the compound concentrations in kg/ha were converted into mg/kg, considering the application rate, the fraction reaching soil, the highest formation fractions of the metabolites in soil (max. $frac_{mol,soil}$), a soil bulk density of 1.5 kg/l and a thickness of the soil layer of 5 cm. The calculated PECs in soil (actual and time weighted average) are given in Table B.8.3-2. The highest molar fractions of the metabolites in soil were calculated in the study of Dressel and Beigel (2001), reported in chapter B.8.1.2.2 (Table B.8.1-29).

Table B.8.3-1: Worst-case field half-lives standardised to a reference temperature of 20 °C and 15 °C (used for PEC-calculations) and highest molar fraction of metabolites in soil (max. $frac_{mol,soil}$)

	Worst-case DT_{50} standardised to 20 °C [d]	Worst-case DT_{50} standardised to 15 °C [d]	Highest molar fraction in soil (max. $frac_{mol,soil}$)
tritosulfuron	32.7	49	1.00
635M01	90.0	133	0.30
635M02	115.5	171	0.27
635M03	126.0	187	0.16
635M04 (AMTT)	23.1	34	0.19

Table B.8.3-2: Predicted actual ($PEC_{s,act}$) and time weighted average environmental concentrations ($PEC_{s,twa}$) of tritosulfuron, 635M01, 635M02, 635M03 and 635M04 (AMTT) in soil (0 - 5 cm)

	tritosulfuron		635M02		635M03		635M01		635M04 (AMTT)	
DAT* [d]	$PEC_{s,act}$ [mg/kg]	$PEC_{s,twa}$ [mg/kg]	$PEC_{s,act}$ [mg/kg]	$PEC_{s,twa}$ [mg/kg]	$PEC_{s,act}$ [mg/kg]	$PEC_{s,twa}$ [mg/kg]	$PEC_{s,act}$ [mg/kg]	$PEC_{s,twa}$ [mg/kg]	$PEC_{s,act}$ [mg/kg]	$PEC_{s,twa}$ [mg/kg]
0	0.067	0.067	0.018	0.018	0.011	0.011	0.020	0.020	0.013	0.013
1	0.066	0.066	0.018	0.018	0.011	0.011	0.020	0.020	0.012	0.013
2	0.065	0.066	0.018	0.018	0.011	0.011	0.020	0.020	0.012	0.012
4	0.063	0.065	0.018	0.018	0.011	0.011	0.020	0.020	0.012	0.012
7	0.060	0.063	0.017	0.018	0.010	0.011	0.019	0.020	0.011	0.012
28	0.045	0.055	0.016	0.017	0.010	0.010	0.017	0.019	0.007	0.010
50	0.033	0.048	0.015	0.016	0.009	0.010	0.015	0.018	0.005	0.008
100	0.016	0.036	0.012	0.015	0.007	0.009	0.012	0.016	0.002	0.005

DAT*: days after treatment

B.8.4 Fate and behaviour in water (Annex IIA 7.2.1; Annex IIIA 9.2.1, 9.2.3)

B.8.4.1 Hydrolytic degradation

Singh, M. and Thornton, S. (1997a): Hydrolysis of ^{14}C-BAS 635 H (phenyl label) in aqueous media. BASF RegDoc# 1996/5057; WAS 2001-210

Guidelines: EPA 161-1

GLP: yes

Test system:

Hydrolysis of ^{14}C-phenyl labeled tritosulfuron (specific radioactivity 576000 dpm/µg, radiochemical purity 99.2 %, chemical purity 98.2 %) was tested in aqueous buffer solutions at 50 °C at three different pH-values (pH 4, 7, and 9), and at 25 °C at four different pH-values (pH 4, 5, 7, 9). One sample was taken at each sampling time and analysed by radio-HPLC. The concentration of tritosulfuron in the buffer solutions was 5.7 mg/l and 5.5 - 5.7 mg/l for

the tests at 50 °C and 25 °C, respectively. The solutions were incubated in the dark under sterile conditions. Sampling times for the tests at 50 °C were 0, 22, (plus 28 at pH 4), 46, (52 pH 9), 70, 92, 116 hours and for the tests at 25 °C samples were analysed on day 0, 1, 3, 6, 8, 10 (except pH 9), 14, 16, 22, 24, and 35 days after application.

Findings:
At 50 °C, tritosulfuron is unstable at all pH values investigated. The hydrolysis products were not identified. The recovery of the radioactivity for all samples were > 95 % of the applied. After 4.8 days (116 h) 12.4 %, 88.6 % and 12.9 % of the applied radioactivity was recovered as unchanged tritosulfuron at pH 4, 7 and 9, respectively.
At 25 °C the recovery during the study was > 96 % of the applied radioactivity for all samples. The recoveries and the amounts of tritosulfuron and metabolites (HPLC analysis) in % of the applied radioactivity are given in Table B.8.4-1. After 35 days 64.3 %, 93.2 %, 98.5 % and 26.4 % were identified as unchanged tritosulfuron at pH 4, 5, 7 and 9, respectively.
Tritosulfuron was stable at pH 5 and 7. In both systems minor amounts of metabolite 635M02 (max. 3.5 % at pH 5) and metabolite 635M01 (max. 2.3 % at pH 7) could be detected. The main hydrolysis products at pH 4 were 635M02 with maximum amounts of 26.3 % and 635M01 with a maximum of 10.9 % of the applied radioactivity.
At pH 9, two additional peaks (designated as H1 and H5 in the original report) were detected, both representing a mixture of different compounds. H1 reached 60 % of applied radioactivity at day 35. H1 consisted mainly of 635M01 and of an unstable substance yielding 635M01 (H1 at day 35 consists of 32.6 % 635M01, 4.2 % TAR H3‘ and 19.8 % TAR 635M19. 635M19 is an unstable precursor of 635M01. Therefore, the peak H1 in the original report is referred to as 635M01 in Table B.8.4-1. The peak H5 consisted mainly of the adduct of BAS 635 H with the pH 9 tris-buffer. It reached only minor amounts (maximum 4.9 % on day 35) and is summed up in the table column "others". 635M03 was detected only at pH 9 in trace amounts below 1% TAR.
The degradation kinetics were calculated based on pseudo first-order kinetics. A summary is given in Table B.8.4-2. The active substance hydrolysed very slowly at pH 5 and 7. No half-lives are given for these two pHs at 25 °C because they would exceed twice the study duration (> 70 days). The DT_{50} at pH 7 was 38 days at 50 °C. At pH 4 and 9, the test substance hydrolysed rapid at 50 °C (DT_{50} of 1.6 days at both pH values) but slowly at 25 °C with a DT_{50} of 56 and 20 days for pH 4 and 9, respectively.

Table B.8.4-1: HPLC evaluation of [phenyl-^{14}C] tritosulfuron and its hydrolysis products in aqueous buffer solution at 25 °C (in % of applied radioactivity)

pH	DAT	Tritosulfuron	635M01	635M02	635M03	others*	recovery
4	0	98.9	n. d.	1.4	n. d.	n. d.	100.3
	1	97.4	0.7	1.7	n. d.	n. d.	99.7
	3	94.5	1.6	3.9	n. d.	n. d.	100.0
	6	90.0	2.4	6.6	n. d.	n. d.	98.9
	8	86.7	3.3	7.7	n. d.	n. d.	97.7
	10	85.1	4.2	9.4	n. d.	n. d.	98.6
	14	82.5	5.5	13.2	n. d.	n. d.	101.2
	16	80.0	6.1	13.5	n. d.	n. d.	99.5
	22	74.2	7.9	17.9	n. d.	n. d.	99.9
	24	72.1	8.2	19.7	n. d.	n. d.	100.0
	35	64.3	10.9	26.3	n. d.	n. d.	101.5

pH	DAT	Tritosulfuron	635M01	635M02	635M03	others*	recovery
5	0	98.6	n. d.	1.2	n. d.	n. d.	99.8
	1	97.3	n. d.	1.2	n. d.	n. d.	98.5
	3	97.5	0.5	1.3	n. d.	n. d.	99.4
	6	97.0	0.5	1.4	n. d.	n. d.	98.9
	8	94.6	0.6	1.3	n. d.	n. d.	96.5
	10	96.8	0.7	1.4	n. d.	n. d.	99.0
	14	96.8	1.4	2.1	n. d.	n. d.	100.3
	16	94.3	1.2	2.4	n. d.	n. d.	97.8
	22	94.9	1.3	2.4	n. d.	n. d.	98.6
	24	93.9	1.5	2.6	n. d.	n. d.	98.0
	35	93.2	1.7	3.5	n. d.	n. d.	98.5
7	0	98.0	n. d.	0.7	n. d.	n. d.	98.7
	1	96.3	n. d.	0.9	n. d.	n. d.	97.2
	3	95.4	n. d.	1.1	n. d.	n. d.	96.5
	6	96.3	n. d.	1.5	n. d.	n. d.	97.7
	8	96.2	n. d.	1.1	n. d.	n. d.	97.3
	10	97.7	n. d.	1.2	n. d.	n. d.	98.8
	14	96.7	0.7	1.7	n. d.	n. d.	99.1
	16	96.0	1.1	1.9	n. d.	n. d.	99.0
	22	95.3	1.4	1.3	n. d.	n. d.	98.0
	24	95.2	0.9	1.1	n. d.	n. d.	97.2
	35	98.5	2.3	2.0	n. d.	n. d.	102.8
pH	DAT	Tritosulfuron	635M01*	635M02	635M03	others**	recovery
9	0	93.7	2.3	1.2	n. d.	n. d.	97.3
	1	89.8	6.3	1.1	n. d.	n. d.	97.2
	3	79.3	14.8	1.2	n. d.	0.7	96.1
	6	74.3	19.9	2.0	n. d.	1.0	97.3
	8	83.6	7.3	3.2	n. d.	3.3	97.5
	14	48.3	44.1	3.0	n. d.	2.6	98.0
	16	48.6	42.3	3.2	n. d.	3.3	97.4
	22	40.5	48.7	3.6	n. d.	4.8	97.7
	24	50.4	38.5	3.7	0.4	4.5	97.5
	35	26.4	59.6	4.5	0.9	4.9	96.3

* includes 635M01, 635M19 and peak H3'
** others: peak H5 in original report

Table B.8.4-2: DT_{50} (days) values of [phenyl-^{14}C] labeled tritosulfuron under hydrolytic conditions

pH	25 °C	r^2	50°C	r^2	20 °C (calc.)
4	56	0.99	1.6	0.99	61
5	> 70	estimated	not measured		
7	> 70	estimated	38	0.91	> 70
9	20	0.92	1.6	0.99	21

Comment:
The study is acceptable.

Singh, M. and Thornton, S. (1997b): Hydrolysis of ^{14}C-BAS 635 H (triazine label) in aqueous media. BASF RegDoc# 1996/5091; WAS 2001-211

Guidelines: EPA 161-1

GLP: yes

Test system:
Hydrolysis of [^{14}C-triazine] labeled tritosulfuron (specific radioactivity 555600 dpm/µg, radiochemical purity 99.4 %, chemical purity 98.3 %) was tested in aqueous buffer solutions at 50°C at three different pH-values (pH 4, 7, and 9), and at 25 °C at four different pH-values (pH 4, 5, 7, 9). One sample was taken at each sampling time and analysed by radio-HPLC. The concentration of tritosulfuron in the buffer solutions was 6.7 mg/l and 6.7 – 7.4 mg/l for the tests at 50 °C and 25 °C, respectively. The solutions were incubated in the dark under sterile conditions. Sampling times for the tests at 50 °C were 0, 1, 2, 3, 4, and 5 days after application and for the tests at 25 °C samples were analysed on day 0, 1, 3, 7, 9, 15, 17, 21 (except pH 5), 23, 28, and 31 days after application.

Findings:
At 50 °C, tritosulfuron is unstable at all pH values investigated. The hydrolysis products were not identified. The recovery of the radioactivity for all samples were > 96 % of the applied. After 5 days 12.4 %, 87.1 % and 33.3 % of the applied radioactivity was recovered as unchanged tritosulfuron at pH 4, 7 and 9, respectively.
At 25 °C the recovery during the study was > 96 % of the applied radioactivity for all samples, except two samples wit 91.9 and 95 % (pH 9 day 3 and 7, respectively). The recoveries and the amounts of tritosulfuron and metabolites (HPLC analysis) in % of the applied radioactivity are given in Table B.8.4-3. After 35 days 55.7 %, 78.1 %, 90.9 % and 24.6 % were identified as unchanged tritosulfuron at pH 4, 5, 7 and 9, respectively.
Tritosulfuron was stable at pH 5 and 7. In both systems minor amounts of metabolite 635M01 (max. 2.1 % at pH 7) and metabolite 635M04 (AMTT) (max. 3.1 % at pH 5) could be detected.
The main hydrolysis products at pH 4 were 635M04 (AMTT) with maximum amounts of 22.0 % (complementary to 635M02 in the phenyl label) and 635M01 with a maximum of 8.2 % of the applied radioactivity. At pH 9 one main hydrolysis product was formed: metabolite 635M01. One major peak (equivalent 635M19) in the report was shown to be an unstable precursor of 635M01 and therefore is summed up together with 635M01 in Table B.8.4-3. This results in a maximum concentration of 635M01 of 55 % (including 20.6 % 635M19) TAR at pH 9 after 31 days.
The degradation kinetics were calculated based on pseudo first-order kinetics. A summary is given in Table B.8.4-4. The active substance hydrolysed very slowly at pH 5 and 7. No half-lives are given for these two pHs at 25 °C because they would exceed twice the study duration (> 62 days). The DT_{50} at pH 7 was 33 days at 50 °C. At pH 4 and 9, the test substance hydrolysed rapid at 50 °C (DT_{50} of 1.5 and 3.1 days, respectively) but slowly at 25 °C with a DT_{50} of 39 and 17 days for pH 4 and 9, respectively.

Table B.8.4-3: HPLC evaluation of [triazine-^{14}C] tritosulfuron and its hydrolysis products in aqueous buffer solution at 25 °C (in % of applied radioactivity)

pH	DAT	Tritosulfuron	635M01	635M04 (AMTT)	others**	recovery
4	0	100.1	n. d.	n. d.	n. d.	100.1
	1	94.6	n. d.	2.1	1.2	97.9
	3	86.8	1.7	3.4	7.9	99.8
	7	77.3	2.5	6.6	13.0	99.3
	9	75.6	3.6	8.2	11.7	99.1
	15	67.3	4.8	13.5	15.6	101.1
	17	67.1	5.7	13.4	14.8	100.9
	21	63.7	6.3	16.3	16.9	103.2
	23	61.5	6.9	17.6	16.2	102.2
	28	57.6	7.9	21.7	14.4	101.6
	31	55.7	8.2	22.0	15.1	101.0
5	0	98.6	n. d.	n. d.	n. d.	98.6
	1	97.4	n. d.	1.0	1.3	99.6
	3	91.9	0.8	1.1	5.6	99.4
	7	86.5	0.9	1.4	11.3	99.9
	9	85.3	1.1	1.4	12.2	100.0
	15	82.5	1.3	1.8	14.5	100.1
	17	81.4	1.4	1.8	16.2	100.7
	23	83.5	1.4	2.4	14.9	102.2
	28	82.9	1.5	3.1	12.0	99.4
	31	78.1	1.7	2.7	12.7	95.1
7	0	97.4	n. d.	n. d.	n. d.	97.4
	1	94.5	n. d.	1.2	1.3	97.0
	3	96.1	n. d.	0.8	1.4	98.3
	7	93.3	n. d.	1.3	1.6	96.2
	9	93.4	n. d.	1.4	2.6	97.4
	15	94.0	1.0	1.8	3.2	100.0
	17	96.1	1.2	1.5	1.0	99.8
	21	96.5	1.5	2.1	1.4	101.5
	23	96.7	1.5	1.7	0.9	100.8
	28	93.1	2.1	2.2	1.9	99.3
	31	90.9	1.8	2.0	3.6	98.3

pH	DAT	Tritosulfuron	635M01* (635M19)	635M04 (AMTT)	others**	recovery
9	0	99.5	n. d.	n. d.	1.7	101.2
	1	98.5	n. d.	1.3	1.0	100.8
	3	89.4	n. d.	1.3	1.1	91.9
	7	85.2	3.9	1.7	4.3	95.0
	9	87.0	4.8	1.8	7.6	101.2
	15	64.5	23.0 (14.9)	1.9	7.6	97.1
	17	51.8	35.3 (23.2)	2.0	12.3	101.4
	21	42.4	43.1 (26.5)	2.1	13.8	101.4
	23	37.3	46.4 (27.6)	1.3	19.9	104.9
	28	45.5	34.3 (16.3)	1.7	20.3	101.6
	31	24.6	55.0 (20.6)	2.2	19.1	100.8

* includes 635M01 and peak 635M19 (amount of 635M19 is given in brackets)

** others: peaks T1, T2, T3, T4, T5, T6, T8, T11, T13, T15, T17 in original report

Table B.8.4-4: DT_{50} (days) values of [triazine-^{14}C] labeled tritosulfuron under hydrolytic conditions

pH	25 °C	r^2	50 °C	r^2	20 °C (calc.)
4	39	0.95	1.5	0.97	43
5	> 62	estimated	not measured		
7	> 62	estimated	33	0.95	> 62
9	17	0.91	3.1	0.98	18

Comment:
The study is acceptable.

Tong, T.R. and Paulick, R.G. (2001): Hydrolysis of ^{14}C-BAS 635-5(AMTT) in aqueous solution. BASF RegDoc# 2000/5260; WAS 2001-212

Guidelines: EPA 161-1

GLP: yes

Test system:
Hydrolysis of the metabolite [^{14}C-triazine]-635M04 (AMTT) (specific radioactivity 281000 dpm/µg, radiochemical purity > 98 %, chemical purity: 99.9 %) was tested in aqueous buffer solutions at 25 °C at two different pH-values (pH 6.5 and 7.5) under sterile conditions and under non-sterile conditions in a natural water (pH 8.1). Duplicate samples were taken at each sampling time and analysed by radio-HPLC. The concentration of ^{14}C-635M04 (AMTT) in the test solutions was 4.2, 5.4 and 5.3 mg/l for buffer pH 6.5, buffer pH 7.5 and natural water, respectively. The solutions were incubated in the dark. Sampling times were 0, 1, 3, 7, 14, and 30 days after treatment.

Findings:
The metabolite of tritosulfuron 635M04 (AMTT) was stable under all pH value investigated. The recoveries and the amounts of metabolite 635M04 (AMTT) and metabolites (HPLC

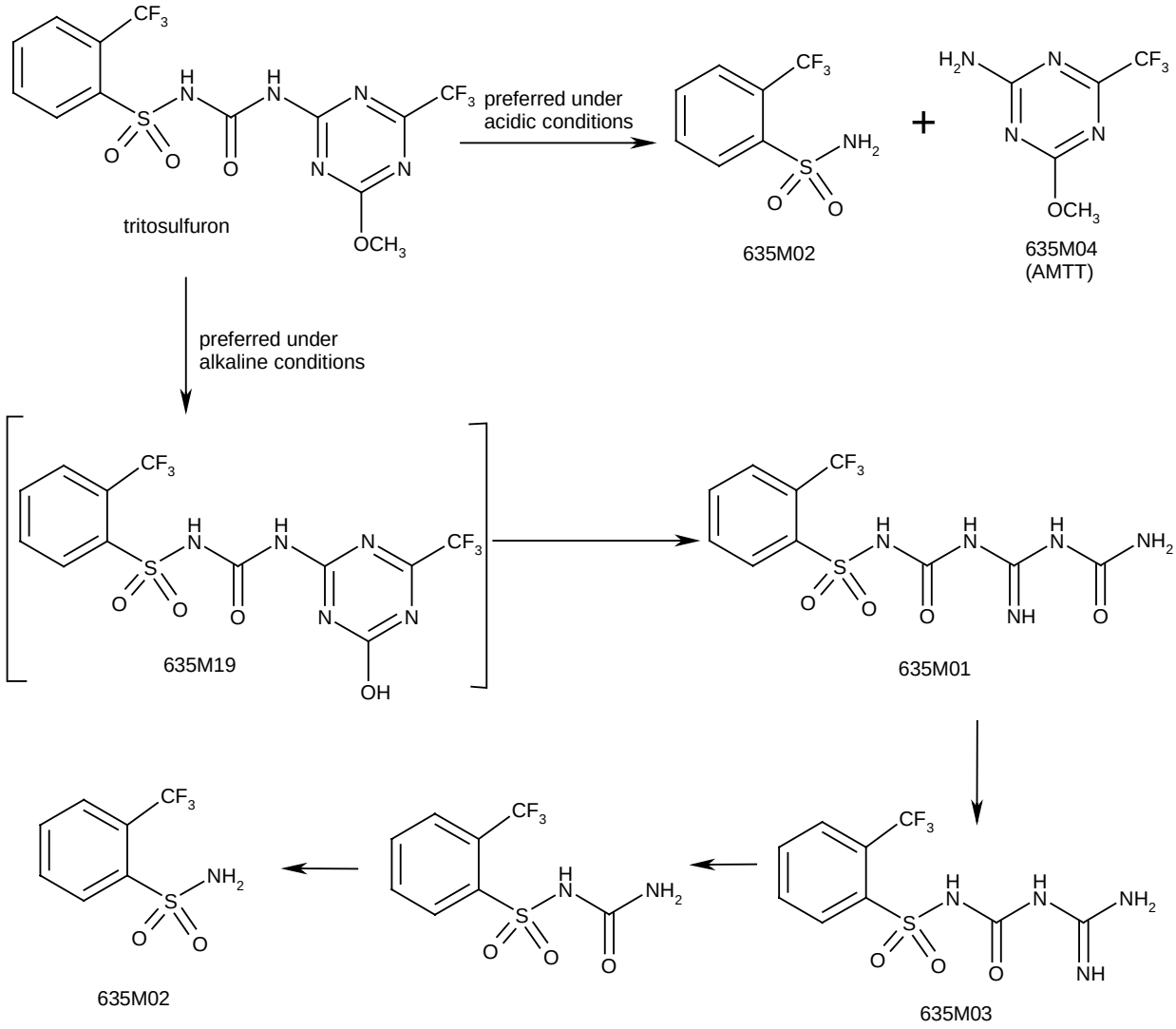
analysis) in % of the applied radioactivity are given in Table B.8.4-5. The recovery was > 99.8 % of the applied radioactivity at all sampling dates. After 30 days 97.0, 93.6 and 96.1 % of the applied radioactivity was identified as unchanged 635M04 (AMTT) at pH 6.5, 7.5 and 8.1, respectively.

Table B.8.4-5: HPLC evaluation of metabolite [triazine-^{14}C] 635M04 (AMTT) and its hydrolysis products in aqueous buffer solution at 25 °C (in % of applied radioactivity)

pH	DAT	635M04 (AMTT)	others	recovery
6.5 (buffer,sterile)	0	96.5	3.5	100.0
	1	97.4	3.6	101.0
	3	97.2	3.8	101.0
	7	97.1	3.6	100.7
	14	97.3	3.9	101.2
	30	97.0	4.1	101.1
7.5 (buffer, sterile)	0	96.2	3.8	100.0
	1	96.3	4.0	100.3
	3	96.5	4.2	100.7
	7	95.6	4.4	100.0
	14	95.0	4.8	99.8
	30	93.6	6.2	99.8
8.1 (natural water, non-sterile)	0	96.0	4.0	100.0
	1	97.1	3.6	100.7
	3	97.2	3.9	101.1
	7	97.1	4.2	101.3
	14	96.3	5.5	101.8
	30	96.1	6.3	102.4

Comment:
The study is acceptable.

Figure B.8.4-1: Proposed hydrolytic pathway of tritosulfuron



B.8.4.2 Photochemical degradation

Scharf, J. (1996): Adsorption coeficient of BAS 635 H at pH 4, pH 7 and pH 9. BASF RegDoc# 1996/10021; LUF 2001-185

Guidelines: BBA IV, 6-1; OECD draft test guideline, part A

GLP: yes

Test system:
UV adsorption spectra of tritosulfuron were measured in aqueous buffer solutions at pH 4, pH 7 and pH 9 between 290 and 800 nm. The test solutions contained 3.3, 3.7 and 3.7 mg tritosulfuron, repsectively, in 100 ml of aqueous pH 4, 7 and 9 Tritisol buffer solutions. The spectrum of the test solutions was measured in steps of 2.5 nm. Absorption coefficients were calculated for wavelength corresponding to the spectral solar photon irradiance data pupblished by Frank & Klöpffer (Chemosphere 17, 1988, 985-994).

Findings:
Above 290 nm the adsorption coefficients found for pH 7 and 9 are quite similar. The spectrum at pH 4 differs: the absorption coefficients at pH 4 were higher (~ factor 2) than the absorption at pH 7 and 9 at all wavelength investigated. This can be explained by the pKa-value of 4.69 (20 °C). The adsorption coefficients were > 10 l mol^{-1} cm^{-1} between 295.5 and 675 nm (up to 775 at pH 4). Therefore, direct phototransformation may be a pathway for dissipation in the environment.

Comment:
The study is acceptable.

Scharf, J. (1998a): Aqueous photolysis of BAS 635 H at pH 5 and pH 7. BASF RegDoc# 1998/10981; LUF 2001-186

Guidelines: FAO REV. 3; EEC 91/414; EPA 161-2; EEC 94/37

GLP: yes

Test system:
Aqueous photolysis of [^{14}C-triazine] tritosulfuron (specific radioactivity 153000 dpm/µg, radiochemical purity 98.3 %, chemical purity 99.8 %) was investigated at pH 5 and 7. Sterilized glass vessels with quartz glass caps containing 20 ml test solution (concentration 10 mg/l) were irradiated in a thermostated block. Each vessel had an air inlet and an air outlet. The incoming air was moistened, sterilised, and the CO_2 was removed. A trapping system for volatiles was connected to each vessel. The thermostated vessels were located under a xenon lamp with a light intensity of about 3 mW/cm^2 and a cut-off for wavelengths < 290 nm to simulate natural sunlight. The duration of the experiment was 15 days under continuous irradiation. Appropriate volumes of each test solution were stored in a climatic chamber to be used as dark control. The temperature was 22 ± 1 °C during the experiments. The solutions were analysed by HPLC and TLC on day 0, 2, 4, 7, 9, 12 and 15 after application.
For the determination of the quantum yield of tritosulfuron, a mixture of p-nitroacetophenone (2×10^{5} M) and pyridine (7.8×10^{-2} M) was used as chemical actinometer according to DULIN and MILL (Environ.Sci.Technol. 16, 1982, 815-820). During each irradiation experiment, two vessels with the actinometer solution were irradiated simultaneously with the test solutions.

Findings:
The recoveries of all samples were > 95.8 % of the applied radioactivity. Tritosulfuron showed no photolytic degradation during the study. The irrigated samples formed maximum amounts of volatile compounds of 0.4 %.
Since no half-life could be calculated for the substance, a degradation rate of 5 % within 15 days was assumed to be able to calculate a maximum quantum yield (theoretical DT_{50} = 203 d). The quantum yield of tritosulfuron was estimated to be less than $1.05 \cdot 10^{-4}$ at pH 5 and less than $2.23 \cdot 10^{-4}$ at pH 7.

Comment:
The study is acceptable.

Götz, N. von (1999): Aqueous photolysis of BH 635-4 under sensitising conditions. BASF RegDoc# 1999/10089; LUF 2001-187

Guidelines: FAO Revised guidelines on environmental criteria for the registration of pesticides revision 3 (28.08.1993)

GLP: yes

Test system:
The aqueous photolysis of metabolite 635M01 was investigated with unlabelled substance (chemical purity: 97.9 %) at a concentration of 6 mg/l in distilled water containing 1 Vol. % acetone as a sensitiser. A thermostated glass vessel containing about 50 ml test solution was irradiated under a xenon lamp with a light intensity of about 3 mW/cm^2 and a cut-off for wavelengths < 290 nm to simulate natural sunlight. The duration of the experiment was 15 days under continuous irradiation. Two samples very analysed on day 0, 1, 6, 9, 13 and 15 after application by HPLC. About 50 ml test solution was stored in a climatic chamber to be used as dark control. The temperature was about 22 °C during the experiments. As the sensitiser is degraded during photolysis with a half-life of about 3 d, on DAT 3, 6, 9 and 13 250 µg acetone, respectively, were added to the system to maintain a quasi-constant sensitizer concentration.

Findings:
The metabolite 635M01 was degraded in a sensitizing aquatic environment with a half-life of 3.6 d as related to continuous irradiation.

Comment:
The study is acceptable. This study should be seen as additional information, because the addition of a sensitiser (acetone) is not according to the guideline for the determination of aqueous photolysis.

B.8.4.3 Biological degradation

B.8.4.3.1 Ready biodegradation

Schwarz, K. (1995): Determination of the biodegradability of Reg.-No. 271 272 in the CO_2-evolution test. BASF RegDoc# 1995/10805; WAS 2001-213

Guidelines: OECD 301 B; ISO 9439; EEC 92/69 (Method C.4-C)

GLP: yes

Test system:
The aerobic biodegradability of tritosulfuron (chemical purity: 95.9 %) was evaluated in a carbon dioxide evolution test. Mixtures of the test substance at a concentration of 60 mg/l, a defined inorganic medium and a non-preadapted inoculum were incubated. The inoculum was activated sludge from laboratory waste water treatment plants which were fed with municipal and synthetic sewage. The test vessels and appropriate controls were incubated and aerated at

room temperature for up to 28 days. The produced carbon dioxide was trapped and measured. The measured amount of carbon dioxide at the end of the test was compared with the maximal theoretical production ($ThCO_2$) and indicated as biodegradation degree in percent. As a reference substance aniline was used.

Findings:
After 28 days, a degree of biodegradation of about 10 % was measured. The test substance was therefore considered as poorly biodegradable in this test.

Comment:
The study is acceptable.

B.8.4.3.2 Water/sediment study

Staudenmaier, H. (1998): Degradation of BAS 635 H in aerobic aquatic environment. BASF RegDoc# 1998/10950; WAS 2001-214

Staudenmaier, H. (2001b): Degradation of BAS 635 H in aerobic aquatic environment. Amendment No. 1, BASF RegDoc# 2001/1008967; WAS 2001-215

Guidelines: BBA IV, 5-1; EPA 162-4

GLP: yes

Test system:
The distribution and degradation of ^{14}C-phenyl and ^{14}C-triazine labeled tritosulfuron was studied separately in two natural systems of water and sediment. The specific radioactivity of the active substance was 9.60 MBq/mg for the phenyl-[^{14}C] label and 9.26 MBq/mg for the [^{14}C- triazine] label, with a radiochemical purity of 99.2 and 99.4 % and a chemical purity of 98.2 and 98.3, respectively. The water/sediment systems were taken from a pond and a pond-like side arm of a river, respectively, both in Rhineland-Palatinate, Germany. The characteristics of the systems used are given in Table B.8.4-6.
A test vessel contained 210 g or 140 g sediment and 285 ml or 290 ml water of the pond and river system, respectively. This correspond to a sediment layer of 2.5 cm and a water layer of 6 cm. After being filled with sediment and water, the flasks were allowed to equilibrate for 20 days. Tritosulfuron was applied to the water at a rate of 12.2 µg as per test vessel which corresponded to approx. 180 % of the maximum recommended rate of 50 g as/ha when related to a 30 cm deep water body. Experiments under sterile conditions were also carried out in both water/sediment systems. For the isolation and identification of degradation products, some water/sediment systems were additionally treated at an application rate of 120 µg as per test vessel. The test vessels were incubated in the dark at a temperature of 20 ± 2^{o} C for up to 100 days. Aeration was achieved by a stream of air over the water surface. Volatile compounds were trapped in ethylenglycole and 0.5 M NaOH, respectively. Sampling intervals were at 0, 0.25, 1, 2, 7, 14, 28, 63 and 100 days after treatment. Single samples were analysed on each sampling date for each system and label.
Water samples were extracted three time after acidification with HCl, the samples were pooled and the radioactivity was determined by LSC. Metabolites were determined by TLC and HPLC. Sediment samples were extracted twice with acetonitrile/water (1 : 1), the extracts were pooled and the radioactivity was determined by LSC. Then, the sediments were extracted

twice with acetonitrile and all extract were pooled and analysed by HPLC and TLC. Bound residues were extracted by 0.5 M NaOH (three times) and then acidified with HCl (pH 1). The radioactivity in the different extractions was determined by LSC.
DT_{50} values of tritosulfuron and metabolites were calculated by using the methods of Timme et. al (using logarithmic data) or by a simple compartment model that was established for the two water/sediment systems which were used for parameter estimation by the computer program Modelmaker v.3 patch 3.0.3 (Cherwell Scientific Publishing Ltd., Oxford, UK). The final compartment model, which was used in Modelmaker considered the distribution of tritosulfuron in the water and sediment and kinetic adsorption and desorption between both compartments. Tritosulfuron adsorbed in the sediment was degraded to metabolite 635M01. Tritosulfuron solved in the water phase was degraded to metabolite 635M02, which occurred in water, only. All degradation rates are described by first order kinetics. Because of highly correlated distribution rates between the water and the sediment, a pragmatic approach was used to determine the DT_{50} values of tritosulfuron in the sediment and the metabolite 635M02 in the water phase. After fitting the model to the data, the calculated concentrations were plotted. Then, the DT_{50} values were estimated by was determining the time between the maximum of a curve and its half.

Table B.8.4-6: Water-sediment study with ^{14}C-tritosulfuron: Characteristics of the systems used

Designation Origin		pond (Kastenbergheide) Rhineland-Palatinate, FRG	river (Berghäuser Altrhein) Rhineland-Palatinate, FRG
Sediment	sand [%] (German	74	32
	silt [%] scheme	10	46
	clay [%] DIN4220)	16	22
	textural class	clayey sand	silty sandy loam
	pH ($CaCl_2$)	6.6	7.5
	organic C [%]	1.1	4.7
	total N [%]	0.06	0.38
	total P [%]	< 0.03	0.11
	CEC [mVal Ba/100g]	12	23.1
Water	pH	7.8	8.0
	TOC [mg/l]	10.1	5.3
	total N [mg/l]	0.8	1.7
	total P [mg/l]	< 3	< 3

Findings:
The oberall recovery of te radioactivity in all vessels ranged between 94.0 and 103.4 % of the amount applied. The distribution and recovery of radioactivity in the pond system treated with ^{14}C-phenyl and ^{14}C-triazine labeled tritosulfuron is given in Table B.8.4-7 and Table B.8.4-8 shows the results of the river system.
The radioactivity slowly moved from the water to the sediment. The radioactivity in the water decreased within 100 days to 73 % TAR (both labels) in the pond system and to 44 % TAR (triazine label) and 50 % TAR (phenyl label) in the river system. In the sediment, the radioactivity correspondingly increased and accounted to about 25 % TAR (pond system) and 50 % TAR (river system) at the end of the incubation period. Mineralisation was low in both systems (≤ 5 % TAR) and no other volatile degradates were detected. The bound residues in the sediment were formed only to a low extent, reaching about 5 % TAR in the pond system and 10 % TAR in the river system. The bound residues of the 100 DAT samples of the river

system were fractionated into humins, humic acids and fulvic acids. Half of the bound radioactivity (about 5 % TAR) was located in the humic acids and humins. The other half was associated with the fulvic acid fraction. Because of the low amounts of radioactivity in the fulvic acid fraction, no chromatographic analysis could be done.
The distribution of tritosulfuron and metabolites formed in the pond and the river system are given in Table B.8.4-9 and Table B.8.4-10, respectively. The degradation of tritosulfuron in one system but with different labels (phenyl and triazine), led to similar amounts of the active substance and metabolites (if identified) at the different sampling dates. Tritosulfuron steadily disappeared from the water phase, reaching about 10 % TAR in the pond system and about 37 % TAR in the river system after 100 days. In the sediment, the amount of tritosulfuron increased to a maximum of about 10 – 13 % TAR and decreased again towards the end of the study. In the pond system, the decrease seemed to be faster than in the river system.
In both water/sediment systems, the same metabolites were detected (635M02, 635M03, 635M01) as in the aerobic soil metabolism, indicating that the route of degradation in surface water systems is similar to soil. 635M01 first appeared in the sediment and reached about 32 – 35 % TAR in the pond system and 11 – 13 % TAR in the river system at the end of the study. It could be detected for the last 3 - 4 sampling times also in the water in both systems, reaching 24 - 29 % TAR after 100 days. 635M03, which is considered as an intermediate between 635M01 and 635M02, never reached more than 4 - 5 % TAR in the water or in the sediment at any sampling time (considering that 635M03-values obtained with the triazine label have to be duplicated, since with this label, 635M03 contained only one ^{14}C-atom instead of two). 635M02 reached maximum amounts of 13 % (pond system) and 15 % TAR (river system) in the water phase during the study but decreased towards the end of the incubation (8 % in both systems). During MS-identification of the degradation products, one more metabolite could be identified which only appeared in trace amounts in water or sediment. It is designated as 635M11 (AHTT) and the proposed structure consists of the demethylated metabolite 635M04 (AMTT).
The degradation of the test substance in the sterilised test vessels was significantly slowed down compared to the viable samples. Although the metabolite pattern was similar. Final degradation to CO_2 or formation of bound residues could not be detected in the sterile samples.
Disappearance times have been calculated for the active substance in the water phase, in the sediment and in the total system and for metabolite 635M02 in the water phase by using the data of the phenyl-labeled substance. The DT_{50} values (1^{st} order) determined by using Modelmaker or Timme&Frehse are given in Table B.8.4-11. Depending on the computer program used, the DT_{50} values of tritosulfuron in the water were 67 or 60 days in the pond system and 32 or 30 days in the river system. The disappearance time of tritosulfuron in the total system was 77 and 36 days in the pond and river system, respectively. The DT_{50} value of tritosulfuron in the sediment (pond: 78 d, river: 36 d) and of metabolite 635M02 in the water phase (pond: 132 d, river: 67 d) are determined graphically. Because the formation of the compounds was not considered, these DT_{50} values represent conservative estimations of the degradation behavior.

Table B.8.4-7: Water-sediment study with ^{14}C-tritosulfuron: Material balance and distribution of radioactivity after application of [^{14}C]-tritosulfuron to the pond water/sediment [% of applied radioactivity]

DAT	water			sediment					CO_2	balance
				extractable residues			bound residues	total		
	EA	aqueous	total	ACN/H_2O	ACN	total				
phenyl-label										
0 h	99.1	1.2	96.7	0.9	0.0	0.9	0.0	1.0	n.d.	97.7
6 h	98.0	1.1	95.5	2.7	0.2	2.9	0.2	3.1	0.0	98.7
1 d	95.8	1.1	94.9	4.9	0.4	5.2	0.3	5.5	0.0	100.5
2 d	95.0	1.0	94.2	5.8	0.4	6.2	0.3	6.5	0.0	100.7
7 d	88.9	1.4	90.8	9.4	0.9	10.3	0.8	11.1	0.0	101.9
14 d	82.6	1.9	84.9	12.7	1.1	13.9	1.5	15.3	0.0	100.3
28 d	76.1	4.9	80.6	14.0	2.2	16.2	1.9	18.2	0.1	98.9
63 d	66.5	9.8	74.4	17.1	2.8	20.0	3.2	23.2	0.8	98.3
100 d	59.7	12.7	73.2	17.4	3.1	20.5	3.8	24.3	0.7	98.2
100 d (s)	64.9	3.2	67.9	25.0	2.4	27.4	1.5	28.9	n.d.	96.8
triazine-label										
0 h	99.3	0.7	95.3	0.4	0.1	0.5	0.1	0.5	n.d.	95.9
6 h	99.0	0.6	99.1	2.3	0.2	2.4	0.3	2.7	0.0	101.8
1 d	97.0	0.7	95.5	4.8	0.3	5.1	0.2	5.3	0.0	100.8
2 d	96.3	0.7	95.0	5.5	0.3	5.8	0.3	6.1	0.0	101.1
7 d	89.7	1.3	89.4	10.2	0.7	10.9	0.6	11.5	0.1	101.0
14 d	83.7	1.7	86.4	11.9	1.2	13.2	0.7	13.9	0.1	100.4
28 d	76.2	4.7	79.8	14.5	2.1	16.5	2.1	18.7	0.4	98.9
63 d	59.6	12.6	75.4	16.5	2.8	19.3	3.5	22.9	0.6	98.9
100 d	54.6	17.8	73.2	17.9	2.8	20.8	4.8	25.5	1.3	100.1
100 d (s)	66.0	3.6	72.3	24.7	2.2	27.0	1.3	28.3	n.d.	100.6

s = sterilised
n.d. = not determined
EA = ethyl acetate

Table B.8.4-8: Water-sediment study with ^{14}C-tritosulfuron: Material balance and distribution of radioactivity after application of [^{14}C]-tritosulfuron to the river water/sediment [% of applied radioactivity]

DAT	water			sediment					CO_2	balance
				extractable residues			bound residues	total		
	EA	aqueous	total	ACN/H_2O	ACN	total				
phenyl-label										
0 h	96.4	1.3	98.6	0.4	0.1	0.5	0.1	0.5	n.d.	99.2
6 h	96.5	1.2	93.5	4.1	0.3	4.4	0.2	4.6	0.0	98.1
1 d	91.3	1.4	91.0	9.3	0.5	9.8	0.4	10.2	0.0	101.2
2 d	88.7	1.2	88.0	11.5	0.5	12.0	0.4	12.4	0.0	100.4
7 d	78.7	1.9	79.1	19.3	1.2	20.4	1.2	21.7	0.1	100.9
14 d	69.7	3.3	71.6	25.7	1.5	27.2	1.9	29.1	0.3	101.1
28 d	53.9	8.7	61.9	27.9	3.5	31.4	5.3	36.7	0.5	99.0
63 d	41.3	11.3	50.5	35.1	2.4	37.6	8.6	46.2	0.7	97.3
100 d	33.8	15.8	49.9	36.6	2.8	39.4	9.8	49.2	1.2	100.4
100 d (s)	50.6	3.7	60.3	39.6	1.6	41.2	1.9	43.1	n.d.	103.4
triazine-label										
0 h	101.4	0.9	99.3	0.3	0.1	0.4	0.0	0.5	n.d.	99.8
6 h	97.3	0.8	96.2	4.1	0.3	4.4	0.2	4.6	0.0	100.9
1 d	91.3	0.8	87.9	10.0	0.6	10.6	0.3	10.9	0.0	98.7
2 d	89.7	1.0	90.0	10.5	0.6	11.1	0.4	11.5	0.0	101.5
7 d	77.5	1.5	79.0	21.2	1.1	22.3	0.9	23.3	0.0	102.2
14 d	68.2	3.3	70.6	25.8	2.2	28.0	1.8	29.8	0.2	100.7
28 d	54.5	10.4	63.9	27.9	2.8	30.7	4.1	34.8	0.5	99.1
63 d	40.1	9.1	50.3	36.5	3.0	39.5	7.7	47.3	0.4	97.9
100 d	30.4	13.4	43.6	38.8	2.7	41.4	9.3	50.8	5.0	99.5
100 d (s)	53.9	3.7	58.7	31.9	1.6	33.5	1.9	35.3	n.d.	94.0

s = sterilised
n.d. = not determined
EA = ethyl acetate

Table B.8.4-9: Water-sediment study with ^{14}C-tritosulfuron: Amounts of tritosulfuron and metabolites in the pond system treated with ^{14}C-phenyl (ph) and ^{14}C-triazine (tr) labeled active substance [% of the applied radioactivity]

DAT	tritosulfuron		635M02		635M03		635M01		635M11 (AHTT)		others	
	ph	tr	ph	tr	ph	tr	ph	tr	ph	tr	ph	tr
water												
0 h	99.1	99.3	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
6 h	98.0	99.0	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
1 d	95.8	97.0	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
2 d	95.0	96.3	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
7 d	88.9	89.7	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
14 d	75.5	83.7	7.1	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
28 d	66.7	72.9	9.3	-	0.2	0.0	3.1	6.5	-	0.0	0.0	0.1
63 d	42.3	44.9	13.0	-	0.7	0.0	18.2	16.6	-	2.8	0.3	0.0
100 d	37.6	37.4	7.5	-	1.3	0.0	24.4	26.0	-	1.9	0.8	2.9
100 d s	54.2	62.6	5.9	-	0.0	0.0	4.8	3.4	-	0.0	0.0	0.0
sediment												
1 d	5.2	5.1	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
2 d	6.2	5.8	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
7 d	9.7	10.9	0.0	-	0.0	0.0	0.6	0.0	-	0.0	0.0	0.0
14 d	10.9	9.3	0.0	-	0.0	0.0	1.5	1.6	-	0.0	1.5	2.3
28 d	10.3	10.4	0.0	-	0.0	0.0	4.0	4.6	-	0.0	1.9	1.6
63 d	7.0	6.5	0.0	-	0.0	0.0	10.9	10.3	-	0.0	2.0	2.6
100 d	6.7	6.5	0.9	-	1.5	0.0	10.7	12.8	-	0.0	0.8	1.4
100 d s	23.8	24.1	0.0	-	0.0	0.0	3.6	2.9	-	0.0	0.0	0.0

s = sterilised

Table B.8.4-10: Water-sediment study with ^{14}C-tritosulfuron: Amounts of tritosulfuron and metabolites in the river system treated with ^{14}C-phenyl (ph) and ^{14}C-triazine (tr) labeled active substance [% of the applied radioactivity]

DAT	tritosulfuron		635M02		635M03		635M01		635M11 (AHTT)		others	
	ph	tr	ph	tr	ph	tr	ph	tr	ph	tr	ph	tr
water												
0 h	96.4	101.4	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
6 h	96.5	97.3	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
1 d	91.3	91.3	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
2 d	86.9	89.7	1.7	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
7 d	72.8	77.5	5.8	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
14 d	55.1	63.3	14.6	-	0.0	0.0	0.0	3.3	-	1.6	0.0	0.0
28 d	39.4	48.4	8.3	-	0.4	0.0	11.3	13.2	-	0.0	0.3	0.0
63 d	23.3	30.4	6.3	-	1.5	$0.6 \cdot 2^{+}$	18.6	14.8	-	0.0	0.0	0.8
100 d	10.3	10.4	8.2	-	3.4	$1.9 \cdot 2^{+}$	27.0	29.3	-	0.0	0.0	1.5
100 d s	45.4	51.6	2.6	-	0.0	0.0	2.6	2.3	-	0.0	0.0	0.0
sediment												
1 d	9.8	9.1	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	1.5
2 d	12.0	10.1	0.0	-	0.0	0.0	0.0	0.0	-	0.0	0.0	1.0
7 d	10.5	10.9	0.0	-	0.0	0.0	2.8	2.6	-	0.0	7.1	8.8
14 d	11.1	12.4	0.0	-	0.0	0.0	9.6	9.4	-	0.0	6.5	6.3
28 d	12.5	11.0	0.0	-	0.0	0.0	14.8	16.6	-	0.0	4.1	3.1
63 d	6.5	11.1	0.0	-	2.2	0.0	24.6	23.5	-	0.0	4.2	4.9
100 d	1.2	3.9	0.0	-	3.9	$2.4 \cdot 2^{+}$	31.6	35.2	-	0.0	2.8	0.0
100 d s	36.9	31.0	0.0	-	0.0	0.0	4.3	2.5	-	0.0	0.0	0.0

$^{+}$ The percent of applied radioactivity must be duplicated for the calculation of the amount of 635M03

s = sterilised

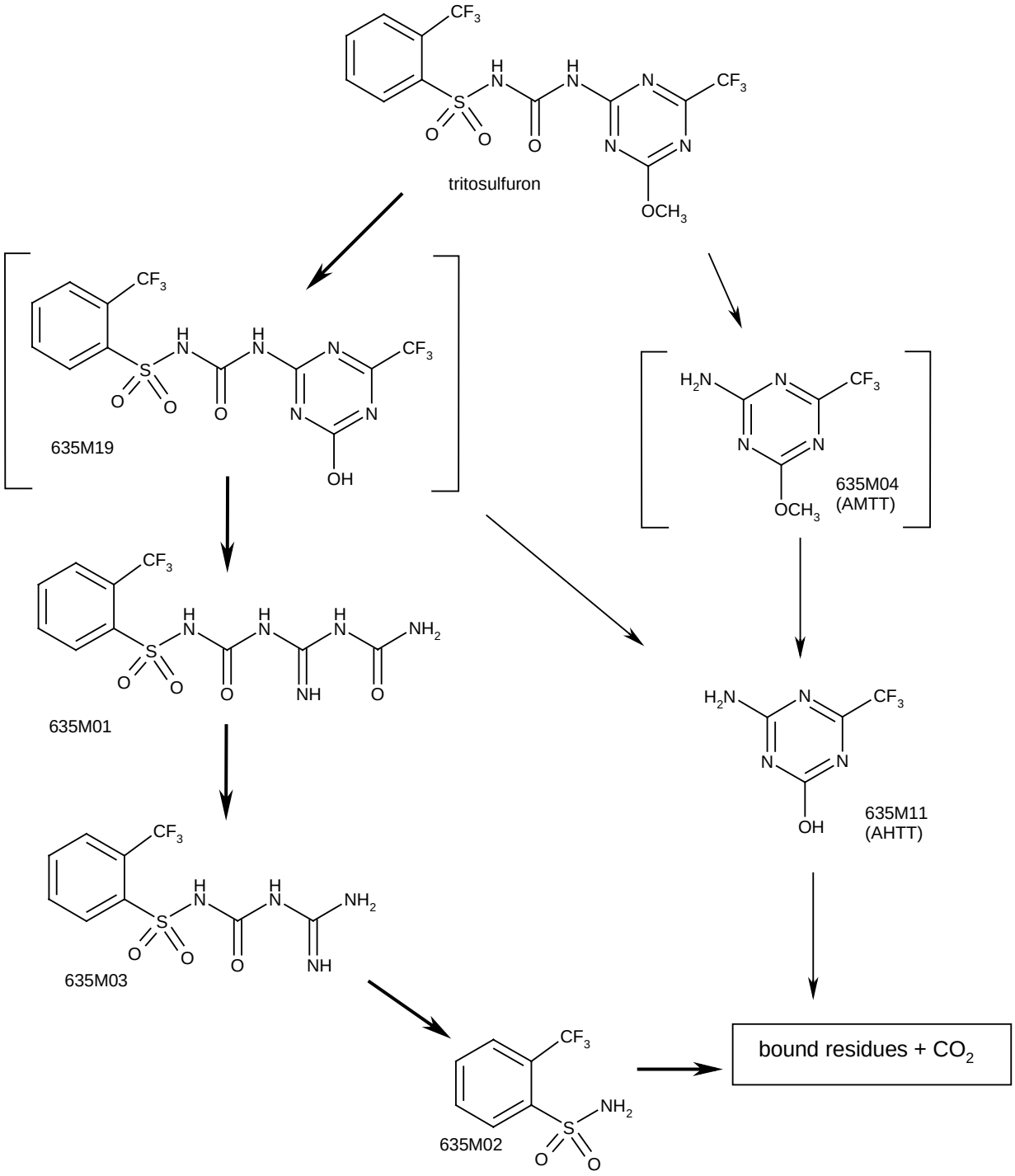
Table B.8.4-11: Water-sediment study with ^{14}C-tritosulfuron: DT_{50} values of tritosulfuron and metabolite 635M02 in the pond and river systems under laboratory conditions calculated by using 1. order kinetics [days]

			Timme&Frehse	r^2	ModelMaker	r^2
pond	tritosulfuron	water	67	0.98	60	0.98, whole compartment
		total system	77	0.98	n.c.	
		sediment	n.c.		78*	
	635M02	water	n.c.		132*	
river	tritosulfuron	water	32	0.97	30	0.98, whole compartment
		total system	36	0.99	n.c.	
		sediment	n.c.		36*	
	635M02	water	n.c.		67*	

* Conservative graphical estimation of the DT_{50} value, because formation was not considered (see text)

Comment:
The study is acceptable.

Figure B.8.4-2: Proposed route of degradation of tritosulfuron in water-sediment



B.8.5 Impact on water treatment procedures (Annex IIIA 9.2.2)

No data. Impact not expected.

B.8.6 Predicted environmental concentrations in surface water and in ground water (Annex IIIA 9.2.1, 9.2.3)

B.8.6.1 Predicted envrionmental concentration in surface water (PEC_{sw})

Platz, K. (2001): Calculation of predicted environmental concentrations (PECsw) for BAS 635 H and metabolites BH 635-2, BH 635-4 and BH 635-5 in static surface waters. BASF RegDoc# 2000/1018549; WAS 2001-218

Dressel, J. (2002): Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-4 and BH 635-5 in static surface waters (PEC_{sw}) and sediment (PEC_{sed}) after drift entry. BASF RegDoc ID 2002/1000213; WAS 2002-96

Dressel, J. (2002): First amendment to Final Report: Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-4 and BH 635-5 in static surface waters (PEC_{sw}) and sediment (PEC_{sed}) after drift entry. BASF RegDoc ID 2002/1003269; WAS 2002-196

Guidelines: None; calculation

GLP: No, not subject of GLP regulations

Predicted actual environmental concentrations ($PEC_{sw,act}$) in static surface waters and time weighted average concentrations ($PEC_{sw,twa}$) were calculated for the herbicidal active ingredient tritosulfuron and the metabolites 635M01, 635M02 and 635M04 (AMTT).
The PEC_{sw} were calculated for tritosulfuron and metabolites for a static water body of 30 cm water depth. The assessments are made for a scenario with arable crops. Tritosulfuron is applied in a single application rate of 50 g as/ha onto cereals and maize in spring. Two entry route were considered: spray drift and run-off. A half life of 67 days was obtained from the water sediment study using the Timme et al. approach (first order kinetics). For the metabolites 635M01 and 635M02, the maximum fractions of the total radioactivity observed in the water phase ($frac_{mol,water}$) were taken into account for the calculation of the initial concentrations of the metabolites: 635M01: 28.1 % TAR , 635M02: 14.6 % TAR. 635M04 was not observed in the water-sediment study. No degradation of the metabolites in the water phase was taken into account.

Entry via spray drift
Different drift scenarios were considered with overspray (as a worst case base line) and with a 1 m buffer for arable crops. Using the 90^{th} percentile drift factors (Ganzelmeier) it is assumed that 2.77 % of the applied amount reach the water body via drift in 1 m buffer distance.

Entry via run-off
A simple approach is applied which assumes that the residues of the plant protection product on soil can potentially reach the surface water via runoff. In case of no buffer zones, a fraction of 0.5 % of the soil residue on day 3 after last application is transported to the surface water body via runoff. It is assumed that the residue reaches the water body in the runoff water only and not absorbed onto eroded soil particles. A partitioning of the compound between runoff water and eroded soil particles is therefore not considered. A field of 100 m x 100 m and an adjacent surface water basin of 30 cm depth, 100 m length and 1 m width is further assumed.

The water volume in the water course is 30000 l. The scenario implies 20 mm precipitation (rain event 3 days after last application) and 50 % (10 mm) runoff, which results in 100 000 l of runoff water that enters the water course. A further reduction factor f_{DILUTE} of 0.5 was applied for the calculation of the $PEC_{sw,ini}$-values by runoff to account for the dilution by the moving water induced by the runoff event.
The application rate of 50 g as/ha, the lowest interception by crops (25 % in the BBCH growth stage 13 - 39 at the time of application for wheat), and the degradation of tritosulfuron in soil (until day 3 after application) was taken into account for calculation of the concentration in soil at the day of the runoff event (see Table B.8.6-1). The average field half-life (first order kinetics, 14.1 d at 20 °C) standardised to 15 °C was considered (half-life at 15 °C = 21.4 d, degradation rate k = 0.03239 1/d).
As a worst case assessment, it was assumed that the runoff event of the metabolites occurs at the day of their maximum concentration in soil. The average maximum concentrations in soil of 635M01, 635M02 and 635M04 (AMTT) as fitted for several field degradation experiments were taken into account (see Dressel and Beigel 2001, Chapter B.8.1.2.2, Table B.8.1-29). As a worst case assessment the considered maximum concentrations of the metabolites are the sum of the findings in all soil layers. The average fitted maximum concentrations of the metabolites in the field studies are given as the molar fraction ($frac_{mol,soil}$) of the active substance (as). They are converted into the mass fraction of the as under consideration of their molar mass. Then the concentration of the metabolite at the day of runoff was calculated by multiplying the application rate of 50 g as/ha by the mass fraction of as of the metabolite (see Table B.8.6-1).

Table B.8.6-1: Concentrations of tritosulfuron and metabolites in soil at the day of runoff

Compound	tritosulfuron	635M01	635M02	635M04 (AMTT)
Application rate of parent [g/ha]	50	-	-	-
Molar mass [g/mol]	445.3	353.3	225.2	194.1
average maximum molar fraction of as $frac_{mol,soil}$[-]	1.000	0.144	0.150	0.122
$C_{soil\ at\ day\ of\ runoff}$ [g/ha]	45.37	5.71	3.79	2.66

Table B.8.6-2: $PEC_{sw,ini}$-values for tritosulfuron, 635M01, 635M02 and 635M04 (AMTT) after different loadings

Entry route	Spray drift loading "overspray" $PEC_{sw,initial}$ [µg/l]	Spray drift loading "1 m buffer zone" $PEC_{sw,initial}$ [µg/l]	Runoff loading "no buffer zone" $PEC_{sw,initial}$ [µg/l]
tritosulfuron	11.6	0.461	0.655
635M01	2.6	0.103	0.083
635M02	0.8	0.034	0.055
635M04	-*	-*	0.039

*the $PEC_{sw,ini}$ via spray drift for BH 635M04 was not considered because it was not formed in the water sediment study.

The loading via runoff leads to higher initial concentrations in surface water for 635M02 than the loading via drift with a buffer zone of 1 m. To consider worst case conditions, the initial PEC_{sw} via runoff is taken into account for the calculation of the actual and the time weighted

average concentrations in surface water for 635M02 and also for 635M04 (AMTT), for which runoff is the possible relevant entry route. The initial, actual and the time weighted average concentrations of tritosulfuron and metabolites 635M01, 635M02 and 635M04 (AMTT) in surface water ($PEC_{sw,act}$ and $PEC_{sw,twa}$) are given in Table B.8.6-2 and Table B.8.6-3.

Table B.8.6-3: $PEC_{sw,act}$ and $PEC_{sw,twa}$ for tritosulfuron, 635M01, 635M02 and 635M04 (AMTT)

		tritosulfuron (drift 1 m buffer)		635M01 (drift 1 m buffer)	635M02 (runoff)	635M02 (drift 1 m)	635M04 (runoff)
Time		$PEC_{sw,act}$	$PEC_{sw,twa}$	$PEC_{sw,twa}$	$PEC_{sw,twa}$	$PEC_{sw,twa}$	$PEC_{sw,twa}$
	[d]	[µg/l]	[µg/l]	[µg/l]	[µg/l]	[µg/l]	[µg/l]
Initial	0	0.46	0.46	0.103	0.055	0.034	0.039
Short-term	1	0.46	0.46	0.103	0.055	0.034	0.039
	2	0.45	0.46	0.103	0.055	0.034	0.039
	4	0.44	0.45	0.103	0.055	0.034	0.039
Long-term	7	0.43	0.45	0.103	0.055	0.034	0.039
	14	0.40	0.43	0.103	0.055	0.034	0.039
	21	0.37	0.41	0.103	0.055	0.034	0.039
	28	0.35	0.40	0.103	0.055	0.034	0.039
	42	0.30	0.37	0.103	0.055	0.034	0.039

B.8.6.2 Predicted envrionmental concentration in sediment (PEC_{sed})

Dressel, J. (2002): Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-4 and BH 635-5 in static surface waters (PEC_{sw}) and sediment (PEC_{sed}) after drift entry. BASF RegDoc ID 2002/1000213; WAS 2002-96

Dressel, J. (2002): First amendment to Final Report: Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-4 and BH 635-5 in static surface waters (PEC_{sw}) and sediment (PEC_{sed}) after drift entry. BASF RegDoc ID 2002/1003269; WAS 2002-196

Guidelines: None; calculation

GLP: No, not subject of GLP regulations

Predicted initial, short-term and long-term concentrations for tritosulfuron and its metabolite 635M01 in sediment (PEC_{sed}) after application are calculated based on the results of a water/sediment study. The assessments are made for an arable crop scenario with a single application of 50 g as/ha. The PEC_{sed}-values are calculated for a sediment of 2 cm depth and a bulk density of 1.3 kg/l. The highest concentration of tritosulfuron in the sediment was observed on day 28 with 12.5 % TAR (total applied radioactivity) in the river sediment with the phenyl-labeled tritosulfuron. The highest concentration of 635M01 in the sediment was observed on day 100 with 35.2 % TAR in the river sediment with the triazine-labeled substance. Overspray and drift entry with 1 m buffer (2.77 % drift) for arable crops were considered. For the calculation of the concentration of metabolite 635M01 in sediment the molar mass was considered.

Table B.8.6-4: PEC_{sed} for tritosulfuron and metabolite 635M01 (loading of water body by overspray and drift in 1 m buffer distance using the 90th percentile drift factor)

	tritosulfuron		635M01	
time	overspray	drift: 1 m buffer	overspray	drift: 1 m buffer
[d]	[mg/kg]	[mg/kg]	[mg/kg]	[mg/kg]
1	0.019	0.00052	0.0000	0.000
2	0.023	0.00064	0.0000	0.000
7	0.020	0.00056	0.0011	0.00003
14	0.021	0.00059	0.0040	0.00011
28	0.024 (= max.)	0.00066 (= max.)	0.0072	0.0002
63	0.013	0.00035	0.0101	0.00028
100	0.002	0.00006	0.0152 (= max.)	0.00042 (= max.)

B.8.6.3 Predicted envrionmental concentration in groundwater (PEC_{gw})

Beigel, C. (2001): Calculation of predicted environmental concentrations (PECgw) for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in groundwater using FOCUS groundwater scenatios for Europe. BASF RegDoc# 2000/1018546; BOD 2002-32

Guidelines: according to report of the FOCUS groundwater scenarios workgroup for Europe

GLP: No, not subject of GLP regulations

The FOCUS Groundwater shells PELMO version 1.1.1 and MACRO version 1.2.1 were used to assess the risk for leaching of tritosulfuron and its soil metabolites following application of 0.05 kg as/ha to maize, spring cereals and winter cereals in the EU. In Table B.8.6-5 interception, application rates are summarised. Application dates are given in Table B.8.6-7.
The half-life values and metabolite formation fractions were calculated from the field dissipation studies based on the proposed dissipation route, first-order kinetics, and using a procedure for standardization to the FOCUS reference conditions of soil temperature (20 °C) and moisture content (pF2), see Chapter B.8.1.2.2. A metabolism scheme was used in the models to describe the fromation and degradation of metabolites in the model. Tritosulfuron can be transformed to metabolites 635M01, 635M02 and 635M04 (AMTT), as well as CO_2, bound residues and other degradates (lumped together in a sink compartment). The average formation fractions for 635M01, 635M02, 635M04 (AMTT) and for the sink are 0.174, 0.165, 0.329 and 0.335, respectively. The standardized, first-order half-life values of tritosulfuron estimated from the field trials, ranged from 2.6 to 32.7 d. The average value of 14.1 d was selected for the simulations. The average standardized, first-order half-life values of 635M01, 635M02, 635M03 and 635M04 (AMTT) which were selected for the simulations are given in Table B.8.6-6. As recommended by FOCUS, the average values of the sorption parameters were used for the simulations. The substance-related input parameters for tritosulfuron and metabolites are listed in Table B.8.6-6.

Table B.8.6-5: Crop-related model input parameters

Input parameter	Unit	Winter cereal scenario	Spring cereal scenario	Maize scenario
application rate	kg/ha	0.05	0.05	0.05
BBCH growth stage		20	13	13
crop interception	%	50	25	25
amount reaching soil	kg/ha/a	0.025	0.0375	0.0375

Table B.8.6-6: Summary of the main input parameters used for the FOCUS simulations

Compound	tritosulfuron	635M02	635M03	635M01	635M04 (AMTT)	Others (sink)
Molecular weight [g/mol]						
	445.3	225.2	310.3	353.3	194.1	-
Sorption input parameters						
Koc [l/kg]	7.4	40.6	30.1	89.0	20.8	-
1/n [-]	0.913	0.957	0.912	0.923	0.935	-
Degradation input parameters						
Formation fraction [-]	-	0.165	-	0.171	0.329	0.335
Formation rate [1/d]	-	0.0081	0.0099	0.0084	0.0162	0.0165
DT_{50} [d] at 20 °C	14.1	64.4	67.7	69.9	9.7	-

The PEC_{gw}-values for leaching of tritosulfuron and metabolites 635M01, 635M02, 635M03, and 635M04 (AMTT) at 1m depth for the different locations scenarios relevant for maize, spring and winter cereals applications, generated with FOCUS-PELMO version 1.1.1, are listed in Table B.8.6-7. The PEC_{gw}-values (predicted 80^{th} percentile concentrations for leaching at 1m depth) of tritosulfuron and the toxicologically relevant metabolite 635M04 (AMTT) under preferential flow conditions for the different crop scenarios in Châteaudun, generated with MACRO FOCUS version 1.2.1, are listed in Table B.8.6-8. The leaching concentrations below the FOCUS-defined 0.001 µg/l limit for relevance of the models are expressed as 0.000 µg/l.

Table B.8.6-7: PEC_{gw}-values for tritosulfuron, 635M01, 635M02, 635M03 and 635M04 (AMTT) simulated with FOCUS-PELMO v1.1.1

Location	Application time	PECgw (80th percentile concentration) (µg/l)				
		tritosulfuron	635M02	635M03	635M01	635M04 AMTT
winter cereal scenario						
Châteaudun	01/04	0.008	0.156	0.097	0.01	0.001
Hamburg	01/04	0.066	0.218	0.166	0.040	0.008
Jokionen	01/06	0.082	0.216	0.129	0.018	0.008
Kremsmünster	01/04	0.079	0.207	0.153	0.059	0.014
Okehampton	01/04	0.089	0.189	0.152	0.067	0.014
Piacenza	01/04	0.074	0.232	0.178	0.071	0.009
Porto	10/03	0.006	0.058	0.032	0.002	0.001
Sevilla	10/03	0.000	0.007	0.002	0.000	0.000
Thiva	10/03	0.000	0.105	0.053	0.001	0.000
spring cereal scenario						
Châteaudun	31/03	0.004	0.179	0.097	0.006	0.001
Hamburg	22/04	0.063	0.324	0.237	0.046	0.009
Jokionen	01/06	0.143	0.296	0.166	0.018	0.009
Kremsmünster	22/04	0.075	0.305	0.213	0.065	0.011
Okehampton	22/04	0.099	0.309	0.224	0.064	0.017
Porto	31/03	0.002	0.060	0.025	0.001	0.000
maize scenario						
Châteaudun*	22/05	0.015	0.212	0.124	0.012	0.002
Hamburg	26/05	0.084	0.347	0.240	0.048	0.013
Kremsmünster	26/05	0.050	0.273	0.183	0.033	0.006
Okehampton	15/06	0.083	0.298	0.223	0.050	0.011
Piacenza*	05/06	0.062	0.254	0.218	0.091	0.010
Porto	22/05	0.001	0.036	0.010	0.000	0.000
Sevilla*	28/03	0.000	0.000	0.000	0.000	0.000
Thiva	11/05	0.000	0.060	0.023	0.000	0.000

*Scenarios with irrigation

Table B.8.6-8: PEC_{gw} of tritosulfuron and metabolite 635M04 (AMTT) in Châteaudun with preferential flow (simulations performed with FOCUS-MACRO v1.2.1)

Crop	Application time (julian days)	PEC_{gw} (µg/l)	
		tritosulfuron	635M04 (AMTT)
Winter cereals	91	0.012	0.002
Spring cereals	90	0.017	0.003
Maize	144	0.064	0.009

B.8.7 Fate and behaviour in air (Annex IIA 7.2.2; Annex IIIA 9.3)

The low vapour pressure of tritosulfuron (< $1.0 \cdot 10^{-5}$ Pa, see Chapter 1, Section B.2.1.3.1) and the Henry's constant (< $1.012 \cdot 10^{-4}$ Pa m^3 mol^{-1}, see Chapter 1, Section B.2.1.3.2) indicates little potential for volatilisation from either soil or plant surfaces. Despite of this fact studies about the volatilisation from plant and soil and a calculation of photo-oxidative degradation in the troposphere (DT_{50}: 0.44 d (24 h-day, see Chapter 1, Section B.2.1.10)) were performed. The results of the volatilisation study are described below:

B.8.7.1 Volatilisation studies

Scharf, J. (1998b): Laboratory study on the volatilisation of BAS 635 H after application of BAS 635 00 H on soil and plant surfaces. BASF RegDoc# 1998/10982; LUF 2001-189

Guidelines: BBA IV, 6-1

GLP: yes

Test system:
The volatilization study was performed with the formulation BAS 635 00 H (containing nominal 71.4 % tritosulfuron) based on a field application rate of 50 g active substance/ha. The formulation was mixed with about 11 % triazine-2,4-[^{14}C]-labeled tritosulfuron to enable a total balance. The specific radioactivity of the labeled tritosulfuron was 555600 dpm/µg, the radiochemical purity was > 95 %. Soil and plant were treated in a special glass container. The formulation was applied via a nozzle (1.2 bar) to a small dish filled with soil (first experiment), and to a dish with a plant (bush bean, soil covered; second experiment). The soil characteristics were: 94 % sand, 6 % silt, 0 % clay, organic carbon 0.8 %, pH 5.9, MWHC 24 g/100 g dry soil. The soil test was performed at a soil moisture of 60 % MWHC.
Application losses were determined by rinsing the glass container and the whole equipment with methanol. The treated soil and plants were kept in a special volatilization chamber with adjustable air flow rate (about 200 l/h) and air temperature (20 ± 3 °C). The wind speed was adjusted to 1 m/s. The radioactive volatiles were trapped in charcoal traps. These traps were sampled 1, 3, 6, and 24 h after application. At the end of the study, the remaining radioactivity in soil and plant was determined.

Findings:
The total recovery of radioactivity was 101 and 102 % for the plant and the soil experiment, respectively. The volatilization rates of tritosulfuron in the BAS 635 00 H formulation were about 3 % from the plant surface and 2 % from the soil surface.

Comment:
The study is acceptable.

B.8.8 Predicted environmental concentrations in air (Annex IIIA 9.3)

Not applicable. The low vapour pressure of tritosulfuron (< $1.0 \cdot 10^{-5}$ Pa, see Chapter 1, Section B.2.1.3.1) and the Henry's constant (< $1.012 \cdot 10^{-4}$ Pa m^3 mol^{-1}, see Chapter 1, Section B.2.1.3.2) indicates little potential for volatilisation from either soil or plant surfaces.

The study of the volatilisation behaviour of tritosulfuron from plant and soil surfaces show that only about 3 % of the active substance volatilise within 24 hours after application. Tritosulfuron has no relevant tendency to enter the air.
Furthermore, the DT_{50} of the photochemical-oxidative degradation is lower than 6 hours.

B.8.9 Definition of the residue (Annex IIA 7.3)

The major metabolites in soil are 635M01, 635M02 and 635M03. Metabolite 635M04 (AMTT) did not occur in soil degradation studies in the laboratory or in the field > 10 % and was not expected to occur in significant amounts in groundwater. The entry of the metabolites 635M01, 635M02 and 635M03 in ground water can not be excluded, because the concentrations exceeded 0.1 µg/l in lysimeter studies and model calculations. 635M01, 635M02 (both > 10 %) and 635M03 (< 10 %) can occur in surface water. In sediment metabolite 635M01 can be formed in significant amounts.

Therefore tritosulfuron and the metabolites 635M01, 635M02 and 635M03 should be included in the definition of the residues relevant to the environment.

The metabolites 635M01, 635M02 and 635M03 shows no biological activity, but the toxicological relevance in groundwater is open for metabolite 635M01 and 635M02. Ecotoxicological studies (chronic earthworm test) have to be submitted for 635M01, 635M02 and 635M03 for the risk assessment in soil. The ecotoxicological risk assessment of metabolite 635M01 in surface water is not yet finished (Lemna study required).

B.8.10 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	Kellner O.	1997	The aerobic soil metabolism of bas 635 H (14C-Triazine). 1997/11242 GLP, unpublished BOD2001-486	Y	BAS
AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	Kellner O.	1998	The aerobic soil metabolism of BAS 635 H (14C-phenyl). 1998/10619 GLP, unpublished BOD2001-484	Y	BAS
AIIA-7.1.1.1.1; AIIA-7.1.1.2.1	Staudenmaier H.	1999	Degradation behaviour of BAS 635 H in lysimeter soil. 1999/11823 GLP, unpublished BOD2001-485	Y	BAS

[7] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	Kellner O.	1998	The anaerobic soil metabolism of BAS 635 H (14C-triazine). 1998/10893 GLP, unpublished BOD2001-491	Y	BAS
AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	Kellner O.	1998	The anaerobic soil metabolism of BAS 635 H (14C-phenyl). 1998/10891 GLP, unpublished BOD2001-490	Y	BAS
AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	Venkatesh K.	1996	Photolysis of 14C-BAS 635 H (triazin label) on soil. 1996/5226 GLP, unpublished BOD2001-489	Y	BAS
AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	Venkatesh K.	1996	Photolysis of 14C-BAS 635 H (phenyl label) on soil. 1996/5209 GLP, unpublished BOD2001-488	Y	BAS
AIIA-7.1.1.2.1	Gottesbueren B.	1998	Estimation of the transformation coefficients of BAS 635 H during aerobic metabolism in soil. 1998/10617 not GLP, unpublished BOD2001-494	Y	BAS
AIIA-7.1.1.2.1	Gottesbüren B.	2001	Calculation of the DT50-values of BAS 635 H at 10°C derived from DT50-values at 20°C. 2001/1008965 not GLP, unpublished BOD2001-499	Y	BAS
AIIA-7.1.1.2.1	Kellner O.	2001	Amendment 1 Soil degradation rates of 14C-BAS 635 H (incl. metabolites BH 635-2,-3,-4) under laboratory conditions. 2001/1008970 GLP, unpublished BOD2001-498	Y	BAS
AIIA-7.1.1.2.1	Kellner O.	2001	Amendment 1 The anaerobic soil metabolism of BAS 635 H (14C-triazine). 2001/1008968 GLP, unpublished BOD2001-497	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.1.1.2.1	Kellner O.	2001	Amendment 1 The anaerobic soil metabolism of BAS 635 H (14C-phenyl). 2001/1008969 GLP, unpublished BOD2001-496	Y	BAS
AIIA-7.1.1.2.1	Kellner O.	1998	Estimation of the transformation coefficients of BAS 635 H, BH 635-2, BH-3, BH-4 and BH-5 during aerobic soil metabolism of 14C-BAS 635 H (Phenyl and Triazine label). 1998/10662 not GLP, unpublished BOD2001-495	Y	BAS
AIIA-7.1.1.2.2	Dressel J.	2001	Estimation of standardized transformation rates of BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 from field dissipation studies. 2000/1018554 not GLP, unpublished BOD2001-502	Y	BAS
AIIA-7.1.1.2.2	Jackson, S., Smith, K. and McDonell, J.	2001	Field dissipation of BAS 635..H in terrestrial use patterns. BASF 2000/5285 GLP, unpublished BOD2001-731	Y	BAS
AIIA-7.1.1.2.2	Keller, W.	1998	Storage stability of BAS 635 H (271272) residues in soil. BASF 98/10899 GLP, unpublished BOD2001-516	Y	BAS
AIIA-7.1.1.2.2	Kellner O.	2001	Field soil dissipation of BAS 635 H (271 272) in formulation BAS 639 00 H. 2000/1013301 GLP, unpublished BOD2001-501	Y	BAS
AIIA-7.1.1.2.2	Kellner O.	1998	Examination of soil dissipation of BAS 635 H (271272) under field conditions after treatment with formulation BAS 639 00 H. 1998/11244 GLP, unpublished BOD2001-500	Y	BAS
AIIA-7.1.1.2.2	Richter, Th.	2001	Evaluation of residue stability of BAS 635 H (271272) and the following metabolites 335184, 335182, 292564 in soil samples under usual storage conditions. BASF 2000/1013302 GLP, unpublished BOD2001-517	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.1.1.2.2	South, N.L. and Smith, K.	2001	Freezer storage stability study with BAS 635 H, BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in sediment. BASF 2000/5279 GLP, unpublished BOD2001-518	Y	BAS
AIIA-7.1.2	Seher A.	1997	Addendum 2 Soil adsorption/desorption study of 271272 (BAS 635 H). 1997/11062 GLP, unpublished BOD2001-507	Y	BAS
AIIA-7.1.2	Seher A.	1999	Adsorption/desorption - Study of 271272 (BAS 635 H), 292564 (BH 635-2), 335182 (BH 635-3), 335184 (BH 635-4) and 231700 (BH 635-5) on a lysimeter soil. 1999/10085 GLP, unpublished BOD2001-508	Y	BAS
AIIA-7.1.2	Seher A.	1998	Soil adsorption/desorption study of 292564 (BH 635-2). 1998/10713 GLP, unpublished BOD2001-509	Y	BAS
AIIA-7.1.2	Seher A.	1998	Soil adsorption/desorption study of 335184 (BH 635-4). 1998/10612 GLP, unpublished BOD2001-511	Y	BAS
AIIA-7.1.2	Seher A.	1999	Addendum 1 Soil adsorption/desorption study of 231700 (BH 635-5). 1998/11413 GLP, unpublished BOD2001-513	Y	BAS
AIIA-7.1.2	Seher A.	1998	Soil adsorption/desorption study of 231700 (BH 635-5). 1998/11370 GLP, unpublished BOD2001-512	Y	BAS
AIIA-7.1.2	Seher A.	1998	Soil adsorption/desorption study of 335182 (BH 635-3). 1998/10714 GLP, unpublished BOD2001-510	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.1.2	Seher A.	1996	Addendum 1 Soil adsorption/desorption study of 271272 (BAS 635 H). 1996/10748 GLP, unpublished BOD2001-506	Y	BAS
AIIA-7.1.2	Seher A.	1996	Soil adsorption/desorption study of 271272 (BAS 635 H). 1996/10455 GLP, unpublished BOD2001-505	Y	BAS
AIIA-7.1.3.1; AIIA-7.1.3.2	Keller W.	1994	Leaching behaviour of 14C-271272 without soil ageing and after aerobic ageing for 30 days. 1994/10924 GLP, unpublished BOD2001-514	Y	BAS
AIIA-7.1.3.3	Becker-Arnold R.	1998	Outdoor lysimeter study with 14C-BAS 635 H. 1998/11268 GLP, unpublished BOD2001-515	Y	BAS
AIIA-7.1.3.3	Richter T.	2001	Determination of residues of BH 635-5 in several lysimeter leachates. 2000/1013300 GLP, unpublished BOD2001-504	Y	BAS
AIIA-7.1.3.3	Staudenmaier H.	2001	Outdoor lysimeter study with 14C-BAS 635 H. 2000/1013297 GLP, unpublished BOD2001-503	Y	BAS
AIIA-2.9.1; AIIA-7.2.1.1	Singh M.	1997	Hydrolysis of 14C-BAS 635 H (triazine label) in aqueous media. 1996/5091 GLP, unpublished WAS2001-211	Y	BAS
AIIA-2.9.1; AIIA-7.2.1.1	Singh M.	1997	Hydrolysis of 14C-BAS 635 H (phenyl label) in aqueous media. 1996/5057 GLP, unpublished WAS2001-210	Y	BAS
AIIA-7.2.1.1	Tong T.R.	2001	Hydrolysis of 14C-BH 635-5 (AMTT) in aqueous solution. 2000/5260 GLP, unpublished WAS2001-212	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIA-7.2.1.2	Goetz N. von	1999	Aqueous photolysis of BH 635-4 under sensitising conditions. 1999/10089 GLP, unpublished LUF2001-187	Y	BAS
AIIA-2.9.2; AIIA-2.9.3; AIIA-7.2.1.2	Scharf J.	1998	Aqueous photolysis of BAS 635 H at pH 5 and pH 7. 1998/10981 GLP, unpublished LUF2001-186	Y	BAS
AIIA-7.2.1.2	Scharf J.	1996	Absorption coefficient of BAS 635 H at pH 4, pH7 and pH 9. 1996/10021 GLP, unpublished LUF2001-185	Y	BAS
AIIA-7.2.1.3.1	Schwarz K.	1995	Determination of the biodegradability of REG.NO. 271 272 in the CO2-evolution test. 1995/10805 GLP, unpublished WAS2001-213	Y	BAS
AIIA-7.2.1.3.2	Staudenmaier H.	2001	Amendment 1 Degradation of BAS 635 H in aerobic aquatic environment. 2001/1008967 GLP, unpublished WAS2001-215	Y	BAS
AIIA-7.2.1.3.2	Staudenmaier H.	1998	Degradation of BAS 635 H in aerobic aquatic environment. 1998/10950 GLP, unpublished WAS2001-214	Y	BAS
AIIA-2.3.2; AIIA-7.2.2	Ohnsorge U.	2000	Physical and chemical properties (Henry's law constant). 2000/1013447 not GLP, unpublished LUF2001-188	Y	BAS
AIIA-2.10; AIIA-7.2.2	Scharf J.	1995	Photochemical oxidative degradation of BAS 635 H. 1995/11094 not GLP, unpublished LUF2001-190	Y	BAS
AIIA-2.10; AIIA-7.2.2	Scharf J.	1998	Laboratory study on the volatilization of BAS 635 H after application of BAS 635 00 H on soil and plant surfaces. 1998/10982 GLP, unpublished LUF2001-189	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[7]
AIIIA-9.1; AIIIA-9.2	Gottesbüren, B.	2001	Calculation of predicted environmental concentrations (PECsed) for BAS 635 H and metabolite BH 635-4 in sediment. 2000/1018552 not GLP, unpublished BOD2001-520	Y	BAS
AIIIA-9.1.3	Hauck T.	2001	Calculation of predicted environmental concentrations for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in soil. 2000/1017054 not GLP, unpublished BOD2001-519	Y	BAS
AIIIA-9.2.1	Beigel C.	2001	Calculation of predicted environmental concentrations (PECgw) for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in groundwater using FOCUS. 2000/1018546 not GLP, unpublished BOD2002-32	Y	BAS
AIIIA-9.2.3	Platz K.	2001	Calculation of predicted environmental concentrations (PECsw) for BAS 635 H and metabolites BH 635-2, BH 635-3, BH 635-4 and BH 635-5 in static surface waters. 2000/1018549 not GLP, unpublished WAS2001-218	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Annex B

Tritosulfuron

B-9: Ecotoxicology

B.9 Ecotoxicology

B.9.1 Effects on birds (Annex IIA 8.1; Annex IIIA 10.1)

B.9.1.1 Studies submitted by the notifier

The listed studies below are the basis for ecotoxicological assessment on birds. In Table B.9.1-1 the avian toxicity data are summarised. Studies were conducted with the batch no. N24 of technical tritosulfuron. Batch no. N24 has a purity of 96.6 % and an impurity content of AMTT of 2.45 %.

Acute oral toxicity

Title:	**Avian Single Dose Oral LD_{50} on the Mallard Duck (*Anas platyrynchos* L.)**
Author(s):	Munk, R. (1997)
BBA-Ref.-No:	AVS2001-141
Guideline:	EPA 71-1
Species:	mallard duck (*Anas platyrhynchos*)
Test substance:	technical tritosulfuron (batch no. N24)
Purity:	96.8 %
Administration:	intubation
Dose levels (nom.):	0/500/1000/2000 mg/kg
NOED:	2000 mg/kg bw
LLD:	> 2000 mg/kg bw
LD_{50}:	> 2000 mg/kg bw
Findings:	Slight amounts of vomit were found at 2000 mg/kg, however, this obviously was attributable to one bird each in the male and female group, so that conclusions from this dose group are not unduely affected. There were no signs of intoxication at any treatment group nor effects on feed consumption and body weight.
valid	yes
GLP compliance:	yes

Title:	**Avian Single dose Oral LD_{50} on the bobwhite quail (*Colinus virginianus*)**
Author(s):	Munk, R. and Küttler, K. (1997)
BBA Ref.-No.:	AVS2001-140
Guideline:	EPA 71-1
Species:	bobwhite quail (*Colinus virginianus*)
Test substance:	technical tritosulfuron (batch no. N24)

Purity:	96.8 %
Administration:	intubation
Dose levels (nom.):	0/500/1000/2000 mg/kg
NOED:	1000 mg/kg bw
LLD:	> 2000 mg/kg bw
LD_{50}:	> 2000 mg/kg bw
Findings:	One mortality each at 500 and 1000 mg/kg were unrelated to treatment; no toxic signs were seen at any treatment group; feed consumption was normal in all treatment groups; body weight was slightly reduced at 2000 mg/kg.
valid	yes
GLP compliance:	yes

Dietary toxicity (subacute)

Title:	**Avian Dietary LC_{50} Test in chicks of the Bobwhite Quail (*Colinus virginianus*)**
Author(s):	Munk, R. (1997)
BBA-Ref.-No.:	AVS2001-143
Guideline:	EPA 71-4 / OECD 206
Species:	bobwhite quail (*Colinus virginianus*)
Test substance:	technical tritosulfuron (batch no. N24)
Purity:	96.8 %
Conc.-levels (nom.):	0/313/625/1250/2500/5000 mg/kg diet
Conc.-levels (eff.):	0/354/742/1389/2413/5107 mg/kg diet
NOEC:	5000 ppm
LLC:	> 5000 ppm
LC_{50}:	> 5000 ppm
Findings:	There was one incidental mortality at 1250 ppm; there were neither signs of intoxication in any treatment group nor effects on body weight and feed consumption.
valid:	yes
GLP compliance:	yes

Title:	**Avian Dietary LC_{50} Test in chicks of the mallard duck (*Anas platyrhynchos*)**
Author(s):	Munk, R. (1997)
BBA-Ref. –No.:	AVS2001-142
Guideline:	EPA 71-4 / OECD 206
Species:	mallard duck (*Anas platyrhynchos*)
Test substance:	technical tritosulfuron (batch no. N24)

Purity:	96.8 %
Conc.-levels (nom.):	0/313/625/1250/2500/5000 mg/kg diet
Conc.-levels (eff.):	0/336/645/1360/2719/5223 mg/kg diet
NOEC:	625 ppm
LLC:	> 5000 ppm
LC_{50}:	> 5000 ppm
Findings:	There were observed no signs of intoxication at any treatment group; body weight increase was lower at 1250 ppm and above; feed consumption was reduced at 5000 ppm.
valid:	yes
GLP compliance:	yes

Avian reproduction

Title:	**BAS 635 H – 1-Generation Reproduction Study on the mallard duck (*Anas platyrhynchos*) by Administration in the Diet**
Author(s):	Zok, S. (1999)
BBA-Ref.-No.:	AVS2001-145
Guideline:	EPA 71-4 / OECD 206
Species:	mallard duck (*Anas platyrhynchos*)
Test substance:	technical tritosulfuron (batch no. N24)
Purity:	95.9 %
Exposure period:	22 w
Conc.-levels (nom.):	0/100/300/1000 mg/kg diet
Conc.-levels (eff.):	0/97/288/954 mg/kg diet
NOEC:	300 mg/kg diet
Findings:	At 1000 ppm the number of 14-day-survivors related to hatchlings was reduced. Apart from that there were no treatment-related effects on adult birds and reproduction.
valid:	yes
GLP compliance:	yes

Title:	**BAS 635 H – 1-Generation Reproduction Study on the Bob white Quail (*Colinus virginianus*) by Administration in the Diet**
Author(s):	Munk, R. (1998)
BBA-Ref.-No.:	AVS2001-144
Guideline:	EPA 71-4 / OECD 206
Species:	bobwhite quail (*Colinus virginianus*)
Test substance:	technical tritosulfuron (batch no. N24)
Purity:	95.9 %
Exposure duration:	22 w
Conc.-levels (nom.):	0/100/300/1000 mg/kg diet

Conc.-levels (eff.): 0/99/282/976 mg/kg diet
NOEC: 1000 ppm
Findings: There were no treatment-related effects on parent birds and reproduction
valid: yes
GLP compliance: yes

Table B.9.1-1 Summary of avian toxicity data (tests with technical tritosulfuron - batch no. N24)

Test material	Species	Test	NOED / NOEC / NOAEL	LD_{50}/LC_{50}	Unit
active substance (BAS 635 H)	bobwhite quail	acute	1000	> 2000	mg/kg bw
active substance (BAS 635 H)	mallard duck	acute	2000	> 2000	mg/kg bw
active substance (BAS 635 H)	bobwhite quail	subacute (5-day-dietary)	5000	> 5000	mg/kg diet
active substance (BAS 635 H)	mallard duck	subacute (5-day-dietary)	625	> 5000	mg/kg diet
active substance (BAS 635 H)	mallard duck	reproduction (one-generation-test)	300	-	mg/kg diet
active substance (BAS 635 H)	bobwhite quail	reproduction (one-generation-test)	1000	-	mg/kg diet

B.9.1.2 Other studies (Annex IIIA 10.1.2, 10.1.3, 10.1.4)

Supervised field trials were not conducted due to the favourable toxicity/exposure ratios (see below).

Acceptance of bait, granules, or treated seeds by birds is not applicable, because formulations of BAS 635 H are to be applied exclusively as sprays.

B.9.1.3 Risk assessment for birds

Birds may be exposed to tritosulfuron containing plant protection products mainly by the consumption of contaminated feed. Depending on species this may be insects or green plant material. The risk assessment will be based on a maximum rate of 0.05 kg as/ha that is intended for maize and cereals against dicotyledonous weeds.

Exposure assessment: Residue levels of tritosulfuron containing plant protection products treated food items (plants and insects) are estimated according to Hoerger and Kenaga (1972). In order to consider the worst-case condition it is assumed that birds feed exclusively on contaminated material and that herbivorous birds have a daily feed demand of 25 % of their body weight and insectivorous birds of 40 % of their body weight.
Because of the intended use with cereal short grass are considered as the most suitable feed item to calculate the "initial residue in food items" in the case for herbivorous birds. Therefore, the correction factor of 112 (short grass) is used. For the calculation of the "initial residue in food items" for insectivorous birds the correction factor of 29 (small insects) is used. It results in a maximum daily intake of 1.4 mg/kg bw and 0.58 mg/kg bw, respectively.

Table B.9.1-2: Exposure assessment for birds

culture/use	maximum application rate (kg as/ha)	feed	typical maximum residue[1] (mg as/kg)	initial residue in food items (mg as/kg)	relative feed demand (%)	maximum daily intake (mg as/kg bw/d)
maize / cereals	0.05	vegetation (short grass)	112*R	5.6	25	1.4
maize / cereals	0.05	insects	29*R	1.45	40	0.58

[1] according to Hoerger and Kenaga (1972); R = application rate in kg/ha

Toxicity/exposure ratios: For the acute TER the LD_{50} is related to the maximum daily intake; for the short-term TER the LC_{50} is related to the initial residue; for the long-term TER the NOEC from the reproduction test is related to the initial residue. All TER-values are far above the Annex-VI-triggers. Hence, the risk to birds is considered as very low.

Table B.9.1-3: Toxicity/Exposure Ratios for birds

culture/use	feed	time-scale	Toxicity/Exposure Ratio	TER-trigger
maize/cereals	vegetation	acute (active substance BAS 635 H)	TER_a > 2000/1.4 = > 1429	10
maize/cereals	vegetation	short-term (active substance)	TER_{st} 625/5.6 = 111	10
maize/cereals	vegetation	long-term (active substance)	TER_{lt} = 300/5.6 = 53	5
maize/cereals	insects	acute (active substance)	TER_a > 2000/0.58 = > 3448	10
maize/cereals	insects	short-term (active substance)	TER_{st} 625/1.45 = 431	10
maize/cereals	insects	long-term (active substance)	TER_{lt} = 300/1.45 = 207	5

B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2)

B.9.3 Toxicity data

Fish - acute toxicity

Title:	**Acute toxicity study on the common carp (*Cyprinus carpio L.*)**
Author:	Munk, R. (1996)
BBA-Ref.-No.:	WAT2001-437
Test substance:	technical tritosulfuron
Purity:	96.8 %
Guideline:	EPA 72-1
Test species:	*Cyprinus carpio*
Exposure mode:	static
Conc. levels (nom.):	0; 50; 100 mg/l
Conc. levels (meas.):	91.6 - 96.2 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes; limit-test
GLP compliance: yes

Title: **Reg.No. 271272 - Acute toxicity study on the blue gill sunfish (*Lepomis macrochirus*) in a static system (96 hours)**
Author: Munk, R. (1996)
BBA-Ref.-No.: WAT2001-436
Test substance: technical tritosulfuron
Purity: 96.8 %
Guideline: EPA 72-1
Test species: *Lepomis macrochirus*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100 mg/l
Conc. levels (meas.): 96.9 - 100.8 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes; limit-test
GLP compliance: yes

Title: **Reg.No. 271272 - Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792) in a static system (96 hours)**
Author: Munk, R. (1996)
BBA-Ref.-No.: WAT2001-435
Test substance: technical tritosulfuron
Purity: 96.8 %
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100 mg/l
Conc. levels (meas.): 96.9 - 100.8 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes; limit-test
GLP compliance: yes

Title: **AMTT, techn. CAS - Nr. (5311-05-7) Acute toxicity study on the zebra fish (*Brachydanio rerio* HAM. and BUCH.)**
Author: Munk, R. (1997)
BBA-Ref.-No.: WAT2001-441
Test substance: metabolite 635M04 (BH635-5)
Guideline: EPA 72-1
Test species: *Brachydanio rerio*
Exposure mode: static
Conc. levels (nom.): 0; 21.5; 46.4; 100; 215; 464 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	46.4			170

valid: yes
GLP compliance: yes

Title: **Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792) in a static system (96 hours)**
Author: Zok, S. (1999)
BBA-Ref.-No.: WAT2001-438
Test substance: 635M02 (BH 635-2) metabolite
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100; 100; 100 mg/l
Conc. levels (meas.): 95.3 - 99.4 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes; limit-test
GLP compliance: yes

Title: **Reg No. 335 182 (BH 635-3) Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792)**
Author: Zok, S. (1999)
BBA-Ref.-No.: WAT2001-439
Test substance: metabolite 635M03 (BH 635-3)
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100; 100; 100 mg/l
Conc. levels (meas.): 15.7 - 93-0 %

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes
GLP compliance: yes

Title: **Reg. No. 335 184 (BH 635-4) Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792)**
Author: Munk, R. (1998)
BBA-Ref.-No.: WAT2001-440
Test substance: metabolite 635M01 (BH 635-4)
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100; 100; 100 mg/l
Conc. levels (meas.): 40.4 - 96.4 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	50	100	10	> 100

valid: yes; limit-test
GLP compliance: yes

Title: **Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792) in a static system (96 hours)**
Author: Munk, R. (1997)
BBA-Ref.-No.: WAT2001-458
Test substance: formulation BAS 635 00 H
tritosulfuron 73.45 %
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 50; 100; 100; 100 mg/l

Results (mg/l) related to measured concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality				> 114.72

valid: yes
GLP compliance: yes

Title: **Report Twinpack BAS 635 00 H incl. BAS 152 00 S Acute toxicity study on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792) in a static system (96 hours)**
Author: Zok, S. (2000)
BBA-Ref.-No.: WAT2001-459
Test substance: mixture 70 g BAS 63500 H + 1.5 L BAS 15200 S
tritosulfuron
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 100; 100; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	100			> 100

valid: no; there is no description or common name of BAS 15200 S available
GLP compliance: yes

Fish - prolonged toxicity

Title:	**Sublethal toxic effects on the rainbow trout (*Oncorhynchus mykiss* WALBAUM 1792) in a flow-through system (28 days)**
Author:	Munk, R. (1997)
BBA-Ref.-No.:	WAT2001-442
Test substance:	technical tritosulfuron
Purity:	95.9 %
Guideline:	OECD 204
Test species:	*Oncorhynchus mykiss*
Exposure mode:	flow-through
Conc. levels (nom.):	2.15, 4.64, 10, 21.5 mg/l
Conc. levels (meas.):	> 80 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
28 d	Mortality	21.5			
28 d	Growth	21.5			
28 d	Behaviour	21.5			

Remarks: pH > 8

valid: yes
GLP compliance: yes

Invertebrates - acute toxicity

Title:	**Effect of BAS 635 H on *Daphnia magna* STRAUS in a Static Acute Toxicity Test**
Author:	Dohmen, G.P. (1998)
BBA-Ref.-No.:	WAT2001-443
Test substance:	technical tritosulfuron
Purity:	95.9 %
Guideline:	OECD 202 I
Test species:	*Daphnia magna*
Exposure mode:	static
Conc. levels (nom.):	0; 10; 18; 32; 56; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	100			> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 -2 on the Immobility of *Daphnia magna* STRAUS in a 48 hour Static, Acute Toxicity Test**
Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-444
Test substance: metabolite 635M02 (BH 635-2)
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	56			> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 -3 on the Immobility of *Daphnia magna* STRAUS in a 48 hour Static, Acute Toxicity Test**
Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-445
Test substance: metabolite 635M03 (BH 635-3)
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	> = 100			> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 -4 on the Immobility of *Daphnia magna* STRAUS in a 48 hour Static, Acute Toxicity Test**

Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-446
Test substance: metabolite 635M01 (BH 635-4)
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	> = 100			> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 -5 on the Immobility of *Daphnia magna* STRAUS in a 48 hour Static, Acute Toxicity Test**

Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-447
Test substance: metabolite 635M04 (BH 635-5)
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	> = 100			> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 00 H on the Immobility of *Daphnia magna* STRAUS**

Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-460
Test substance: formulation BAS 635 00 H
tritosulfuron 73.45 %
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l
Conc. levels (meas.): 91.7 - 95.3 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	100			> 100

valid: yes
GLP compliance: yes

Title: **BAS 635 00 H + BAS 152 00 S - Determination of the acute effect on the swimming ability of the water flea *Daphnia magna* STRAUS**

Author: Jatzek (2001)
BBA-Ref.-No.: WAT2001-461
Test substance: mixture 70 g BAS 63500 H + 1.5 L BAS 15200 S
tritosulfuron
Guideline: OECD 202 I
Test species: *Daphnia magna*

Conc. levels (nom.): 0; 6.25; 12.5; 25; 50; 100 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	100			> 100

valid: no; there is no description or common name of BAS 152 00 S available
GLP compliance: yes

Invertebrates - long-term toxicity

Title:	**Effect of BAS 635 on Mortality and Reproduction of *Daphnia magna***
Author:	Dohmen, G.P. (2000)
BBA-Ref.-No.:	WAT2001-448
Test substance:	technical tritosulfuron
Purity:	95.9 %
Guideline:	OECD 202 II
Test species:	*Daphnia magna*
Exposure mode:	semi-static
Conc. levels (nom.):	10, 18, 32, 56, 100 mg/l
Conc. levels (meas.):	> 80 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
21 h	Mortality	100			
21 h	Growth	56	100	5	
21 h	Reproduction	56	100	20	

valid:	yes
GLP compliance:	yes

Algae

Title:	**Effect of BAS 635 H on the Growth of the Blue-Green Alga *Anabaena flos-aquae***
Author:	Dohmen, G.P. (1999)
BBA-Ref.-No.:	WAT2001-450
Test substance:	technical tritosulfuron
Purity:	95.9 %
Guideline:	OECD 201
Test species:	*Anabaena flos-aquae*
Exposure mode:	static
Conc. levels (nom.):	0; 0.02; 0.04; 0.07; 0.13; 0.25; 0.50; 1.00 mg/l
Conc. levels (meas.):	95.3 - 96.0 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Biomass		0.04	10	0.19
96 h	Growth		0.06	10	0.26

valid:	no; growth factor of 2.9 is too low; no exponential growth
GLP compliance:	yes

Title: **Effect of BAS 635 H on the Growth of the Blue-green alga Anabaena flos-aquae**

Author: Kubitza, J. (2002)
BBA-Ref.-No.: WAT2002-89
Test substance: technical tritosulfuron
Guideline: OECD 201 (another alga)
Test species: *Anabaena flos-aquae*
Exposure mode: static
Conc. levels (nom.): 0; 0.02; 0.04; 0.07; 0.13; 0.25; 0.5; 1.0 mg/l
Conc. levels (meas.): 78 - 103.7 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC50
96 h	Biomass				0.58
96 h	Growth				> 1

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 H on the Growth of the Green Alga *Pseudokirchneriella subcapitata***

Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-449
Test substance: technical tritosulfuron
Guideline: OECD 201
Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static
Conc. levels (nom.): 0; 0.01; 0.02; 0.04; 0.08; 0.16; 0.32; 0.64; 1.28 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		0.04	10	0.23
72 h	Growth		0.13	10	1.09

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635-2 on the Growth of the Green Alga *Pseudokirchneriella subcapitata***

Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-451
Test substance: metabolite 635M02 (BH 635-2)
Guideline: OECD 201

Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l
Conc. levels (meas.): 99 - 105 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		21.5	10	> 100
72 h	Growth		82.6	10	> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635-3 on the Growth of the Green Alga *Pseudokirchneriella subcapitata***
Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-452
Test substance: metabolite 635M03 (BH 635-3)
Guideline: OECD 201
Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l
Conc. levels (meas.): 99.5 - 103.5 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		101	10	> 100
72 h	Growth		> 100	10	> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635-4 on the Growth of the Green Algae *Pseudokirchneriella subcapitata***
Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-453
Test substance: metabolite 635M01 (BH 635-4)
Guideline: OECD 201
Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static
Conc. levels (nom.): 0; 10; 18; 32; 56; 100 mg/l
Conc. levels (meas.): 101 - 107 %

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		52	10	> 100
72 h	Growth		> 100	10	> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635-5 on the Growth of the Green Alga *Pseudokirchneriella subcapitata***
Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-454
Test substance: metabolite 635M04 (BH 635-5)
Guideline: OECD 201
Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		71	10	> 100
72 h	Growth				> 100

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 00 H on the Growth of the Green Alga *Pseudokirchneriella subcapitata***
Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-462
Test substance: formulation BAS 635 00 H
tritosulfuron 73.45 %
Guideline: OECD 201
Test species: *Pseudokirchneriella subcapitata*
Exposure mode: static
Conc. levels (nom.): 0; 0.01; 0.03; 0.1; 0.2; 0.4; 0.8; 1.6 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass		0.07	10	0.42
72 h	Growth		0.3	10	2.71

valid: yes
GLP compliance: yes

Aquatic plants

Title: **Effect of BAS 635 H on the Growth of *Lemna gibba* G3**
Author: Dohmen, G.P. (1999)
BBA-Ref.-No.: WAT2001-455
Test substance: technical tritosulfuron
Guideline: ASTM: E1415-91
Test species: *Lemna gibba*
Exposure mode: static
Conc. levels (nom.): 0; 0.003; 0.0075; 0.015; 0.03; 0.06; 0.12 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
7 d	Biomass				0.0255
7 d	Growth	0.0075	0.0226	20	0.0476

valid: yes
GLP compliance: yes

Title: **Effect of BAS 635 00 H + BAS 152 00 S in the Growth of *Lemna gibba* in a Seven Day Static**
Author: Dohmen, G.P. (2001)
BBA-Ref.-No.: WAT2001-463
Test substance: mixture 70 g BAS 63500 H + 1.5 L BAS 15200 S tritosulfuron
Guideline: OECD-Draft
Test species: *Lemna gibba*
Exposure mode: static
Conc. levels (nom.): 0; 0.005 (0.099), 0.01 (0.199); 0.02 (0.398); 0.04 (0.796); 0.08 (1.591); 16 (3.182) mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
7 d	Fronds		0.0078	10	0.0355
7 d	Growth		0.0195	10	0.0618

valid: no; there is no description or common name of BAS 152 00 S available
GLP compliance: yes

Bacteria

Title: **Determination of the inhibitory effect of BAS 635 H on the cell multiplication of the bacterium *Pseudomonas putida***
Author: Maisch (1998)
BBA-Ref.-No.: WAT2001-457
Test substance: technical tritosulfuron
Purity: 95.9 %
Guideline: special method
Test species: *Pseudomonas putida*
Exposure mode: static
Conc. levels (nom.): 0; 39.1; 78.1; 156; 313; 625; 1250; 2500; 5000; 10000 mg/l

Results (mg/l) related to nominal concentrations

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
16 h	Respiration rate		< = 10000	10	> 10000

valid: yes
GLP compliance: yes

Summary of aquatic toxicity data

Test material	Species	Duration		NOEC (mg/l)	EC_{50} (mg/l)	
Tritosulfuron	*C. carpio*	96 h (st)	Mortality	50	> 100	Nom
Tritosulfuron	*L. macrochirus*	96 h (st)	Mortality	50	> 100	Nom
Tritosulfuron	*O. mykiss*	96 h (st)	Mortality	50	> 100	Nom
Tritosulfuron	*O. mykiss*	28 d (fl)	Mortality	21.5		Nom
			Growth	21.5		Nom
			Behaviour	21.5		Nom
Tritosulfuron	*D. magna*	48 h (st)	Mortality	100	> 100	Nom
Tritosulfuron	*D. magna*	21 h (ss)	Mortality	100		Nom
			Growth	56		Nom
			Reproduction		56	Nom
Tritosulfuron	*A. flos-aquae*	96 h (st)	Biomass		0.19	Nom #
			Growth		0.26	Nom
Tritosulfuron	*A. flos-aquae*	96 h (st)	Biomass		0.58	Nom
			Growth		> 1	Nom
Tritosulfuron	*P. subcapitata*	72 h (st)	Biomass		0.23	Nom
			Growth		1.09	Nom
Tritosulfuron	*L. gibba*	7 d (st)	Biomass		0.0255	Nom
			Growth	0.0075	0.0476	Nom
Tritosulfuron	*P. putida*	16 h	Growth		> 10000	Nom
635M04 (BH 635-5, AMTT)	*B. rerio*	96 h (st)	Mortality	46.4	170	Nom
635M02 (BH 635-2)	*O. mykiss*	96 h (st)	Mortality	50	> 100	Nom
635M02 (BH 635-2)	*D. magna*	48 h (st)	Mortality	56	> 100	Nom
635M02 (BH 635-2)	*P. subcapitata*	72 h (st)	Biomass		> 100	Nom
			Growth		> 100	Nom
635M03 (BH 635-3)	*O. mykiss*	96 h (st)	Mortality	50	> 100	Nom
635M03 (BH 635-3)	*D. magna*	48 h (st)	Mortality	> = 100	> 100	Nom
635M03 (BH 635-3)	*P. subcapitata*	72 h (st)	Biomass		> 100	Nom
			Growth		> 100	Nom
635M01 (BH 635-4)	*O. mykiss*	96 h (st)	Mortality	50	> 100	Nom
635M01 (BH 635-4)	*D. magna*	48 h (st)	Mortality	> = 100	> 100	Nom
635M01 (BH 635-4)	*P. subcapitata*	72 h (st)	Biomass		> 100	Nom
			Growth		> 100	Nom
635M04 (BH 635-5, AMTT)	*D. magna*	48 h (st)	Mortality	> = 100	> 100	Nom
635M04 (BH 635-5, AMTT)	*P. subcapitata*	72 h (st)	Biomass		> 100	Nom
			Growth		> 100	Nom
BAS 635 00 H	*O. mykiss*	96 h (st)	Mortality		> 114	Meas
BAS 635 00 H	*D. magna*	48 h (st)	Mortality	100	> 100	Nom
BAS 635 00 H	*P. subcapitata*	72 h (st)	Biomass		0.42	Nom
			Growth		2.71	Nom
70 g 63500 H + 1.5 L BAS 15200 S	*O. mykiss*	96 h (st)	Mortality	100	> 100	Nom

70 g 63500 H + 1.5 L BAS 15200 S	*D. magna*	48 h (st)	Mortality	100	> 100	Nom
70 g 63500 H + 1.5 L BAS 15200 S	*L. gibba*	7 d (st)	Fronds		0.0355	Nom
			Growth		0.0618	

fl = flow-through; st = static; ss = semi-static; sm = special method; # = not valid

One test with *Anabaena flos-aquae* is not valid because growth was not sufficient (WAT 2001-450). Recently, a new study has been submitted where growth is acceptable (WAT 2002-89). The toxicity values from the tests with the mixture of formulated product and adjuvans "Citowett New" are given as the concentration of BAS 63500 H/L in these tests. The active substance is more toxic than the formulated product for the most sensitive organism *L. gibba* (EC_{50} of 0.025 mg/l). All metabolites tested are clearly less toxic than the active substance and should be regarded as ecotoxicologically not relevant. However, the most important metabolite 635M01 (BH 635-4) was not tested with the most sensitive group of organisms in the tests with the active substance. Due to the low log P_{ow} and partioning into sediment no further data on bioaccumulation and toxicity to sediment-dwellers must be submitted. However, a test with the metabolite 635M01 (BH 635-4) on *Lemna* should be submitted to conduct a final risk assessment.

B.9.4 Preliminary Risk Assessment

Currently, higher aquatic plants are the most sensitive group of organisms and the EC_{50} of 0.025 mg/L are relevant for the risk assessment. Based on the maximum application rate of 0.05 kg as/ha the following TER-values are to be calculated:

Distance [m]	PEC [mg/l]	Toxicity [mg/l]	TER
0	0.0167	0.025	1.5
1	0.00046	0.025	54

TER-values in a distance of 1 m is higher than the relevant trigger of 10 indicating an acceptable risk to non-target aquatic organisms.

Tritosulfuron must be labelled with R 50 and R 53.

B.9.5 Effects on other terrestrial vertebrates (Annex IIIA 10.3)

There were conducted neither wild mammal toxicity studies nor field studies.

The acute oral LD_{50} of tritosulfuron for rats is 4700 mg as/kg body weight (test conducted with the batch no. N12 – 0.16-0.24 % AMTT), the long-term risk for rats is 600 ppm (mg/kg food) (batch no. N34 – 0.024 % AMTT). The latter value was determined in a two generation study and represents the NOAEL (see section B.06, Toxicology).

B.9.5.1 Risk assessment for mammals

Mammals may be exposed to tritosulfuron mainly by the consumption of contaminated feed. Highest residues will be in vegetation, therefore, herbivorous species are considered as worst-case. The risk assessment will be based on a maximum rate of 0.05 kg as/ha as intended for maize and cereals.

Exposure assessment: Residue levels of tritosulfuron containing plant protection products treated food items (plants) are estimated according to Hoerger and Kenaga (1972). In order to consider the worst-case condition it is assumed that mammals feed exclusively on contaminated material and that they have a daily feed demand of 25 % of their body weight.

Because of the intended use with cereals short grass are considered as the most suitable feed item to calculate the "initial residue in food items". Therefore, the correction factor of 112 (short grass) is used.

Table B.9.5-1: Exposure assessment for mammals

culture/ use	maximum application rate (kg as/ha)	feed	typical maximum residue[1] (mg as/kg)	initial residue in food items (mg as/kg)	relative feed demand (%)	maximum daily intake (mg as/kg bw)
maize / cereals	0.05	short grass	112*R	5.6	25	1.4

[1] according to Hoerger and Kenaga (1972); *R = application rate in kg/ha

Toxicity/exposure ratios: For the acute TER the LD_{50} is related to the maximum daily intake; for the long-term TER the NOAEL from the reproduction study is related to the initial residue. All TER-values are above the Annex-VI-triggers. Hence, the risk to mammals is considered as very low.

Table B.9.5-2 Toxicity/exposure ratios for mammals:

culture/use	feed	time-scale	Toxicity/Exposure ratio
maize / cereals	short grass	acute	$TER_a = 4700/1.4 = 3357$
maize / cereals	short grass	long-term / reproduction (two-generation-study)	$TER_{lt} = 600/5.6 = 107$

If the risk assessment is done on the basis of the endpoint resulted from batch no. N24 (AMTT impurity 2.45 %) the calculated $TER_{reproduction}$ value does not reach Annex VI-Trigger. Hence, from the ecotoxicological point of view it must be strongly supported the requirement concerning "Toxicology and Metabolism" that an Annex I inclusion is only supported for technical tritosulfuron with a specified AMTT content of less than 0.02 %.

B.9.6 Effects on bees (Annex IIA 8.3.1; Annex IIIA 10.4)

B.9.6.1 Acute toxicity (Annex IIA 8.3.1, Annex IIIA 10.4)

B.9.6.1.1 Acute oral toxicity of tritosulfuron (technical)

Title:	**Effects of Reg. No. 271272 on the honeybee (*Apis mellifera L.)* in laboratory trials**
Author:	Sack, D. (1998)
BBA-Ref.-Nr.:	2001-35
Testguideline:	EPPO-guideline No. 170
GLP compliance:	yes
Test design:	test substance: Reg. No. 271272 - tritosulfuron reference substance: dimethoate control: aceton treated
Test procedure:	5 doses of test substance: 25, 50, 100, 150 and 200 µg/bee for oral and contact toxicity 3 replicates with 10 bees each per dose assessment of mortality 1, 2, 4, 24 and 48 hours after application.

Results:		
	oral administration:	48h LD_{50} > 200 µg as/bee
	contact administration:	48h LD_{50} > 200 µg as/bee
	control mortality:	< 15 %
	dimethoate oral toxicity:	0.19 µg/bee
	dimethoate contact toxicity:	0.38 µg/bee

B.9.6.1.2 Acute oral and contact toxicity of formulated tritosufuron to honeybees

Title:	**Assessment of side-effects of BAS 63500 H + BAS 152005 to the Honey Bee, *Apis mellifera L.*, in the laboratory**
Author:	Kling, A. (2001)
BBA-Ref.-Nr.:	2001-36
Testguideline:	EPPO-guideline No. 170
GLP compliance:	yes
Test design:	test substance: BAS 63500 H (content 71.4 % as nominal) + adjuvant BAS 152005 (40 % as nominal) reference substance: Perfektion (400 g as/l dimethoate) control: water treated in the contact test and 50 % sucrose fed in the oral test
Test procedure:	test was performed as a limit-test, i.e. the test substance was applied only in one high concentration: 100 µg/bee; duration 48 h; 5 replicate, with 10 bees each.

Results:		
	test substance:	oral LD_{50} – 121.62 µg/bee
	test substance:	contact LD_{50} - > 100 µg/bee
	reference substance:	oral LD_{50} – 0.11 µg/bee
	reference substance:	contact LD_{50} - > 0.13 µg/bee
	control mortality:	< 15 %

B.9.6.2 Bee brood feeding test (Annex IIA 8.3.1.2)

Tests are not required as the test substance is not an IGR.

B.9.6.3 Residue test (Annex IIIA 10.4.2)

Tests are not required, as the test substance is of low toxicity to honeybees.

B.9.6.4 Cage test (Annex IIIA 10.4.3)

Tests are not required, as the test substance is of low toxicity to honeybees.

B.9.6.5 Field test (Annex IIIA 10.4.4)

Tests are not required, as the test substance is of low toxicity to honeybees.

B.9.6.6 Tunnel test (Annex IIIA 10.5.5)

Tests are not required, as the test substance is of low toxicity to honeybees.

B.9.6.7 Risk assessment for honeybees

Risk assessment is done according to EPPO/Coe Risk Assessment Scheme:

Hazard Quotient = LD_{50}^{-1} x g as/ha.

The calculation is based on the highest amount of the active substance/ha: 50 g/ha.

Results:

tritosulfuron technical:	HQ oral = 0.25
tritosulfuron technical:	HQ contact = 0.25
formulation: BAS 63500 H + BAS 152005:	HQ oral = 0.41
formulation: BAS 63500 H + BAS 152005:	HQ contact = 0.5

All hazard quotients are clearly below the trigger of 50. This indicates a negligible risk for honeybees by the practical use of tritosulfuron-containing products.

B.9.7 Effects on other arthropod species (Annex IIA 8.3.2; Annex IIIA 10.5)

B.9.7.1 Acute toxicity (Annex IIA 8.3.2, Annex IIIA 10.5.1)

Laboratory tests

Predatory mites

Title:	**Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite *Typhlodromus pyri* Scheuten (Acari, Phytoseiidae) -Dose response design-**
Author:	Goßmann, A. (2000)
BBA-Ref.-No.:	ANA2001-480
Test substance:	mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S
Guideline:	Typhlodromus (Louis und Ufer 1995)
Test species:	*Typhlodromus pyri*
Developmental stage:	protonymphs
Substrate:	glass
Exposure route:	dried residues
Exposure duration:	14 d (7+7)

Results:

Appl. rate (g/ha + ml/ha)	Mortality (%) 7 d	Sublethal effects (%)
2.6 + 46.3	3.4	2 (Fertility)
7.8 + 138.9	7.2	16 (Fertility)
23.3 + 416.7	26.1 *	39 (Fertility)
70 + 1250	73.5 *	/
210 + 3750	94.3 *	/

* = sign. (Mann-Whitney U-test, $p < 0.05$)

Remarks:	LR_{50}: 40.1 g/ha BAS 635 00 H + 716.1 ml/ha BAS 152 00 S (confidence limits 31.2 g/ha BAS 635 00 H + 557.1 ml/ha BAS 152 00 S and 51.4 g/ha BAS 635 00 H + 917.9 ml/ha BAS 162 00 S)
valid:	yes
GLP compliance:	yes

Title: **Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite *Typhlodromus* pyri (Acari: Phytoseiidae) in an extended laboratory trial**

Author:	Bühler, A. (2001)
BBA-Ref.-No.:	ANA2001-486
Test substance:	mixture BAS 635 00 H + BAS 152 00 S (tritosulfuron 71.4 %)
Guideline:	Typhlodromus (Blümel et al. 2000)
Test species:	*Typhlodromus pyri*
Developmental stage:	protonymphs
Substrate:	natural substrate (discs of *Phaseolus vulgaris*, diameter 5 cm)
Exposure route:	deposit
Exposure duration:	14 d

Results:

Appl. rate (g/ha + ml/ha) (%)	Mortality (%)	Sublethal effects
3.5 + 62.5	0	0 (+ 60) (Fertility)
70 + 1250	3.6	0 (+ 27) (Fertility)

Remark:	increase in fertility compared to control
valid:	yes
GLP compliance:	yes

Title: **Effects of BAS 635 00 H + BAS 152 00 S on the parasitoid *Aphidius rhopalosiphi* (Hymenoptera: braconidae) in a laboratory trial**

Author:	Ufer, A. (2001)
BBA-Ref.-No.:	ANA2001-481
Test substance:	mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S
Guideline:	Aphidius (Mead-Briggs 1992)
Test species:	*Aphidius rhopalosiphi*
Developmental stage:	imagines
Substrate:	glass
Exposure route:	dried residues
Exposure duration:	48 h

Results:

Appl. rate (g/ha + ml/ha)	Mortality (%)	Sublethal effects (%)
210 + 3750	10	30 (Parasitation capacity)

valid: yes
GLP compliance: yes

Plant dwelling species

Title: **Effects of BAS 635 00 H + BAS 152 00 S on the lacewing *Chrysoperla carnea* Steph. (Neuroptera, Chrysopidae) in the laboratory**

Author: Drexler, A. (2000)
BBA-Ref.-No.: ANA2001-485
Test substance: mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S
Guideline: Chrysopa (Bigler 1988)
Test species: *Chrysopa carnea*
Developmental stage: larvae
Substrate: glass
Exposure route: dried residues
Exposure duration: 13-15 d

Results:

Appl. rate (g/ha + ml/ha)	Mortality (%)	Sublethal effects (%)
3.5 + 62.5	0	0 (+ 14) (Fertility)
70 + 1250	0	0 (+ 11) (Fertility)

Remark: increase in fertility compared to control
valid: yes
GLP compliance: yes

Soil dwelling species

Title: **Effects of BAS 635 00 H + BAS 152 00 S on the ground dwelling predator *Poecilus cupreus* (Coleoptera, Carabidae) in a laboratory trial**

Author: Bühler, A. (2000)
BBA-Ref.-No.: ANA2001-482
Test substance: mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S

Guideline: Poecilus (Heimbach 1992)
Test species: *Poecilus cupreus*
Developmental stage: imagines
Substrate: quarz sand
Exposure route: overspray/deposit
Exposure duration: 14 d

Results:

Appl. rate (g/ha + ml/ha)	Mortality (%)	Sublethal effects (%)
70 + 1250	0	0 (Food uptake)

valid: yes
GLP compliance: yes

Soil dwelling species

Title: Effects of BAS 635 00 H + BAS 152 00 S on the reproduction of rove beetles *Aleochara bilineata* Gyll. (Coleoptera, Staphylinidae) in the laboratory

Author: Drexler, A. (2001)
BBA-Ref.-No.: ANA2001-483
Test substance: mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S
Guideline: Aleochara (Moreth 1992)
Test species: *Aleochara bilineata*
Developmental stage: imagines
Substrate: quarz sand
Exposure route: overspray/deposit
Exposure duration: 28 d

Results:

Appl. (g/ha + ml/ha)	Sublethal effects (%)
70 + 1250	14 (Parasitation capacity)

valid: yes
GLP compliance: yes

Soil dwelling species

Title: **Effects of BAS 635 00 H + BAS 152 00 S on the wolf spider *Pardosa spec*. (Araneae, Lycosidae) in the laboratory**

Author: Schmitzer, St. (2001)
BBA-Ref.-No.: ANA2001-484
Test substance mixture BAS 635 00 H (tritosulfuron 71.4 %) + BAS 152 00 S
Guideline: Pardosa (Heimbach et al. 2000)
Test species: *Pardosa spp.*
Developmental stage: adults
Substrate: quarz sand
Exposure route: overspray/deposit
Exposure duration: 14 d

Results:

Appl. rate (g/ha + ml/ha)	Mortality (%)	Sublethal effects (%)
70 g + 1250	0	0 (+ 23) (Food uptake)

Remark increase in food uptake compared to the control
valid: yes
GLP compliance: yes

Table B.9.7-1 Summary of arthropod toxicity data with a mixture of BAS 635 00 H and BAS 152 00 S

Species	Substrate	Develop. stage	Dosage (g/ha + ml/ha)	Effects (%) lethal	sublethal
Predatory mites (ANA2001-480, ANA 2001-486)					
T. pyri	I	Protonymphs	2.6 + 46.3	3.4	2 (F)
T. pyri	I	Protonymphs	7.8 + 138.9	7.2	16 (F)
T. pyri	I	Protonymphs	23.3 + 416.7	26.1 *	39 (F)
T. pyri	I	Protonymphs	70 + 1250	73.5 *	/
T. pyri	I	Protonymphs	210 + 3750	94.3 *	/
T. pyri	N	Protonymphs	3.5 + 62.5	0	0 (+ 60) (F)
T. pyri	N	Protonymphs	70 + 1250	3.6	0 (+ 27) (F)

Parasitoids (ANA2001-481)

Aph. rhopal.	I	Imagines	210 + 3750	10	30 (P)

Plant dwelling species (ANA2001-485)

C. carnea	I	Larvae	3.5 + 62.5	0	0 (+14) (F)
C. carnea	I	Larvae	70 + 1250	0	0 (+11) (F)

Soil dwelling species (ANA 2001-482, ANA 2001-483, ANA 2001-484)

P. cupreus	I	Imagines	70 + 1250	0	0 (FA)
A. bilineata	I	Imagines	70 + 1250		14 (P)
Pardosa sp.	I	Adults	70 + 1250	0	0 (+23) (FA)

I = Inert substrate, N = natural substrate, F = Fertility, P = Parasitation capacity, FA = Food uptake

B.9.7.2 Risk assessment

Non-target arthropods are likely to be exposed to formulated tritosulfuron by direct spray, contact or fresh or dry residues. Oral uptake of contaminated pollen, nectar and honey dew, prey or via host organisms is considered of minor importance. As a tier one worst-case exposure scenario, the predicted environmental exposure of non-target arthropods is assumed to be equivalent to the maximum nominal field rate. The nominal field rate is 70 g BAS 635 00 H/ha (corresponding to 50 g as tritosulfuron/ha) + 1250 ml BAS 152 00 S/ha.

Two tests with *T pyri* were conducted. In the test on glass plates (ANA 2001-480) a LR_{50} of 40.1 g BAS 635 00 H + 716.1 ml/ha BAS 152 00 S was determined. On natural substrate (ANA 2001-486) in both tested rates of 3.5 g/ha BAS 635 00 H + 62.5 ml/ha BAS 152 00 S and 70 g/ha BAS 635 00 H + 1250 ml/ha BAS 152 00 S no effects on mortality and reproduction were observed. *Aphidius rhopalosiphi* was tested at 210 g/ha BAS 635 00 H + 3750 ml/ha BAS 152 00 S and showed at this rate a mortality of 10 % and a reduction of the parasitation capacity of 30 %. The tests with the plant dwelling species *Chrysoperla carnea* and the soil dwelling species *Poecilus cupreus*, *Aleochara bilineata* and *Pardosa spec*. showed no or low effects up to 70 g BAS 635 00 H + 1250 ml/ha BAS 152 00 S.

The available data indicate that *T. pyri* was the most sensitive species. As in the test on natural substrate no effects on mortality and no reduction of fertility were observed, the risk for non-target terrestrial arthropods is considered acceptable.

B.9.8 Effects on earthworms (Annex IIA 8.4; Annex IIIA 10.6.1)

B.9.8.1 Acute toxicity (Annex IIA 8.4.1, Annex IIIA 10.6.1.1)

Title:	**Effect of BAS 635 H on mortality and biomass of the earthworm *Eisenia foetida***
Author:	Dohmen, G.P. (1998)
BBA-Ref.-No.:	ARW2001-93
Test substance:	technical tritosulfuron
Purity:	95.9 %
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	240/350/500/700/1000 mg/kg
Findings:	
LC_{50}:	> 1000 mg/kg
Lowest lethal conc.:	> 1000 mg/kg
NOEC:	1000 mg/kg
valid:	yes
GLP compliance:	yes

Title:	**Acute toxicity (14 days) of BH 635-2 to the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil**
Author:	Lührs, U. (1998)
BBA-Ref.-No.:	ARW2001-94
Test substance:	metabolite 635M02 (BH 635-2)
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	62.5/125/250/500/1000 mg/kg
Findings:	
LC_{50}:	> 1000 mg/kg
Lowest lethal conc.:	500 mg/kg
NOEC:	250 mg/kg
valid:	yes
GLP compliance:	yes
Remark:	not the whole amount of the test substance was dissolved completely (see report on page 18)

Title:	**Acute toxicity (14 days) of BH 635-3 to the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil**
Author:	Lührs, U. (1998)
BBA-Ref.-No.:	ARW2001-95
Test substance:	metabolite 635M03 (BH 635-3)
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	62.5/125/250/500/1000 mg/kg
Findings:	
LC_{50}:	> 1000 mg/kg
Lowest lethal conc.:	> 1000 mg/kg
NOEC:	500 mg/kg
valid:	yes
GLP compliance:	yes
Remark:	not the whole amount of the test substance was dissolved completely (see report on page 18)

Title:	**Acute toxicity (14 days) of BH 635-4 to the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil**
Author:	Lührs, U. (1998)
BBA-Ref.-No.:	ARW2001-96
Test substance:	metabolite 635M01 (BH 635-4)
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	62.5/125/250/500/1000 mg/kg
Findings:	
LC_{50}:	> 1000 mg/kg
Lowest lethal conc.:	> 1000 mg/kg
NOEC:	1000 mg/kg
valid:	yes
GLP compliance:	yes

Title:	**Acute toxicity (14 days) of BH 635-5 to the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil**
Author:	Lührs, U. (1998)
BBA-Ref.-No.:	ARW2001-97
Test substance:	metabolite 635M04 (BH 635-5)
Guideline:	OECD 207

Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	62.5/125/250/500/1000 mg/kg
Findings:	
LC_{50}:	671 (592-761) mg/kg
Lowest lethal conc.:	500 mg/kg
NOEC:	250 mg/kg
valid:	yes
GLP compliance:	yes

Title: **Acute toxicity (14 days) of BH 635 00 H + BAS 152 00 S to the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil**

Author:	Lührs, U. (2000)
BBA-Ref.-No.:	ARW2001-98
Test substance:	formulation BAS 635 00 H (71.4 % tritosulfuron) + BAS 152 00 S
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	62.5/125/250/500/1000 mg/kg (sum product + adjuvant) e.g. 62.5 mg/kg corresponds to 2.99 mg/kg BAS 635 00 H + 59.51 BAS 152 00 S
Findings:	
LC_{50}:	> 1000 mg/kg
Lowest lethal conc.:	> 1000 mg/kg
NOEC:	1000 mg/kg
valid:	yes
GLP compliance:	yes

Table 9.8-1: Summary of earthworm toxicity data

Test material	Species	Test	NOEC mg/kg	LC_{50} mg/kg	Ref.
tritosulfuron (BAS 635 H)	*Eisenia fetida*	acute	1000	> 1000	ARW2001-93
635M02 (BH 635-2) (metabolite)	*Eisenia fetida*	acute	250	> 1000	ARW2001-94
635M03 (BH 635-3) (metabolite)	*Eisenia fetida*	acute	500	> 1000	ARW2001-95
635M01 (BH 635-4) (metabolite)	*Eisenia fetida*	acute	1000	> 1000	ARW2001-96
635M04 (BH 635-5, AMTT) (metabolite)	*Eisenia fetida*	acute	250	671	ARW2001-97
BAS 63500 H + BAS 152 00 S	*Eisenia fetida*	acute	1000	> 1000	ARW2001-98

B.9.8.2 Risk assessment

Since log Pow is < 2, the toxicity data are not divided by the factor of 2 (see EPPO risk assessment scheme for soil organisms).

Table B.9.8-1: TERa and TERlt for earthworms

Test substance	Toxicity data mg as/kg	PEC initial (mg as/kg) *	Time scale	TER
technical tritosulfuron (BAS 635 H)	> 1000	0.067	acute	> 14 925
BAS 635 00 H + BAS 152 00 S (formulation + adjuvant)	> 34.2	0.067	acute	> 510
metabolite 635M02 (BH 635-2)	> 1000	0.018	acute	> 55 555
metabolite 635M03 (BH 635-3)	> 1000	0.011	acute	> 90 909
metabolite 635M01 (BH 635-4)	> 1000	0.020	acute	> 50 000
metabolite 635M04 (BH 635-5)	671	0.013	acute	51 615

* see chapter B.08.03

The acute TER values for the active substance, the formulation and the metabolites 635M02 (BH 635-2), 635M03 (BH 635-3), 635M01 (BH 635-4) and 635M04 (BH 635-5) are above the relevant triggers and therefore it is concluded that the acute risk for earthworms is acceptable.

As the metabolites 635M02 (BH 635-2), 635M03 (BH 635-3) and 635M01 (BH 635-4) show a slow degradation pattern in soil, the longterm risk of these metabolites for earthworms has to be assessed.

B.9.9 Effects on other soil non-target macro-organisms (Annex IIIA 10.6.2)

No data on other soil non-target macro-organisms are required, as $DT_{90\ field} < 365$ days.

B.9.10 Effects on soil non-target micro-organisms (Annex IIA 8.5; Annex IIIA 10.7)

B.9.10.1 Nitrogen conversion (Annex IIA 8.5; Annex IIIA 10.7)

Title: **Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, nitrogen turnover**

Author: Wachter, S. (2001)
BBA-Ref.-No.: BMF2001-77
Test substance: mixture BAS 635 00 H + BAS 152 00 S (tritosulfuron 71.4 %)
Guideline: OECD (N)
Type of test: N-mineralisation
Activity: N-mineralisation
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-1: Effects of BAS 635 00 H + BAS 152 00 S on nitrogen conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand	0.070 + 1.25 0.350 + 6.25	- 0.95 + 6.1	28	yes

Title: **Effects of BH 635-2 on the nitrogen turnover in soil**

Author: Krieg, W. (1998)
BBA-Ref.-No.: BMF2001-73
Test substance: metabolite 635M02 (BH635-2)
Guideline: BBA 1-1 (N)
Type of test: N-mineralisation

Activity: N-mineralisation
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-2: Effects of 635M02 (BH 635-2) on nitrogen conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand A	0.05 0.25	+ 2.0 + 4.2	28	yes
Loamy sand B	0.05 0.25	± 0 + 0.8	28	yes

Loamy sand A: clay 9 %, silt 12 %, sand 79 %,
Loamy sand B: clay 13 %, silt 18 %, sand 69 %

Title: Effects of BH 635-3 on nitrogen conversion in soil

Author: Krieg, W. (1999)
BBA-Ref.-No.: BMF2001-74
Test substance: metabolite 635M03 (BH 635-3)
Guideline: BBA 1-1 (N)
Type of test: N-mineralisation
Activity: N-mineralisation
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-3: Effects of 635M03 (BH 635-3) on nitrogen conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand A	0.05 0.25	- 1.2 + 3.4	28	yes
Loamy sand B	0.05 0.25	- 6.5 - 3.9	28	yes

Loamy sand A: clay 9 %, silt 12 %, sand 79 %,
Loamy sand B: clay 13 %, silt 18 %, sand 69 %

Title: **Effects of BH 635-4 on the nitrogen turnover in soil**

Author: Krieg, W. (1999)
BBA-Ref.-No.: BMF2001-75
Test substance: metabolite 635M01 (BH 635-4)
Guideline: BBA 1-1 (N)
Type of test: N-mineralisation
Activity: N-mineralisation
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-4: Effects of 635M01 (BH 635-4) on nitrogen conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand A	0.05 0.25	+ 0.9 - 1.7	28	yes
Loamy sand B	0.05 0.25	+ 0.5 + 1.2	28	yes

Loamy sand A: clay 9 %, silt 12 %, sand 79 %,
Loamy sand B: clay 13 %, silt 18 %, sand 69 %

Title: **Effects of BH 635-5 on the nitrogen turnover in soil**

Author: Krieg, W. (1999)
BBA-Ref.-No.: BMF2001-76
Test substance: metabolite 635M04 (BH 635-5)
Guideline: BBA 1-1 (N)
Type of test: N-mineralisation
Activity: N-mineralisation
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-5: Effects of BH 635-5 on nitrogen conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand A	0.05 0.25	+ 1.2 + 0.2	28	yes
Loamy sand B	0.05 0.25	- 0.9 - 2.5	28	yes

Loamy sand A: clay 9 %, silt 12 %, sand 79 %,
Loamy sand B: clay 13 %, silt 18 %, sand 69 %

B.9.10.2 Carbon conversion (Annex IIA 8.5; Annex IIIA 10.7)

Title: **Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, short-term respiration**

Author: Wachter, S. (2001)
BBA-Ref.-No.: BMF2001-78
Test substance: mixture BAS 635 00 H + BAS 152 00 S (tritosulfuron 71.4 %)
Guideline: OECD (C)
Type of test: C-mineralisation
Activity: short term respiration
Amendment: 2 g glucose/100 g soil
valid: yes
GLP compliance: yes

Findings:

Table B.9.10-6: Effects of BAS 635 00 H + BAS 152 00 S on carbon conversion

Type of soil	Application rate (kg/ha + l/ha)	Effects compared to untreated control (%)	Test duration (d)	Influence tolerable
Loamy sand	0.070 + 1.25 0.350 + 6.25	+ 6.7 - 1.8	28	yes

B.9.10.3 Risk assessment

The influence of the mixture BAS 635 00 H + BAS 152 00 S on nitrogen and carbon conversion is < 25 % compared to the untreated control. The metabolites 635M02 (BH 635-2), 635M03 (BH 635-3), 635M01 (BH 635-4) and 635M04 (BH 635-5) have been tested concerning N-mineralisation in two different loamy sand soils. The effect was < 25 %

compared to the control for all metabolites. For the metabolites no carbon conversion was tested.
When applying tritosulfuron containing plant protection products according to the recommended pattern of use, no lasting effects on microbial activities are to be expected.

B.9.11 Effects on other non-target organisms (flora and fauna) believed to be at risk (Annex IIA 8.6)

Effects on non-target terrestrial plants

Tritosulfuron is an active substance belonging to the sulfonylureas. It is a systemic herbicide acting via the blockage of the enzyme acetolactate-synthase (ALS). The herbicidal action is mainly via the leaves. The application rate is 70 g product/ha (corresponding to 50 g tritosulfuron/ha) + 1.25 l/ha adjuvant.

Seedling emergence test (PFL 2001-66)
A seedling emergence test was done with 6 plant species with the formulation BAS 635 00 H (71.4 % tritosulfuron) in a mixture with the adjuvant BAS 152 00 S (40 % purity). The ratio of mixing was 1:17.9. Six doses were tested. The highest tested dose was 35 g BAS 635 00 H + 625 ml BAS 152 00 S/ha. Assessment of phytotoxicity was done 7, 14 and 21 days after treatment, plant height and fresh weight were evaluated after 21 days. The seedling emergence in the control was > 65 % for all tested plant species.

Table B.9.11-1: Results of the seedling emergence test

Species	Family	ED_{50} (g BAS 635 00 H/ha)		ED_{50} (ml BAS 152 00 S/ha)	
Linum usitatissimum	Linaceaea	> 35	e,h,w	> 625	e,h,w
Brassica napus	Brassicaceae	28.9	h	516.1	h
Pisum sativum	Leguminosae	> 35	e,h,w	> 625	e,h,w
Phacelia tanacetifolia	Hydrophyllaceae	21.5	w	384	w
Avena sativa	Poaceae	> 35	e,h,w	> 625	e,h,w
Allium cepa	Liliaceae	> 35	e,h,w	> 625	e,h,w

e = seedling emergence, h = plant height, w = fresh weight

Concerning phytotoxicity, there were no effects on the monocotyledonous species and *Pisum sativum*. For *Linum usitatissimum* symptoms were observed at the highest rate of 35 g BAS 635 00 H + 625 ml BAS 152 00 S. For *Brassica napus* symptoms were observed for the rates > 8.75 BAS 635 00 F + 156 ml BAS 152 00 S and for *Phacelia tanacetifolia* at > 17.5 g BAS 635 00 F + 313 ml BAS 152 00 S.
The most sensitive species was *Phacelia tanacetifolia*.

Vegetative vigor (PFL 2001-67)
A vegetative vigor test was done with 6 plant species with the formulation BAS 635 00 H (71.4 % tritosulfuron) in a mixture with the adjuvant BAS 152 00 S (40 % purity). The ratio of mixing was 1:17.9. Several doses were tested. The highest tested dose was 49.5 g BAS 635 00 H + 884 ml BAS 152 00 S/ha for *Brassica napus* and *Linum usitatissimum* and 35 g BAS 635 00 H + BAS 152 00 S for all other species. Assessment of phytotoxicity was

done 7, 14 and 21 days after treatment, plant height and fresh weight were evaluated after 21 days.

Table B.9.11-2: Results of the vegetative vigor test

Species	**Family**	**ED_{50} (g BAS 635 00 H/ha)**	**ED_{50} (ml BAS 152 00 S/ha)**
Linum usitatissimum	Linaceaea	25.5 w	455.2 w
Brassica napus	Brassicaceae	4.3 w	76.4 w
Pisum sativum	Leguminosae	11.8 w	210.5 w
Phacelia tanacetifolia	Hydrophyllaceae	> 35 h,w	> 625 h,w
Avena sativa	Poaceae	> 35 h,w	> 625 h,w
Allium cepa	Liliaceae	> 35 h,w	> 625 h,w

h = plant height, w = fresh weight

For the monocotyledonous species there was no visual damage observed. For *Linum usitatissimum*, *Brassica napus* and *Pisum sativum* visual damages were observed for all tested rates, for *Phacelia tanacetifolia* visual damage was observed for rates > 12.37 g BAS 635 00 H + BAS 152 00 S.
The most sensitive species was *Brassica napus* with an ED_{50} of 4.3 g BAS 635 00 H + 76.4 ml BAS 152 00 S/ha.

Field test with *Brassica napus* (PFL 2001-68)

A field test with *Brassica napus* was conducted with six treatment rates up to 35 g product BAS 635 00 H (corresponding to 25 g as tritosulfuron/ha) + 625 ml BAS 152 00 S/ha. Four replicates/treatment were done on 10 m^2 plots. Application was done at growth stage BBCH 10-16 using a plot sprayer with 250 l water/ha. Assessment for plant damage was done 7, 22 and 42 days after application. After 51 days shoot fresh weight was determined.
Plant damage was observed from 1.5 g as /ha onwards. Whereas in the 1.5 g and the 3 g as/ha treatment there was a nearly complete recovery until the end of the study, the other concentrations of 6, 12.5 and 25 g as/ha showed severe damage. The ED_{50} for shoot weight was 6.2 g as/ha (corresponding to 8.7 g BAS 635 00 H/ha + 165 ml BAS 152 00 S/ha). The NOAEC for plant damage was 1.5 g as/ha.

Field test with *Pisum sativum* (PFL 2001-69)

A field test with *Pisum sativum* was conducted with six treatment rates up to 35 g product BAS 635 00 H (corresponding to 25 g as tritosulfuron/ha) + 625 ml BAS 152 00 S/ha. Four replicates/treatment were done on 10 m^2 plots. Application was done at growth stage BBCH 13-15 using a plot sprayer with 250 l water/ha. Assessment for plant damage was done 7, 22 and 42 days after application. After 85 days grain weight was determined.
Plant damage was observed from 1.5 g as /ha onwards. Whereas in the 1.5 g and the 3 g as/ha treatment there was a complete recovery until the end of the study and in the 6 g as/ha treatment there was some recovery, the concentrations of 12.5 and 25 g as/ha showed severe damage. The ED_{50} for grain weight was between 6 and 12.5 g as/ha (corresponding to > 8.4 g BAS 635 00 H + 160 ml BAS 152 00 S/ha and < 17.5 BAS 635 00 H + 310 ml BAS 152 00 S). The NOAEC for plant damage was 3 g as/ha.

Field test with *Linum usitatissimum* (PFL 2001-70)

A field test with *Linum usitatissimum* was conducted with six treatment rates up to 35 g product BAS 635 00 H (corresponding to 25 g as tritosulfuron/ha) + 625 ml BAS 152 00 S/ha. Four replicates/treatment were done on 10 m^2 plots. Application was done at growth stage BBCH 14-18 using a plot sprayer with 250 l water/ha. Assessment for plant damage was done 7, 22 and 42 days after application. After 50 days shoot fresh weight was determined.
Only slight and not persisting plant damage was observed up to 3 g as/ha. The concentrations of 12.5 and 25 g as/ha showed lasting damage. An ED_{50} for shoot weight could not be determined, because there was no statistically significant effect at the highest rate of 25 g as/ha. The NOAEC for plant damage was > 3 g as/ha.

Risk assessment
Risk assessment is based on the ED_{50} of *Brassica napus* of 4.3 g BAS 635 00 H + 76.4 ml BAS 152 00 S/ha, which was the most sensitive species in the vegetative vigor test in the laboratory, and on the ED_{50} of 8.7 g BAS 635 00 H + 156 ml BAS 152 00 S/ha in the field. The TER of 4.5 for the field test is considered acceptable.

Table B.9.11-3: Risk assessment for BAS 635 00 H + BAS 152 00 S concerning non-target terrestrial plants based on the species *Brassica napus*

Distance from treated area (m)	**Drift (%)**	**Amount of drift (g product/ha)**	**TER lab. (ED_{50} 4.3 g/ha)**	**TER field (ED_{50} 8.7 g/ha)**
1	2.77	1.94	2.2	4.5
5	0.57	0.399	10.8	21.8

Herbicidal activity (PFL2002-68)

The metabolites 635 M01 (BH 635-4), 635 M02 (BH 635-2), 635 M03 (BH 635-3) and 635 M04 (BH 635-5) were tested in the greenhouse at pre-emergence application. The tests were done with 6 species (5 dicotyledonous and one monocotyledonous species) with 3 replicates in comparison with an untreated control. Four application rates were tested.

The results of the untreated control are not reported. The assessment of the effects was done on day 8 and day 21.

Table B.9.11-4: Effects of BAS 635 H metabolites on plants (phytotoxicity in %)

	kg/ha	Setaria viridis		Abutilon		Chenop. album		Matricaria inodora		Stellaria media		Veronica	
		day		day		day		day		day		day	
		8	21	8	21	8	21	8	21	8	21	8	21
635 M04	0.5	0	0	2	0	12	5	27	7	3	0	0	0
	0.25	0	0	0	0	7	3	13	3	0	0	0	0
	0.125	0	0	0	0	0	0	13	0	0	0	0	0
	0.0625	0	0	0	0	0	0	3	0	0	0	0	0

	kg/ha	Setaria viridis day 8	21	Abutilon day 8	21	Chenop. album day 8	21	Matricaria inodora day 8	21	Stellaria media day 8	21	Veronica day 8	21
635 M02	0.5	0	0	0	0	8	3	24	5	7	0	3	3
	0.25	0	0	0	0	3	3	13	0	3	0	0	3
	0.125	0	0	0	0	0	0	3	0	0	0	0	0
	0.0625	0	0	0	0	0	0	3	0	0	0	0	0
635 M03	0.5	0	0	2	0	2	12	0	2	0	0	3	0
	0.25	0	0	0	0	2	5	0	0	0	0	0	0
	0.125	0	0	0	0	0	0	0	0	0	0	0	0
	0.0625	0	0	0	0	0	0	0	0	0	0	0	0
635 M01	0.5	2	2	3	0	13	10	5	3	0	0	0	0
	0.25	0	0	0	0	3	3	3	3	0	0	0	0
	0.125	0	0	0	0	0	3	3	0	0	0	0	0
	0.0625	0	0	0	0	0	0	0	0	0	0	0	0

The metabolites 635 M04 and 635 M02 showed some effects on *Matricaria inodora*, but these were low at the lowest test rate of 0.0625 kg/ha. This rate is much higher than the maximum expected amount of the metabolites in soil taking into account the molecular weight (the theoretical maximum amount of 635 M04 is 21.8 g/ha and for 635 M02 it is 25.3 g/ha).

B.9.12 Effects on biological methods of sewage treatment (Annex IIA 8.7)

An EC_{50} of >10000 mg/l for *Pseudomonas putida* was determined indicating no unacceptable risk on biological methods of sewage tretment plants.

B.9.13 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.1.1	Munk, R.	1997	Report Reg.-No.271 272 - Avian single-dose oral LD50 on the mallard duck (Anas platyrhynchos). 13W0167/95037 /BAS 97/10947 GLP, unpublished AVS2001-141	N	BAS

[8] Only notifier listed

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.1.1	Munk, R. and Küttler, K.	1997	Report Reg.-No.271 272 - Avian single-dose oral LD50 on the bobwhite quail (Colinus virginianus). 11W0167/95036 /BAS 97/10377 GLP, unpublished AVS2001-140	N	BAS
AIIA-8.1.2	Munk, R.	1997	Report Reg.-No.271 272 - Avian dietary LC50 test in chicks of the bobwhite quail (Colinus virginanus). 31W0167/95038 GLP, unpublished AVS2001-143	N	BAS
AIIA-8.1.2	Munk, R.	1997	Report Reg.-No.271 272 - Avian dietary LC50 test in chicks of the mallard duck (Anas platyrhynchos L.) + Amendment No. 1. 32W0167/95039 GLP, unpublished AVS2001-142	N	BAS
AIIA-8.1.3	Munk, R.	1998	BAS 635 H - 1-generation reproduction study on the bobwhite quail (Colinus virginanus) by administration in the diet. 71W0167/95040 GLP, unpublished AVS2001-144	N	BAS
AIIA-8.1.3	Zok, S.	1999	BAS 635 H - 1-generation reproduction study on the mallard duck (Anas platyrhynchos) by administration in the diet. 72W0167/95041 GLP, unpublished AVS2001-145	N	BAS
AIIA-8.2.1	Munk, R.	1996	Reg.-No. 271272 - Acute toxicity study on the common carp (Cyprinus carpio L.) in a static system (96 hours). 96/10981 GLP, unpublished WAT2001-437	Y	BAS
AIIA-8.2.1	Munk, R.	1998	Reg.-No. 335 184 (BH 635-4) Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 98/10934 GLP, unpublished WAT2001-440	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.2.1	Munk, R.	1997	AMTT, techn. CAS - Nr. (5311-05-7) Acute toxicity study on the zebra fish (Brachydanio rerio HAM. and BUCH.) in a static system (96 hours). 97/11694 GLP, unpublished WAT2001-441	Y	BAS
AIIA-8.2.1	Munk, R.	1997	Sublethal toxic effects on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a flow-through system (28 days). 1998/11527 GLP, unpublished WAT2001-442	Y	BAS
AIIA-8.2.1	Munk, R.	1996	Reg.-No. 271272 - Acute toxicity study on the blue gill sunfish (Lepomis macrochirus) in a static system (96 hours). 96/10980 GLP, unpublished WAT2001-436	Y	BAS
AIIA-8.2.1	Munk, R.	1996	Reg.-No. 271272 - Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 96/10979 GLP, unpublished WAT2001-435	Y	BAS
AIIA-8.2.1	Zok, S.	1999	Reg.-No. 335 182 (BH 635-3) Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 1999/11413 GLP, unpublished WAT2001-439	Y	BAS
AIIA-8.2.1	Zok, S.	1999	Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 1999/10578 GLP, unpublished WAT2001-438	Y	BAS
AIIA-8.2.4	Dohmen, G.P.	2001	Effect of BAS 635 -2 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012469 GLP, unpublished WAT2001-444	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.2.4	Dohmen, G.P.	2001	Effect of BAS 635 -3 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012471 GLP, unpublished WAT2001-445	Y	BAS
AIIA-8.2.4	Dohmen, G.P.	2001	Effect of BAS 635 -5 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012473 GLP, unpublished WAT2001-447	Y	BAS
AIIA-8.2.4	Dohmen, G.P.	2001	Effect of BAS 635 -4 on the Immobility of Daphnia magna STRAUS in a 48 hour Static, Acute Toxicity Test. 2000/1012472 GLP, unpublished WAT2001-446	Y	BAS
AIIA-8.2.4	Dohmen, G.P.	1998	Effect of BAS 635 H on Daphnia magna STRAUS in a Static Acute Toxicity Test. 97/11190 GLP, unpublished WAT2001-443	Y	BAS
AIIA-8.2.5	Dohmen, G.P.	2000	Effect of BAS 635 on Mortality and Reproduction of Daphnia magna. 2000/1012433 GLP, unpublished WAT2001-448	Y	BAS
AIIA-8.2.6	Dohmen, G.P.	1999	Effect of BAS 635-3 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10321 GLP, unpublished WAT2001-452	Y	BAS
AIIA-8.2.6	Dohmen, G.P.	1999	Effect of BAS 635-2 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 99/10320 GLP, unpublished WAT2001-451	Y	BAS
AIIA-8.2.6	Dohmen, G.P.	1999	Effect of BAS 635-4 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10322 GLP, unpublished WAT2001-453	Y	BAS
AIIA-8.2.6	Dohmen, G.P.	1999	Effect of BAS 635-5 on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/10323 GLP, unpublished WAT2001-454	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.2.6	Dohmen, G.P.	1999	Effect of BAS 635 H on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/11021 GLP, unpublished WAT2001-449	Y	BAS
AIIA-8.2.6	Kubitza, J.	2002	Effect of BAS 635 H on the Growth of the Blue-green alga Anabaena flos-aquae. 2002/1004393 GLP, unpublished WAT2002-89	N	BAS
AIIA-8.2.8	Dohmen, G.P.	1999	Effect of BAS 635 H on the Growth of Lemna gibba G3. 1999/11144 GLP, unpublished WAT2001-455	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Bühler, A.	2001	Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite Typhlodromus pyri (Acari:Phytoseiidae) in an extended laboratory trial. 63871 ! BASF2000/1012464 GLP, unpublished ANA2001-486	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Bühler, A.	2000	Effects of BAS 635 00 H + BAS 152 00 S on the ground dwelling predator Poecilus cupreus (Coleoptera, Carabidae) in a laboratory trial. 57045 ! BASF2000/1012452 GLP, unpublished ANA2001-482	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Drexler, A.	2000	Effects of BAS 635 00 H + BAS 152 00 S on the lacewing Chrysoperla carnea Steph. (Neuroptera, Chrysopidae)) in the laboratory. 7572046 ! BASF2000/1012454 GLP, unpublished ANA2001-485	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Drexler, A..	2001	Effects of BAS 635 00 H + BAS 152 00 S on the reproduction of rove beetles Aleochara bilineata Gyll. (Coleoptera, Staphylinidae)) in the laboratory. 7573070 ! BASF2000/1012455 GLP, unpublished ANA2001-483	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Goßmann, A.	2000	Effects of BAS 635 00 H + BAS 152 00 S on the predatory mite Typhlodromus pyri Scheuten (Acari, Phytoseiidae) -Dose response design-. 7571063 ! BASF2000/1012453 GLP, unpublished ANA2001-480	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.3.2; AIIIA-10.5.1	Schmitzer, St.	2001	Effects of BAS 635 00 H + BAS 152 00 S on the wolf spider Pardosa spec. (Araneae, Lycosidae)) in the laboratory. 7574065 ! BASF2000/1012456 GLP, unpublished ANA2001-484	Y	BAS
AIIA-8.3.2; AIIIA-10.5.1	Ufer, A..	2001	Effects of BAS 635 00 H + BAS 152 00 S on the parasitoid Aphidius rhopalosiphi (Hymenoptera: braconidae) in a laboratory trial. 57048 ! BASF2000/1012463 GLP, unpublished ANA2001-481	Y	BAS
AIIA-8.4.1	Dohmen, G.P.	1998	Effect of BAS 635 H on mortality and biomass of the earthworm Eisenia foetida. 19534 ! BASF97/11325 GLP, unpublished ARW2001-93	Y	BAS
AIIA-8.4.1	Lührs, U.	1998	Acute toxicity (14 days) of BH 635-5 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4560021 ! BASF98/11396 GLP, unpublished ARW2001-97	Y	BAS
AIIA-8.4.1	Lührs, U.	1998	Acute toxicity (14 days) of BH 635-4 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4550021 ! BASF98/11397 GLP, unpublished ARW2001-96	Y	BAS
AIIA-8.4.1	Lührs, U.	1998	Acute toxicity (14 days) of BH 635-3 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4540021 ! BASF98/11367 GLP, unpublished ARW2001-95	Y	BAS
AIIA-8.4.1	Lührs, U.	1998	Acute toxicity (14 days) of BH 635-2 to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 4530021 ! BASF98/11265 GLP, unpublished ARW2001-94	Y	BAS
AIIA-8.5	Krieg, W.	1999	Effects of BH 635-3 on the nitrogen turnover in soil. 48362 ! BASF99/10041 GLP, unpublished BMF2001-74	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.5	Krieg, W.	1999	Effects of BH 635-4 on the nitrogen turnover in soil. 48363 ! BASF99/10042 GLP, unpublished BMF2001-75	Y	BAS
AIIA-8.5	Krieg, W.	1999	Effects of BH 635-5 on the nitrogen turnover in soil. 483634! BASF99/10043 GLP, unpublished BMF2001-76	Y	BAS
AIIA-8.5	Krieg, W.	1998	Effects of BH 635-2 on the nitrogen turnover in soil. 48361 ! BASF98/11161 GLP, unpublished BMF2001-73	Y	BAS
AIIA-8.5; AIIIA-10.7.1	Wachter, S.	2001	Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, short-term respiration. 20001124/02-ABMF ! BASF 2000/1012476 GLP, unpublished BMF2001-78	Y	BAS
AIIA-8.5; AIIIA-10.7.1	Wachter, S.	2001	Assessment of the side effects of BAS 635 00 H + BAS 152 00 S on the activity of the soil microflora, nitrogen turnover. 20001124/01-ABMF ! BASF 2000/1012475 GLP, unpublished BMF2001-77	Y	BAS
AIIA-8.6; AIIIA-10.8	Frank, P.	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects of the test item on seedling emergence of terrestrial plants. 71 171 / BASF2000/1012474 GLP, unpublished PFL2001-66	Y	BAS
AIIA-8.6; AIIIA-10.8	Oberwalder, Chr.	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of Flax (Linum usitatissimum) under field conditions. 71 175-3 ! BASF2000/1012466 GLP, unpublished PFL2001-70	Y	BAS
AIIA-8.6; AIIIA-10.8	Oberwalder, Chr.	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of Pea (Pisum sativum) under field conditions. 71 175-2 ! BASF2000/1012465 GLP, unpublished PFL2001-69	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIA-8.6; AIIIA-10.8	Oberwalder, Chr.	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects on vegetative vigour of oilseed rape (Brassica napus L.) under field conditions. 71 175-1! BASF2000/1012461 GLP, unpublished PFL2001-68	Y	BAS
AIIA-8.6; AIIIA-10.8	Reuter, St.	2001	BAS 635 00 H+BAS 152 00 S: A toxicity test to determine the effects of the test item on vegetative vigour of terrestrial plants. 71 173 ! BASF2000/1012470 GLP, unpublished PFL2001-67	Y	BAS
AIIA-8.6; AIIIA-10.8	Westphalen, K.-O.	1997	Herbicide tests of metabolites of SCR 271 272 H (= a.i. of BAS 635 H) on plants in the greenhouse at pre emergence application. Reg.Doc.#BASF98/10434 not GLP, unpublished PFL2002-68	Y	BAS
AIIA-8.7	Maisch	1998	Determination of the inhibitory effect of BAS 635 H on the cell multiplication of the bacterium Pseudomonas putida. 98/10080 GLP, unpublished WAT2001-457	Y	BAS
AIIA-8.7	Schwarz	1995	Determination of the Biodegradability of Reg.-No.271 272 in the CO2-Evolution Test. 95/10805 GLP, unpublished WAT2001-456	Y	BAS
AIIIA-10.2.1	Dohmen, G.P.	1999	Effect of BAS 635 00 H on the Growth of the Green Alga Pseudokirchneriella subcapitata. 1999/11147 GLP, unpublished WAT2001-462	Y	BAS
AIIIA-10.2.1	Dohmen, G.P.	2001	Effect of BAS 635 00 H on the Immobility of Daphnia magna STRAUS. 2000/1012484 GLP, unpublished WAT2001-460	Y	BAS
AIIIA-10.2.1	Munk, R.	1997	Report BAS 635 00 H Acute toxicity study on the rainbow trout (Oncorhynchus mykiss WALBAUM 1792) in a static system (96 hours). 97/10820 GLP, unpublished WAT2001-458	Y	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[8]
AIIIA-10.4	Kling A.	2001	Assessment of the Side Effects of BAS 635 00 H + BAS 152 00 S to the Honey Bee, Apis mellifera L. in the Laboratory. BASF98/10117 GLP, unpublished BIE2001-39	Y	BAS
AIIIA-10.4	Sack, D.	1998	Effect of Reg.-No. 271 272 on the Honeybee (Apis mellifera L.) in Laboratory Trials. BASF98/10117 GLP, unpublished BIE2001-38	Y	BAS
AIIIA-10.6.1.1	Lührs, U.	2000	Acute toxicity (14 days) of BH 635 00 H + BAS152 00 S to the earthworm Eisenia fetida (Savigny 1826) in artificial soil. 7575021 ! BASF2000/1012457 GLP, unpublished ARW2001-98	Y	BAS

Codes of owner

BAS: BASF Aktiengesellschaft

Appendix 1

Tritosulfuron

Standard Terms and Abbreviations

B.10 Appendices

B.10.1 Appendix I: Standard terms and abbreviations

Part 1 Technical Terms

A	ampere
ACH	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50 %
ALT	alanine amitrotransferase (SGPT)
AMD	automatic multiple development
ANOVA	analysis of variance
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application

cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days past inoculation
DRES	dietary risk evaluation system
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionisation detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector

FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulose virus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hl	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
Hs	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilisation concentration
ICM	integrated crop management
ID	ionisation detector

IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	in vitro fertilisation
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
l	litre
LAN	local area network
LASER	light amplification by stimulated emission
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LCLo	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDLo	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration

MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
ml	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mol
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue limit or level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NAEL	no adverse effect level
nd	not detected
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter content
op	organophosphorus pesticide
Pa	Pascal
PAD	pulsed amperometric detection

2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
PIXE	proton induced X-ray emission
pK_a	negative logarithm (to the base 10) of the dissociation constant
PNEC	predicted no effect concentration
po	by mouth (per os)
P_{ow}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
R_f	ratio of fronts
RfD	reference dose
RH	relative humidity
RL_{50}	residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	reversed phase material
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second

SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedure
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{1/2}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TCLo	toxic concentration low
TID	thermionic detector, alkali flame detector
TDLo	toxic dose low
TDR	time domain reflectrometry
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit

TOC	total organic chlorine
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comité des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe

ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export an Import of Dangerous Chemicals
EHC (number)	Environment Health Criteria (number)
EHCD	Environmental Health Criteria Document
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organisation
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organisation of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GIFAP	Groupement International des Association Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organisation
IMO	International Maritime Organisation
IOBC	International Organisation for Biological Control of noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organisation
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives

JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticides Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organisation
WTO	World Trade Organisation
WWF	World Wide Fund for Nature

Appendix 2

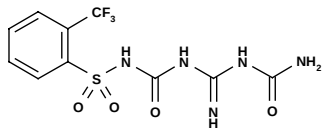
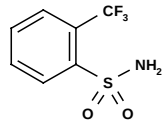
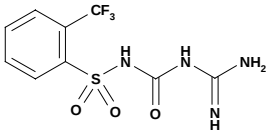
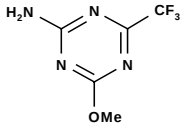
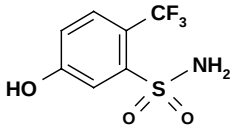
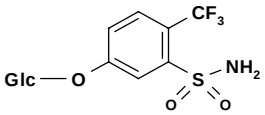
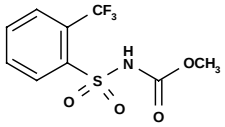
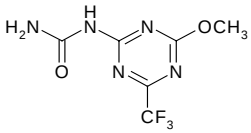
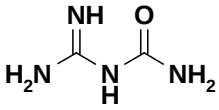
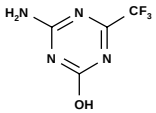
Tritosulfuron

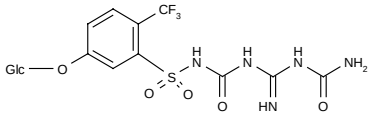
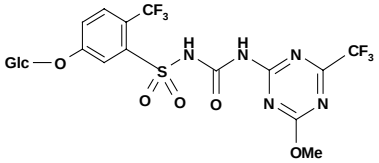
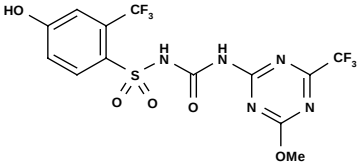
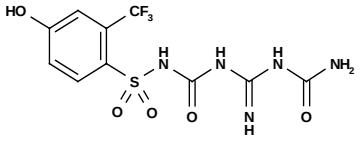
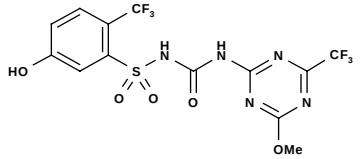
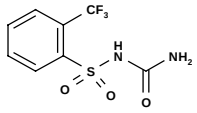
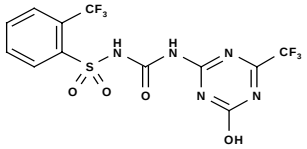
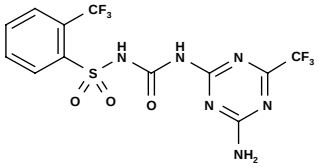
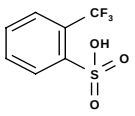
Specific Terms and Abbreviations

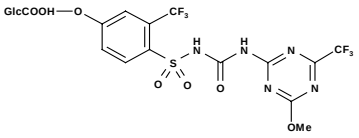
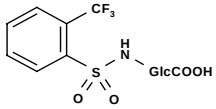
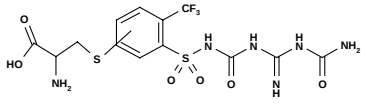
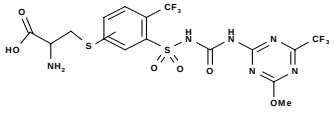
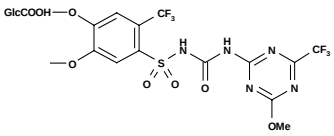
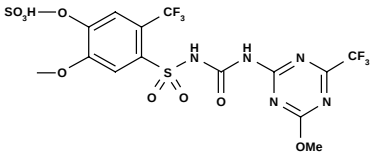
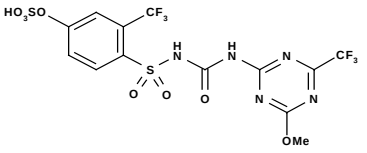
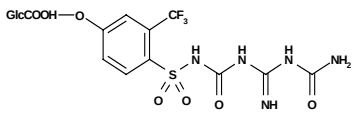
B.10.2 Appendix II: Specific terms and abbreviations

DAP	days after planting
DAT	days after treatment
DMSO	dimethylsulphoxide
ERR	extractable radioactive residue
PAS	pure active substance
RRR	residual radioactive residue
TAS	technical active substance
TRR	total radioactive residue
BrdU	5-Bromodeoxyuridine
CHO	Chinese hamster ovary
HPRT	Hypoxanthine-phosphoribosyl-transferase
PCNA	Proliferating cell nuclear antigen
TUNEL	Terminal deoxyribosyl-transferase mediated dUTP(deoxyuridinetriphosphate) nick end labelling

List of metabolites of tritosulfuron found in different matrices

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M01		1-(carbamoylamidino)-3-(2-trifluoromethyl-benzenesulfonyl) urea	335 184 (BH 635-4)	rat, maize, rotat. crops, soil, water, sediment
635M02		2-trifluoromethyl-benzenesulfonamide	TBSA, 292 564 (BH 635-2)	rat, goat, hen, rotat. crops, soil, water, sediment
635M03		1-amidino-3-(2-trifluoromethyl-benzenesulfonyl) urea	335 182 (BH 635-3)	rotat. crops, soil, water, sediment
635M04		2-amino-4-methoxy-6-(trifluoromethyl)-1,3,5-triazine	AMTT, 231 700 (BH 635-5)	rat, goat, hen, rotat. crops, soil, water
635M06		3-Hydoxy-6- trifluoromethyl-benzenesulfonamide	n.a.	maize, rotat. crops
635M07		5-(hexopyranosyloxy)-2-(trifluoromethyl)benzene-sulfonamide	n.a. 347 666	maize
635M08		N-(Methoxycarbonyl)-2-trifluoromethyl-benzenesulfonamide	n.a.	rat
635M09		*N*-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]urea	n.a. 347 667	goat, hen
635M10		Amino{[amino(imino)methyl]amino}oxomethane	n.a. 432 8983	rotat. crops
635M11		2-amino-4-hydroxy-6-trifluoromethyl-1,3,5-triazine	276 164 (BH 635-14)	rat, water

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M12		3-{[({[[(aminocarbonyl)amino]-(imino)methyl]amino}carbonyl)-amino]sulfonyl}-4-(trifluoromethyl)-phenyl hexopyranoside	n.a.	rotat. crops
635M13		3-{[({[4-methoxy-6-(trifluoro-methyl)-1,3,5-triazin-2-yl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl hexopyranoside	n.a.	maize, rotat. crops
635M15		3-{[({[4-methoxy-6-(trifluoro-methyl)-1,3,5-triazin-2-yl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl hexopyranoside	n.a.	rat
635M16		1-{[({[[(aminocarbonyl)amino]-(imino)methyl]amino}carbonyl)-amino]sulfonyl}-4-hydroxy-2-(trifluoromethyl) benzene	n.a.	rat
635M17		1-[(4-methoxy-6-trifluoromethyl)-1,3,5-triazin-2-yl]-3-(5-hydroxy-2-trifluoromethyl-benzenesulfonyl) urea	373 906 (BH 635-16)	rat, maize, rotat. crops, water
635M18		1-{[(aminocarbonyl)amino]-sulfonyl}-2-(trifluoromethyl) benzene	n.a.	rat, rotat. crops
635M19		2-hydroxy-4-(trifluoromethyl)-6-{[({[2(trifluoromethyl)phenyl]-sulfonyl}amino)carbonyl]amino}-1,3,5-triazine	n.a.	rat, soil, water
635M21		1-[(4-amino-6-trifluoromethyl)-1,3,5-triazin-2-yl]-3-(2-trifluoro-methyl-benzenesulfonyl) urea	362 561 (BH 635-15)	rat
635M23		2-(trifluoromethyl)benzene sulfonic acid	324 543 (BH 635-1 as Na-Salt)	rat, rotat. crops

Code	Structure	Chemical Name [CAS]/or IUPAC Name	Trivial Name, Codes used	Found in matrix
635M24		n.a.	n.a.	rat
635M25		n.a.	n.a.	rat
635M28		e.g. [3-{[({[[(aminocarbonyl) amino](imino)methyl]amino}-carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl] cysteine	n.a.	rat
635M29		[3-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-4-(trifluoromethyl)phenyl] cysteine	n.a.	rat
635M30		n.a.	n.a.	rat
635M31		2-methoxy-4-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-5-(trifluoromethyl)phenyl hydrogen sulfate	n.a.	rat
635M32		4-{[({[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]amino}carbonyl)amino]sulfonyl}-3-(trifluoromethyl)phenyl hydrogen sulfate	n.a.	rat
635M34		n.a.	n.a.	rat