Monograph

02 August 2002

Beflubutamid

Volume 1

Report and
Proposed Decision

Rapporteur Member State: Germany

Contents

Level 1

Beflubutamid

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)

This monograph is submitted to support first inclusion of the new active substance beflubutamid in Annex I of the Council Directive 91/414/EEC, according to Commission Regulations (EEC) No 3600/92 and (EC) No 993/94.

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

There were two notifiers for the new active ingredient beflubutamid: Stähler Agrochemie and UBE Industries. One dossier is submitted on behalf of the above mentioned notifiers. The dossier has been regarded to be complete.

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)

TASK FORCE

Applicant:	**Contact:**
Stähler Agrochemie GmbH & Co. KG PO Box 2047 21660 Stade Germany	Ms. G. Stähler Telephone: +49 (0) 4141 920441 Telefax: +49 (0) 4141 920410 e-mail: Staehler-agro@staehler.com
UBE Industries, Ltd, Ube Building, 2-3-11, Higashi-Shinagawa, Shinagawa-Ku, Tokyo 140-8633, Japan	Mr. Seiji Takamura Telephone: +81-3-5460-3234 Telefax: +81-3-5460-3394 E-mail: 14566u@ube-ind.co.jp
Local representative UBE Europe GmbH, Immermannstrasse 65B, 40210 Düsseldorf, Germany	Mr. Yuki Nishida Telephone: +49-211-178830 Telefax: +49-211-3613297

1.3.2 Common name and synonyms (Annex IIA 1.3)

Beflubutamid (ISO, proposed)

1.3.3 Chemical name (Annex IIA 1.4)

IUPAC: (*RS*)-*N*-benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide

CAS: 2-[4-fluoro-3-(trifluoromethyl)phenoxy]-*N*-(phenylmethyl)butanamide

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

a.s.: UR-50601, UBH-820
formulation: ASU 95 510 H (Beflubutamid/Isoproturon)

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

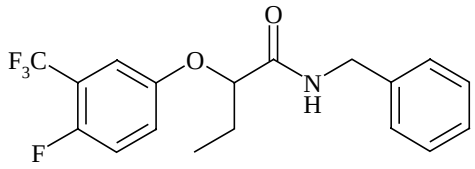
CAS: 113614-08-7
CIPAC: 662
EEC: not assigned
EINECS: not assigned

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

Molecular formular: $C_{18}H_{17}F_4NO_2$ (racemate)

Molecular mass: 355.12 g/mol

Structural formula:



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

Manufacuturer:
UBE Industries, Ltd,
UBE building, 2-3-11,
Higashi-shinagawa, Shinagawa-ku,
Tokyo 140-8633,
Japan

Person to contact: as applicant (see 1.3.1)

Manufacturing sites: Confidential information, see Annex C.

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)

≥ 970 g/kg (based on the analysis of material produced in a pilot plant)

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: Herbaflex

Code number: Plant protection product: ASU 95 510 H

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

Stähler Agrochemie
GmbH & Co. KG
P.O. Box 20 47
21660 Stade
Germany

Contact person: Gisela Stähler
Tel. No.: +49 (0) 4141 92 04 41
Fax No.: +49 (0) 4141 92 04 10

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

Suspension Concentrate (SC)

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)

UR-50601 or beflubutamid (ISO common name proposed) as a phenoxybutamid is a herbicidally active novel substance. The formulated product Herbaflex [ASU 95 510 H (UBH-820/isoproturon)] is a suspension concentrate (SC) containing 85 g/L beflubutamid and 500 g/L isoproturon. The product is intended to be used in agriculture against annual dicotyledonous and grass weed species after germination of the weeds.

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

Beflubutamid (UR-50601) is intended to be used as a selective post-emergence herbicide in winter cereals (Northern and Southern Europe) and durum wheat (Southern Europe). Beflubutamid is meant to control annual dicotyledonous weed species after germination of the weeds.

Beflubutamid is taken up mainly by the seedlings and to a lesser extent by roots and leaves. Limited translocation occurs, mainly by the symplast. UR-50601 inhibits the plant enzyme phytoene desaturase (PDS) of the carotenoid biosynthetic pathway leading to the photooxidation of chlorophyll, thus inducing typical bleaching symptoms.

Beflubutamid induces strong chlorosis of the new developing plant tissues. Subsequent to application of beflubutamid the entire plant (costae, intercostal area and stem) starts whitening. As soon as the vegetation point is affected, the young plant ceases growing and further development is suppressed. The treated weeds decay or remain that small, that they are overgrown by the developing cereals.

As an PDS-inhibitor, beflubutamid belongs to the mode of action group F1 according to the HRAC (Herbicide Resistance Action Committee) classification. The resistance risk of weeds to the active substance beflubutamid can be considered as to be potentially low.

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

Beflubutamid is intended to be used as a selective post-emergence herbicide in winter cereals [winter wheat (TRZAW), winter barley (HORVW), triticale (TTLSS) and rye (SECCW)] in

the Northern European countries and in winter wheat (TRZAW), winter barley (HORVW) and durum wheat (TRZDU) in the Southern European countries. The herbicide Herbaflex is meant to control annual dicotyledonous and grass weed species.

The product is applied as single application with 2.0 to 3.0 L/ha in autumn or spring at BBCH 11-13 (autumn) and BBCH 11-29 (spring) of the weeds and at BBCH 11-29 (autumn) or BBCH 13-29 (spring) of the crop. Thus, 170-255 g beflubutamid per hectare are applied.

The recommended water volumes are 200 to 400 L/ha, resulting in a maximum concentration of the active substance of 1.275 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 authorizations in EU Member States (Annex IIIA 12.1)

Beflubutamid is a new herbicidally active substance to be registered. This application is for the first inclusion of beflubutamid in Annex I of EU Directive 91/414/EEC. Therefore no authorisations are existent in EU Member States.

Level 2

Beflubutamid

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.

2.1.2 Physical and chemical properties

Beflubutamid (pure and technical active substance) is a white solid with damp earth odour. A melting point of 75 °C was determined for PAS, followed by decomposition from 128 °C. The relative density determined at 20 °C is 1.33 g/cm^3. The vapour pressures value is $1.1 \cdot 10^{-5}$ Pa (25 °C). The Henry´s constant at 20 °C was calculated to be $K_H = 1.1 \cdot 10^{-4}$ Pa m³ mol^{-1}. Solubility in water is about 3.5 mg/L without pH dependency. The test substance is soluble (>473 g/L) in acetone, dichloroethane, ethyl acetate and methanol. Lowest solubilities are observed in *n*-heptane (2.18 g/L) and xylene (106 g/L). The log $P_{O/W}$ is 4.28. According to the structure of the a.s. dissociation is unlikely. The substance is not highly flammable or autoflammable, not explosive and without oxidising properties.

Herbaflex is a signalwhite suspension concentrate. It has neither explosive nor oxidising properties. There is no flash point up to 64 °C. Above 64 °C Herbaflex thickened to a paste and there has been observed no auto-flammability below 400 °C. Its pH-value of 7.9 lies within the naturally occurring 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.

2.1.3 Details of uses and further information

2.1.3.1 Details of uses

Beflubutamid is intended to be used as a selective post-emergence herbicide in winter cereals [winter wheat (TRZAW), winter barley (HORVW), triticale (TTLSS) and rye (SECCW)] in the Northern European countries and in winter wheat (TRZAW), winter barley (HORVW) and durum wheat (TRZDU) in the Southern European countries. The Northern Europe indicated are Austria, Belgium, Denmark, Finland, France (North), Germany, Great Britain, Ireland, Luxembourg, Sweden, The Netherlands, the Southern Europe are France (South), Greece, Italy, Portugal, Spain). The herbicide Herbaflex is meant to control annual dicotyledonous and grass weed species.

The product is applied as single application with 2.0 to 3.0 L/ha in autumn or spring at BBCH 11-13 (autumn) and BBCH 11-29 (spring) of the weeds and from BBCH 11-29 (autumn and spring) of the crop. Thus, 170-255 g beflubutamid per hectare are applied. The recommended water volumes are 200 to 400 L/ha, resulting in a maximum concentration of the active substance of 1.275 g/L in the spray liquid.

Limitations in the choice of succeeding crops in regular rotations or in the case of crop failure subsequent to beflubutamid application can not be assessed for the only experiment run on this issue is invalid.

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):

Beflubutamid (UR-50601)

Hazard symbol:	N	(Dangerous for the environment)
Indication of danger:	None	
Risk phrases:	R 50/53	(Toxic to quatic organisms/ may cause long-term adverse effects in the aquatic environment)

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):

ASU 95 510 H (Herbaflex)

Hazard symbol:	Xn	
	N	(Dangerous for the environment)
Indication of danger:	Harmful	
Risk phrases:	R 40	Possible risks of irreversible effects
	R 50/53	(Toxic to quatic organisms/ may cause long-term adverse effects in the aquatic environment)

Reasons for classification
Due to the information available with respect to the second active ingredient contained in the product (isoproturon).

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 the active substance and the impurities in the technical active substance as manufactured.

Beflubutamid in the technical active substance is determined by a HPLC internal standard method on a reversed phase column with UV detection.

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

All methods are fully validated.

2.2.2 Analytical methods for formulation analysis

Analytical methodology is available for the determination of the active substances in the formulation.

Beflubutamid and isoproturon in the formulation are determined by a HPLC external standard method on a reversed phase column with UV detection.

The method is fully validated.

2.2.3 Analytical methods for residue analysis

For the assessment of the analytical methods for the determination of beflubutamid 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	0.05	mg/kg	proposed MRL for cereals grain
soil	0.05	mg/kg	general upper limit. Depending on the outstanding phytotoxic concentration of beflubutamid to the most sensitive species, further data could be requested.
drinking water	0.1	µg/l	EU drinking water limit
surface water	4.5	µg/l	EC_{50} (algae)
air	87	µg/m³	based on a proposed $AOEL_{systemic}$ of 0.29 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 beflubutamid in plant material, soil, drinking water, surface 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	cereal grain green plant straw	GC-PND	0.05	mg/kg	Brielbeck, Marx, 1999
		HPLC-UV	0.05		(metabolite UR-50604)
	wheat grain green plant straw	GC-PND	0.05	mg/kg	Harper, 2000
	cereal grain straw	GC-ECD	0.01	mg/kg	Brielbeck, Marx, 1998
soil		LC-MS	0.01	mg/kg	Todd, 2000
		GC-MS	0.01	mg/kg	Wittig, 2000
water	drinking- surface- ground-	HPLC-UV	0.1	µg/l	Betteley, 1997
	surface-	LC-MS	0.1	µg/l	Todd, 2000
air		HPLC-UV	0.6	µg/m^3	Flack, 2000

2.3 Impact on human and animal health

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

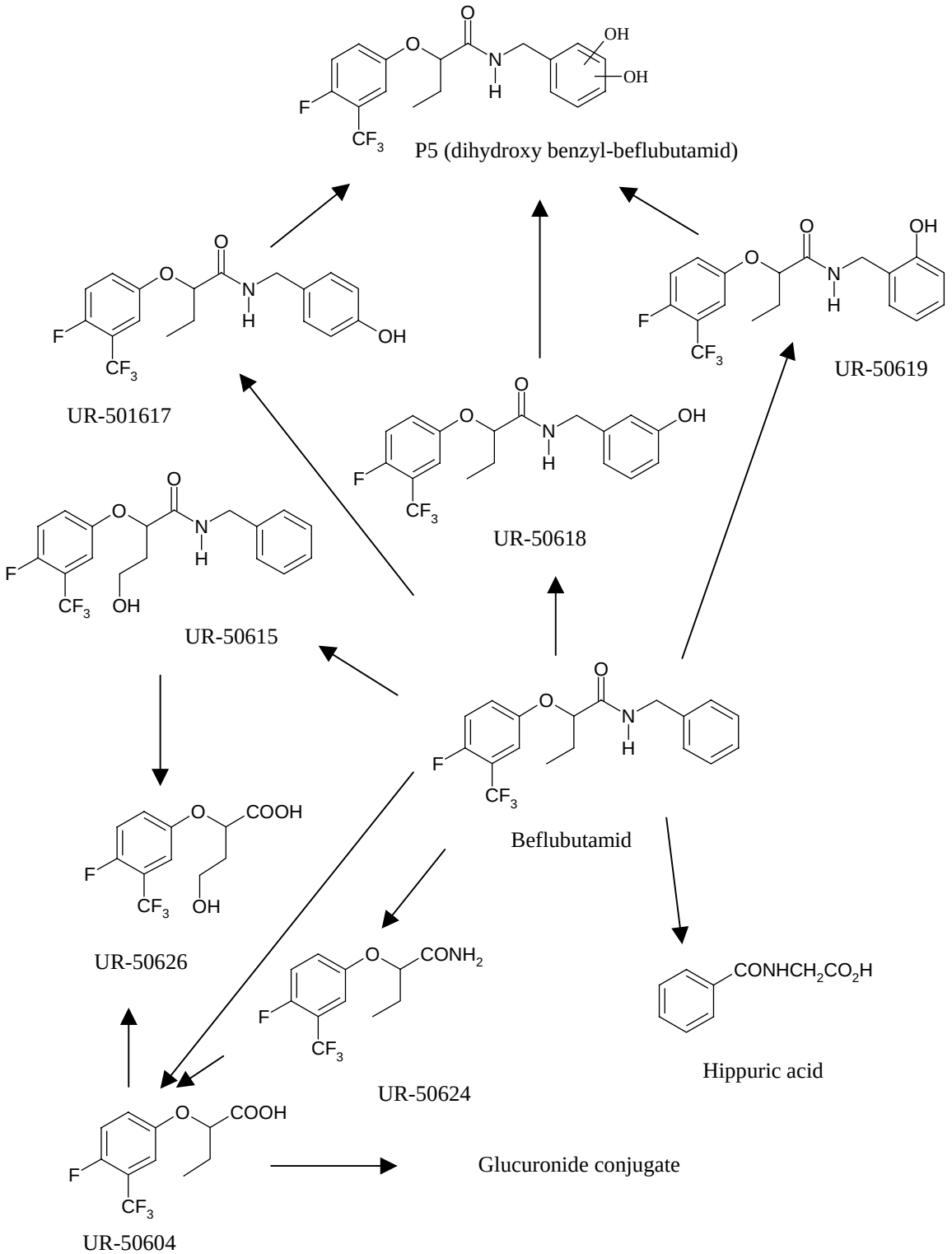
Animal metabolism was studied in rats mainly after oral administration of [^{14}C-phenoxy]beflubutamid at nominal dose levels of 35 and 350 mg/kg bw. [^{14}C-benzylamine]

beflubutamid was used for an additional excretion balance study. The extent of absorption was 93% (male) and 83% (female) after a 35 mg/kg bw dose, and 49% (male) and 56% (female) after a 350 mg/kg bw dose. Excretion was rapid with >90% of the dose being excreted in 48 hours rather in faeces than urine. Excretion in the bile accounted for 85% (male) and 66% (female) of a 35 mg/kg bw dose, and 42% (male) and 47% (female) of a 350 mg/kg bw dose. Whole-blood and plasma analyses indicate that the rate and extent of systemic exposure of rats to radioactivity, (as characterised by C_{max} and AUC_t), increased with increasing dose, however the observed increases in C_{max} and AUC_t were disproportionately lower than predicted from a linear relationship. After repeat dosing there was no indication of accumulation in plasma, however there was some indication of a selective up-take into blood cells.

Whole body autoradiography showed that distribution in tissues was similar for male and female rats, with radioactivity being widely distributed and present in all tissues from rats sacrificed at the time of peak plasma concentration. After a single oral dose of 35 mg/kg bw the highest concentrations (excluding gastrointestinal tract), occurred in the liver and kidney, the organs of metabolism and excretion. The concentrations in the gastrointestinal tract after 6 and 10 hours were similar suggesting that the administered radioactivity was undergoing entero-hepatic circulation. After a single oral dose of 350 mg/kg bw tissue concentrations were 2-6 times higher at 6 hours after dosing than seen at the lower level.

Beflubutamid was rapidly and extensively metabolised. The major metabolite found in the plasma and excreted in the urine from rats treated with [^{14}C-phenoxy]beflubutamid was phenoxybutyric acid (UR-50604) formed by cleavage of the amide bond. Urinary excretion of this metabolite accounted for 23 – 31 % of the administered dose. In faeces the metabolites were hydroxylated derivatives of beflubutamid which were generally eliminated via the bile as glucuronide conjugates. After administration of [^{14}C-benzylamine]beflubutamid the major radiolabelled urine metabolite was hippuric acid. There was no evidence of significant stereoselective metabolism.

Figure 2.3-1: Beflubutamid (UR-50601): Proposed metabolic pathway in rats



UR-50617, UR-50618, UR-50619 eliminated in bile as glucuronide conjugates

2.3.1.2 Acute toxicity studies, local irritation and skin sensitising properties

Beflubutamid is of low toxicity. Slight signs of toxicity (wet fur, hunched posture and pilo-erection) were observed after inhalation of the test material. After application of beflubutamid

to the eye of rabbits slight transient ocular irritation was observed. No skin irritation was observed in rabbits after dermal application. In a Maximisation test according to Magnusson and Kligman, no signs of allergic skin reactions in the test animals were recorded. Based on the test results, no classification is required for acute toxicity of beflubutamid according to the criteria in Council Directive 67/548/EEC.

Table 2.3-1: Summary of acute toxicity studies

Test	Species	Result
LD_{50} oral (Limit test)	Rat	(m/f) > 5000 mg/kg bw
LD_{50} dermal (Limit test)	Rat	(m/f) > 2000 mg/kg bw
LC_{50} inhalation (Nose only)	Rat	(m/f) > 5 mg/l air
Skin irritation	Rabbit	Non irritant
Eye irritation	Rabbit	Non irritant
Skin sensitisation (Magnusson/Kligman Test)	Guinea pig	Non sensitizing

2.3.1.3 Short-term toxicity

In the short-term toxicity studies in rats, mice and dogs, the liver was the target organ identified in all animal species under investigation. In addition, the kidneys, thyroid gland and adrenal glands were affected in rats, mainly evidenced by organ weight changes. All species under investigation revealed decreased body weight gains at the upper dose levels. A summary of the short-term toxicity studies is presented in Table 2.3-2.

Rats: In the 28-day study in rats (0, 50, 400, 3200 ppm) higher kidney weights were recorded in both sexes at 3200 ppm. A reduction in adipose tissue was noted in 1/5 rats at 400 ppm and in 5/5 rats at 3200 ppm. The NOAEL was found to be 400 ppm (39.9 mg/kg bw/d for males; 38.4 mg/kg bw/d for females).
In the 90-day study in rats (0, 100, 400, 3200 ppm) a prolongation of thrombotest clotting time, higher methaemoglobin (males), plasma cholesterol and phospholipid values, increased liver, thyroid, kidney and adrenal weights were noted at the high dose level of 3200 ppm. Histopathological examination revealed centrilobular hypertrophy of hepatocytes and renal pelves dilatation (females). No histopathological changes were noted in the thyroid gland and adrenal glands which may have accounted for increased organ weights. The NOAEL was found to be 400 ppm (29 mg/kg bw/d in males; 35 mg/kg bw/d in females).

Mice: In the 90-day study in mice (0, 400, 1600, 3200, 6400 ppm) higher liver weights and centrilobular hepatocyte hypertrophy was noted in all treated groups. The severity of this finding was increasing with increasing dose levels in male mice whereas females were affected with lower severity at higher dose levels. In addition, females of the two highest dose groups showed a generalised liver hepatocyte hypertrophy and periportal hepatocytes with cytosplasmic eosinophilia. Since the liver is the target organ in all animal species under investigation, the conclusion of the notifier that the liver findings are considered to have arisen solely as the result of an adaptive effect and are not considered to be indicative of toxicity, is not supported. Therefore, the LOAEL was found to be 400 ppm (61 mg/kg bw/d in males; 87 mg/kg bw/d in females) based on the incidence of centrilobular hepatocyte hypertrophy and liver weight changes at this dose level. A NOAEL of 50 ppm (6.4 mg/kg bw/d for males and 8.5 mg/kg bw/d for females) can be derived from the carcinogenicity study in mice.

Dogs: In addition to the liver weight increases and hepatocyte hypertrophy, the 90-day study in dogs (0, 100, 300, and 1000 mg/kg bw/d) showed increased activities of hepatic enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase), an activated partial thromboplastin time (APTT), delayed prothrombin time (PT) as well as degenerative changes in the liver and bile ducts (hepatocyte loss, necrosis, inflammation, bile duct proliferation, prominent major bile ducts). In dogs at 300 and 1000 mg/kg bw/d histopathological changes in the prostate (acinar atrophy/fibrosis), epididymides (absent spermatozoa, round spermatids and spermatocytes in ductules) and testes (degenerate/exfoliate round spermatids and spermatocytes) together with lower gonad weights at the high dose group are of equivocal toxicological relevance. The NOAEL was found to be 100 mg/kg bw/d.

The 12-month study in dogs (0, 12, 60, and 300 mg/kg bw/d) confirmed the findings of the 90-day study with respect to changes in haematological and clinical chemistry parameters, i.e. increased clotting times and increased hepatic enzyme activities as well as lower plasma protein concentrations, liver weight increases together with a similar pattern of histopathological changes but additionally early portal to portal bridging and centrilobular collapse with hepatocyte necrosis occurred. Effects on testes and/or epididymides were not observed in this study. The NOAEL was was found to be 60 mg/kg bw/d .

Table 2.3-2: Summary of short-term toxicity studies with beflubutamid

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
28-day feeding Crl:CD BR rat 0, 50, 400, 3200 ppm	39.9 / 38.4 m/f [400 ppm]	3200 ppm: Higher kidney weight, reduction in adipose tissue.
90-day feeding Crl:CD BR rat 0, 100, 400, 3200 ppm	29 / 35 m/f [400 ppm]	3200 ppm: Prolongation of thrombotest clotting time (m), higher methaemoglobin (m), plasma cholesterol and phospholipid values, higher liver, thyroid, kidney, adrenal weight, centrilobular hypertrophy of hepatocytes (m), renal pelves dilatation (f).
90-day feeding Crl:CD-1 BR mouse 0, 400, 1600, 3200, 6400 ppm	< 61 / 87 m/f [<50/< 50 ppm m/f] (ca. 6.4 / 8.5 m/f [50 ppm], carcinogenicity study	400 ppm: Centrilobular hepatocyte hypertrophy of the liver
90-day oral (gelatine capsule) Beagle dog 0, 100, 300, 1000 mg/kg bw/d	100 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin time, higher liver weights. At 1000 mg/kg bw/d: increase in prothrombin time, higher activities of liver enzymes, degenerative changes in liver and bile duct.
52-week oral (gelatine capsule) Beagle dog 0, 12, 60, 300 mg/kg bw/d	60 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin and prothrombin time, increases in alkaline phosphatase and alanine aminotransferase, reductions in plasma total protein, higher liver weight, liver enlargement, severe degenerative changes in the liver.

m: male; f: female; bw: bodyweight, d: day

2.3.1.4 Genotoxicity studies

The mutagenic potential of beflubutamid was studied in bacteria and mammalian cells *in vitro* by using two gene mutation assays and a chromosome aberration assay (see Table 2.3-3) and *in vivo* by means of a micronucleus test (see
Table 2.3-4). All tests performed showed no mutagenic effect of the test compound. In the *in vivo* micronucleus test no bone marrow toxicity was observed, but at the two highest dose levels systemic toxicity was recorded.

Table 2.3-3: *In vitro* mutagenicity tests

Test system	Test object	Concentration	Purity (%)	Results
Gene mutation assays				
Reverse mutation test for bacteria	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 *uvrA*	Main Test -/+ S9 mix: 312.5, 625, 1250, 2500, 5000 µg/plate	97.61	Negative
Gene mutation test (to thioguanine resistance)	Mouse lymphoma L5178Y cells	Test 1 - S9 mix: 10, 25, 50, 75, 100, 125, 150, 200 µg/ml + S9 mix: 5, 10, 25, 50, 75, 100, 125, 150 µg/ml Test 2 -/+ S9 mix: 1, 5, 10, 25, 50, 75, 100 µg/ml	97.46	Negative
Chromosome aberration assays				
Cytogenetic assay	Cultured human lymphocytes	Test 1 - 21 hr sampling time - S9 mix: 2.5, 5, 10, 20, 30, 40 µg/ml. + S9 mix: 25, 50, 100, 150, 200, 250, 500, 1000 µg/ml 45 hr sampling time - S9 mix: 10, 20, 30, 40, 50, 80, 100 µg/ml + S9 mix: 125, 250, 500, 1000, 5000 µg/ml Test 2 - 21 hr sampling - S9 mix: 10, 20, 30, 40, 50, 60 µg/ml + S9 mix: 150, 200, 250, 500, 750 µg/ml	97.61	Negative

Table 2.3-4: *In vivo* mutagenicity tests in somatic cells

Test system	Test object	Concentration (mg/kg bw)	Purity (%)	Results
Chromosome aberration assays				
Micronucleus test	Male and female CD-1 Swiss mice - bone marrow cells	125, 250, 500	97.46	Negative

2.3.1.5 Long-term toxicity / carcinogenicity studies

The liver was found to be the target organ in rats and mice again after prolonged dietary administration of beflubutamid. In rats the thyroid gland and the kidneys were affected as well. The treatment with beflubutamid had no effects on the survival of both animal species and did not reveal a carcinogenic potential relevant to humans. A summary of the long-term toxicity studies is presented in Table 2.3-5: .

Rat: In the 24-month combined chronic toxicity/carcinogenicity study in rats (0, 50, 400, 3200 ppm; achieved chemical intakes male/female: 2.2/3.0; 17.7/24.4; 150/207 mg/kg bw/d) lower body weight gains (males, 400 ppm, both sexes 3200 ppm), a prolongation of thrombotest clotting time (males, 400 ppm and 3200 ppm) as well as higher plasma cholesterol and phospholipid values (both sexes, 3200 ppm) were observed. Additionally, in female rats at the highest dose level (3200 ppm) higher plasma total protein levels, mainly due to a simultaneous increase of albumin and globulins were recorded. Higher amounts of proteins were noted in the urine of female rats at 3200 ppm at almost all occasions being most evident after 78 weeks of treatment onwards and at week 104 investigation also at 400 ppm. Liver and kidney weights were increased in both sexes at 3200 ppm, thyroid weights were increased in male rats (3200 ppm). At week 105, female rats at 400 and 3200 ppm also showed higher thyroid weights although without statistical significance. Both at the interim and terminal sacrifice centrilobular hepatocyte hypertrophy was noted (males, 400 ppm, both sexes 3200 ppm). In females of the high dose level (3200 ppm) progressive glomerulonephrosis in the kidney was observed with higher incidence at terminal sacrifice.
The incidence of thyroid gland follicular tumours was slightly increased in male rats of the high dose group (3200 ppm) at terminal sacrifice but without reaching statistical significance and with incidences lying in the upper range of historical control data for males. In female rats each one thyroid follicular adenoma and one carcinoma was observed in the 400 ppm and 3200 ppm group, respectively. These neoplastic findings are considered to be without relevance to humans
The NOAEL was was found to be 50 ppm (2.2 mg/kg bw/d for male and 3.0 mg/kg bw/d for female).

Mice: In the 18-month carcinogenicity study in mice (0, 50, 500, 5000 ppm; achieved chemical intakes male/female: 6.4/8.5, 67/78; 723/834 mg/kg bw/d) lower body weight gain (both sexes, 5000 ppm), increased liver and adrenal gland weights (both sexes, 5000 ppm), enlarged and pale liver and liver with pale area(s) (males, 5000 ppm) were noted. Liver centrilobular hepatocyte hypertrophy and hepatocytes with granular cytoplasm was noted in males at 500 ppm, centrilobular/generalised hepatocyte hypertrophy, parenchymal inflammatory cell foci, centrilobular sinusoidal dilation/congestion with pigmented sinusoidal cells was observed in both sexes at 5000 ppm. There were no conclusive histopathological findings in the adrenal glands which may have accounted for increased organ weights.
The incidence of liver tumours was slightly increased in male mice of the high dose group (5000 ppm) but the incidences were well within the historical control data for Crl:CD-1(ICR)BR mice submitted from the performing laboratory.
The NOAEL was was found to be 50 ppm (6.4 mg/kg bw/d for male and 8.5 mg/kg bw/d for female).

Table 2.3-5: Summary of long-term toxicity studies with beflubutamid

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
104-week feeding (combined chronic toxicity/ carcinogenicity) Crl:CD BR rat 0, 50, 400, 3200 ppm	2.2 / 3.0 m/f [50 ppm]	400 ppm: Prolongation of thrombotest clotting time, centrilobular hypertrophy of hepatocytes (m), proteinuria at wk 104 (f)
80-week feeding Crl:CD-1 (ICR) BR mouse 0, 50, 500, 5000 ppm	6.4 / 8.5 m/f [50 ppm]	500 ppm: Centrilobular hepatocyte hypertrophy, hepatocytes with granular cytoplasm.

m: males; f: females; bw: bodyweight

2.3.1.6 Reproductive toxicity / developmental (teratogenicity) studies

Beflubutamid had no adverse effects on fertility and no effects on the parturition process or on peri- and post-natal survival of the offspring at dosages up to 3200 ppm (~243 mg/kg bw/d for males, ~338 mg/kg bw/d for females) over two generations in the Sprague Dawley rat. The below mentioned reproductive and developmental effects on the fetuses were seen in presence of parental/maternal toxicity. A summary of the reproductive toxicity/teratogenicity studies is presented in Table 2.3-6: .

In the **2-generation reproductive toxicity study in rats** the main target organs were the kidney and the liver evidenced by increased organ weights at 800 ppm and/or 3200 ppm in the adults which is in line with changes noted in short- and long-term studies. Reductions in body weight gain were noted at 800 ppm and 3200 ppm in parental animals as well as in the offspring. In the F_1- and F_2-pups body weight gain was decreased mainly during the lactational phase, reflecting impaired pup growth. Additionally, at 800 ppm and 3200 ppm a significant delay in age for vaginal opening occurred among females of the F_1-generation. No clear effect of treatment on the mean age of balano-preputial separation could be demonstrated but a marginal delay was suggested. At necropsy of F_1- and F_2-offspring increased incidences of uni-/bilateral renal cavitation of the kidney and uni-/bilateral hydroureters were noted at 3200 ppm. The findings in the offspring were considered adverse reproductive effects.
The NOAEL for parental and reproductive toxicity was 200 ppm (~ 17 mg/kg bw/d for males; ~19 mg/kg bw/d for females).

Reproduction toxicity studies to investigate **developmental toxicity in the rat** revealed an increased incidence of fetuses with rudimentary/absent renal papilla and with dilated ureters at 300 and 1000 mg/kg bw/d when compared to control and low dose group. One fetus of the 300 mg/kg bw/d group had an absent left kidney and ureter, a duplicated inferior vena cava, and a malpositioned left testis. Left anophthalmia occurred in one fetus of the high dose group versus none in the control and other dose groups. Incomplete ossification of the thoracic vertebral centra occurred at the highest dose tested (1000 mg/kg bw/d). In the dams clinical signs (post-dosing salivation, hair loss), higher water intake as well as a transient reduction in food intake and body weight gain was noted at dose levels of 300 and/or 1000 mg/kg bw/d.
The NOAEL for maternal and developmental toxicity was 100 mg/kg bw/d.

In the **rabbit developmental toxicity study** no treatment-related effect was seen even at the highest dose level tested (100 mg/kg bw/d). Therefore, the pilot study on non-pregnant female

rabbits (Report no. UBE 9/951721) and the preliminary study on pregnant rabbits (Report No. UBE 10/952279) were evaluated in addition. In the pilot study each two non-pregnant female rabbits were exposed to doses of either 100, 500 and 1000 mg/kg bw/d. Marked weight loss and mortalities were noted at the two highest dose-levels, suggesting the maximum tolerated dose level somewhere between 500 and 100 mg/kg bw/d. In the preliminary study groups of 6 pregnant female rabbits received the test material once daily by oral gavage at 0, 100, 200 and 350 mg/kg b/d from Days 6 to 18 of assumed pregnancy. The results from this study support a NO(A)EL for maternal toxicity at 100 mg/kg bw/d, based on emaciation and premature sacrifice of one dam at the next higher dose of 200 mg/kg bw/d. A NOAEL for developmental toxicity can also be suggested at 100 mg/kg bw/d, due to the occurrence of one abortion at 200 mg/kg in the presence of maternal toxicity. Therefore, the results from all studies support NOAELs for maternal toxicity and for developmental toxicity at 100 mg/kg bw/d in the rabbit.

Table 2.3-6: Summary of reproductive toxicity and teratogenicity studies with beflubutamid

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
2-generation study Crl:CD BR rat (Sprague Dawley) 0, 200, 800, 3200 ppm	Parental and reproductive toxicity: ~ 17/~19 m/f (200 ppm)	800 ppm Parental toxicity: Decreased body weight gains, increased kidney weights. Reproductive toxicity: Impairment of body weight development during lactation, delay in age for vaginal opening (F1-females only); At 3200 ppm kidney changes at necropsy.
Developmental toxicity Crl:CD BR rat (VAF/Plus strain) 0, 100, 300, 1000 mg/kg bw/d days 6-15	Maternal toxicity: 100 Developmental toxicity: 100	300 mg/kg bw/d: Maternal toxicity: Increased water consumption, decreased food intake in the period day 6-8 of pregnancy, 1 incidence of post-dose salivation, at 1000 mg/kg bw/d: post-dose salivation, hair loss, bw loss, increased water consumption. Developmental toxicity: Increased incidences of rudimentary and/or absent renal papilla and dilated ureters at 300 and 1000 mg/kg, at 1000 mg/kg: Increased incidences of incomplete ossification of thoracic/lumbar vertebral centra.
Developmental toxicity New Zealand White rabbit 0, 10, 30, 100 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	No treatment-related effects
Preliminary study: Developmental toxicity New Zealand White rabbit 0, 100, 200, 350 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	200 mg/kg bw/d: Maternal toxicity: Emaciation, premature sacrifice Developmental toxicity: Abortion and preimplantation losses at maternally toxic doses.
Pilot study: New Zealand White rabbit (non-pregnant) 100, 500, 1000 mg/kg bw/d	100	500 mg/kg bw/d: Marked body weight loss, mortalities

m: males; f: females; bw: bodyweight

2.3.1.7 Neurotoxicity / Delayed neurotoxicity studies

No signs of neurotoxicity were reported in course of the toxicity studies with beflubutamid, a novel herbicide. Moreover, beflubutamid has no structural relationship to organophosphates and/or carbamates. Therefore, studies on delayed neurotoxicity were not necessary and were not performed.

2.3.1.8 Dermal absorption

No data are available on the extent of dermal absorption of beflubutamid. Therefore, a 100% dermal absorption is assumed (worst case).

2.3.1.9 Further toxicological studies

No specific studies with metabolites and/or further toxicological studies have been conducted.

2.3.1.10 Human Data

No reported poisoning incidents or clinical cases, including irritant and allergenic response to workers during the manufacturing of technical beflubutamid or the application of beflubutamid formulation have been made.

2.3.2 Acceptable Daily Intake (ADI)

The calculation of the acceptable daily intake for beflubutamid technical is based on the results from the combined chronic toxicity/carcinogenicity study in rats. A NOAEL of 50 ppm, approximately 2.2 mg/kg bw/d, from the 104-week rat study is the most sensitive dose for the estimation of the ADI of beflubutamid technical in humans. In the absence of genotoxicity, reproductive toxicity, teratogenicity or oncogenicity, an uncertainty factor of 100 is applied to the NOAEL of 2.2 mg/kg bw/d, resulting in an **ADI of 0.022 mg/kg bw/d**.

This ADI value is not in agreement with the proposal of the notifier who derived an ADI-value of 0.17 mg/kg bw/d based on a NOAEL of 17 mg/kg bw/d from the long-term study in rats and applying a safety factor of 100. The difference in the NOAEL setting in the 104-week study in rats was based on the prolongation of thrombotest clotting time, an increased incidence of centrilobular hepatocyte hypertrophy in male rats and the occurrence of proteinuria in female rats at this dose level.

2.3.3 Acceptable Operator Exposure Level (AOEL)

The plant protection product ASU 95 510 H is a herbicide to be applied by tractor mounted field crop sprayers on cereals. This will lead to exposure of operators, workers and bystanders mainly by the dermal route and to a lesser extent through inhalation. Oral exposure will be negligible. Since no data are available on dermal or inhalation absorption and there is no human data available on which an AOEL could be based, the AOEL is derived on the basis of so-called mid-term toxicity studies, i.e. the subacute/subchronic studies.

For beflubutamid, the lowest relevant oral NOAEL was established in the 90-day feeding study in rats where a NOAEL of approximately 30 mg/kg bw/d was found. Because the extent of absorption after oral administration of a low dose of beflubutamid was almost complete, a correction from the oral AOEL to a systemic AOEL is not needed. Because of the toxicological profile of beflubutamid and in accordance with current EU assessment practice, the standard assessment factor of 100 should be applied resulting in a **systemic AOEL of 0.3 mg/kg bw/d.**

The notifier had proposed a systemic AOEL of 0.29 mg/kg bw/d derived from the NOAEL of 29 mg/kg bw/d for male rats from the 90-day study. The value was rounded up.

2.3.4 Acute Reference Dose (ARfD)

On the basis of the toxicological profile, beflubutamid, a herbicide, is considered unlikely to present an acute hazard for consumers by the ingestion of residue containing food. The acute oral toxicity in rats is low and there are no acute toxicological alerts seen in repeated dose toxicity studies. Furthermore, residues are not to be expected in harvested crops because beflubutamid and its metabolites are degraded rapidly in plants. No significant residues were apparent in the human food and consumer intake via animal products is unlikely due to low levels of residue in plant tissue fed to animals. Therefore, an ARfD is not considered necessary and is not allocated.

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 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.

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

Harmful effects on the health of operators, bystanders, workers, or consumers, are not expected when the plant protection product is used in accordance with good plant protection practice.
With regard to beflubutamid, the potential operator exposure was estimated for the intended use of ASU 95 510 H (product name: Herbaflex), a suspension concentrate (SC) containing two active ingredients: 85 g/l UBH 820 (i.e. UR-50601 = beflubutamid) and 500 g/l isoproturon. It is used as a herbicide and only applications to cereals are intended. Applying the worst case assumption of 100% for the dermal absorption, on the basis of the German model without PPE, the estimated systemic exposure to beflubutamid accounts for up to 108% of the proposed systemic AOEL. In the calculation on the basis of the UK-POEM without PPE, the exposure was 1038% of the AOEL. By wearing of PPE, the estimated operator exposure stays always below the proposed systemic AOEL (German model: 13%; UK-POEM: 84%).

The second active ingredient isoproturon contained in the formulation was not the matter of the exposure assessment.
In view of the recommended application technique in combination with Good Agricultural Practice (GAP), bystanders may be exposed only incidentally, briefly and to relatively low quantities of spray mist compared to an operator. Therefore, it is not likely that the potential exposure of bystanders will exceed the systemic AOEL proposed for beflubutamid.
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

Metabolism studies on wheat plants show very low total radioactive residues in grain after treatment of nominal rates of 255 g ^{14}C-labelled beflubutamid/ha. Unchanged parent compound was not identified in grain but only in straw at levels of up to 0.35 mg/kg. The only identified component reaching the level of 0.01 mg/kg in grain was the metabolite UR-50604 which however, based on the rat metabolism study was considered as being of no toxicological concern.

Therefore, the residue definition for plant materials is proposed as **beflubutamid**.

2.4.1.2 Animals

The metabolism of beflubutamid was investigated in lactating goats. Parent compound was found as the major residue in milk and fat. Hippuric acid (N-benzoylglycine) was a main metabolite in milk, liver and kidney samples of the benzylamine labelled study beside UR-50604 as the main metabolite in kidney of the phenyl labelled study. Taking into account the exaggerated dose rate which caused very low residues in edible tissues in these studies the residue level expected in food of animal origin under practice conditions would be not quantifyable. Furthermore, UR-50604 and hippuric acid are of no toxicological significance as they are present in the rat metabolism study (excreta).

Therefore, the parent compound **beflubutamid** is defined as the residue of concern.

2.4.2 Residues relevant to consumer safety

Intended uses are applied for in small grain cereals only. Residues of beflubutamid and its metabolite UR-50604 in grain and straw could be relevant for consumers or for feeding of domestic animals concerning residues in animal products following feed intake.

A sufficient number of 18 supervised residue trials applying different SC-formulations containing beflubutamid were conducted on barley and wheat in the northern (DE) and southern (ES, IT) parts of Europe.

At normal harvest no residues were detected in grain and straw above the LOQ of 0.05 mg/kg.

From the available data and the validated limit of quantification of the corresponding analysis method the following MRL is proposed:

0.05 mg/kg cereals grain and other food of plant origin.

The consumer safety is guaranteed from the resulting TMDI of 0.002 mg/kg bw (German model) or 0.001 mg/kg bw (WHO model). Both values contribute at 8.3 or 4.7 %, respectively, to the proposed ADI of 0.022 mg/kg bw/d.

2.4.3 Residues relevant to worker safety

ASU 95 510 H (Herbaflex) is applied in cereals, where entering of crops shortly after spraying is not necessary. But the results of the operator exposure estimation have shown that operators are not exposed to critical levels when handling the product under the recommended conditions of use. There is thus no reason to anticipate an unacceptable risk, if a worker should be present after the spraying operation unexpectedly.

2.4.4 Proposed EU MRLs and compliance with existing MRLs

MRL proposal for plant products

Beflubutamid is intended to be used in small grain cereals only. The results of a total of 18 supervised residue trials conducted throughout the EU have been shown that no quantifyable residues of the parent substance nor its metabolites are expected in crop parts to be used as feed or food. This “low-residue-situation” in grain allows an MRL proposal based on the LOQ of the analysis method:

0.05 mg beflubutamid/kg cereals grain and other food of plant origin.

MRL proposal for animal products

Based on the “low-residue situation” in cereals forage, grain and straw found in the supervised residue trials no feeding studies on domestic animals have been conducted.

Since no significant residues in feedingstuffs and no transfer of residues to food of animal origin are expected in practice ***no MRLs are proposed for animal products***.

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

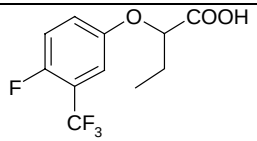
Not applicable since no Codex MRLs have been established yet.

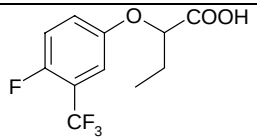
2.5 Fate and behaviour in the environment

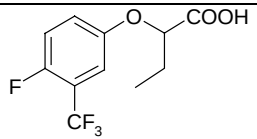
2.5.1 Definition of the residues relevant to the environment

The residue can be defined as beflubutamid and its major metabolite phenoxybutyric acid UR-50604 (soil (aerobic, anaerobic), water/sediment, groundwater)(see Table B.2.5-1). Concerning the herbicidal activity the metabolite UR-50604 is regarded as non-relevant, however, it is ecotoxicological relevant in terrestrial ecosystems. Otherwise, the metabolite UR-50604 has no potential for accumulation in soil. The evaluation of the toxicological relevance of the major metabolite in groundwater is not yet finished due to missing data.

Table B.2.5-1: Assessment of metabolites

Code	Active substance		
UR-50601	beflubutamid		
Metabolites		Occurrence	Assessment of the relevance with regard to
Code	Structural formula	**Soil**	Terrestrial Ecotoxicology
phenoxybutyric acid (UR-50604)		soil (laboratory): max. 26.1% after 7 days (aerobic); max. 23.1 % after 120 days (anaerobic) soil (field): < 10 %	relevant (see chapter 2.6.4)

Code	Active substance				
UR-50601	beflubutamid				
Metabolites		Occurrence	Assessment of the relevance with regard to		
Code	Structural formula	**Ground water**	Pesticidal activity	Toxicology	Aquatic Ecotoxicology
phenoxybutyric acid (UR-50604)		modelling > 0.1 µg/L	not herbicidal active	The evaluation of the toxicological relevance of the major metabolite is not yet finished due to missing data.	not relevant

Code	Active substance		
UR-50601	beflubutamid		
Metabolites		Occurrence **Water/sediment**	Assessment of the relevance with regard to
Code	Structural formula		Aquatic Ecotoxicology
phenoxybutyric acid (UR-50604)		water: max. 36.1/34.6 % after 100 d; sediment: max. 9.4/20.3 % after 100 days	not relevant

2.5.2 Fate and behaviour in soil

Under aerobic conditions beflubutamid was degraded in soil with DT_{50lab} values between 5 – 118 days and DT_{90lab} values of 16 days - > one year. At 10°C a DT_{50lab} of 20 days was determined.

Corresponding field dissipation studies resulted in half lives of 15 – 103 days and in $DT_{90field}$ values of 49 – 343 days for applications in spring (Spain), summer (Germany) and autumn (Spain, United Kingdom). Soil residue studies in laboratory showed concentrations of beflubutamid of 0.083 mg/kg after 30 days (carrots) and 0.056 mg/kg after 30 days (wheat) and 0.005 mg/kg after 193 days.

Mineralisation rates were in the range of 12.2 – 46.8 % after 120/152 days (phenoxy label) and 55.1 % after 152 days (benzylamine label).The formation of non-extractable residues occured to 31.8 – 50.5 % after 120/152 days (phenoxy label) and to 25.8% after 152 days (benzylamine label). No further assessment for non-extractable residues was conducted based on an amount of less than 70% and a mineralisation rate higher than 5 % in 100 days.

Under anaerobic conditions non-extractable residues were formed to 4.1 – 19.4 % in 120 days. No mineralisation (phenoxy label) and 6.1 % of mineralisation (benzylamine label), respectively, after 120 days was observed. The half lives of the active substance were 4 (water phase) and 260 days (soil) and the DT_{90} value 12 days in the water phase. After 10 days of irridation the active substance was still detected to 73.1 – 77.9 %. Consequently, both anaerobic degradation as well as soil photolysis represent minor routes of degradation.

The only major metabolite detected under aerobic and anaerobic conditions in laboratory studies was the phenoxybutyric acid (UR-50604) in amounts of 9 – 26.1 % and of 23.1 %, respectively.

In all laboratory studies the metabolite UR-50604 was formed and degraded during the study periods. Only the calculated DT_{50} values of 5 and 6 days in the Wick and Evesham3 soils are considered as valid although they may not represent worst case values. In field studies the metabolite was determined only between 59 – 126 days after application in concentrations of < 10 – 16 µg/kg. In soil residue studies (laboratory) concentrations of 0.024 mg/kg (carrot) and 0.019 mg/kg of the metabolite (wheat) after 30 days were determined. Therefore, the metabolite has no potential for accumulation in soil.

Based on the results of adsorption/desorption studies with K_{oc} values between 852 – 1793 beflubutamid can be classified as low mobile whereas the major metabolite is a very high mobile substance with K_{oc} values ranging from 6 – 22.

Simulation of the leaching behaviour for scenarios under realistic worst case conditions for different European regions showed no entry of the active substance in annual averaged concentrations > 0.001 µg/l. Therefore, a potential for groundwater contamination can be excluded for the active substance. Regarding the metabolit UR-50604, the Rapporteur conducted FOCUS-PELMO calculations for the scenarios “Hamburg” and “Piacenza” with concentrations of 0.113 and 0.224 µg/L, respectively. Therefore, groundwater contamination of the major metabolite UR-50604 can not be excluded. This metabolite can be defined as non-relevant regarding ecotoxicology and biological acitivity. The evaluation of the toxicological relevance of the major metabolite is not yet finished due to missing data.

2.5.3 Fate and behaviour in water

Under sterile conditions at 50°C beflubutamid showed no degradation at pH values of 5, 7 and 9. The major metabolite UR50604 also was stable at pH of 7 at 25°C.

Photolytical degradation of beflubutamid in water was determined with a half-life of 48 days (pH 7, 25°C). The major metabolite UR50604 degraded photolytically with DT_{50} values of 21 (pH5), 24 (pH 7) and 20 (pH 9) days.

In water/sediment studies half-lives of beflubutamid were 16/20 days for the water phases and 49/64 days for the whole system. Corresponding DT_{90} values were 53/66 days and 164/212 days, respectively. After 100 days beflubutamid was detected in the sediments to 23.3/13.7% (phenoxy label) and to 29.5/27.0% (benzylamine label).-Mineralisation occured to 7.6/10.7% (phenoxy-label) and 32.1/41.6% (benzylamine label) after 100 days. Non-extractable residues were formed in the same period to 11.9/12.4% and 28.8/19.7%, respectively.

The only major metabolite detected was the phenoxybutyric acid UR-50604 with maximum values of 36.1/34.6% in the water phases and of 9.4/20.3% in the sediments (phenoxy label) after 100 days.

2.5.4 Fate and behaviour in air

The active substance is a semivolatile substance due to the vapor pressure of 1.1×10^{-5} Pa at 25°C . Volatilisation from soil and/or plants should occur only in minor amounts. Once in the atmosphere beflubutamid is degraded with DT_{50} of 3.5 hours (12h day) and 15.7 hours (24 h day), respectively, by photochemical oxidative degradation and therefore no long range transport is expected.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

The toxicity of beflubutamid to mammals and birds is low. Taking into account the intended use then even under worst case assumptions all toxicity-exposure-ratios are well above the Annex-VI-triggers, i.e. the risk to terrestrial vertebrates is acceptable.

Acute toxicity to mammals: LD_{50} >5000 mg/kg bw
Long-term toxicity to mammals: NOAEL 200 ppm (reproductive NOAEL from rat multi-gen study)

Acute toxicity to birds: LD_{50} >2000 mg/kg bw
Dietary toxicity to birds: LC_{50} >5200 ppm
Reproductive toxicity to birds: NOEL 1000 ppm

2.6.2 Effects on aquatic species

The available toxicity data submitted for the active substance, the metabolite UR-50604 and the formulated product fulfil the requirements of Annex II and III and are therefore sufficient for a final assessment. The formulated product and the metabolite are not more toxic than the active substance which is relevant for the overall risk assessment. Fish and Daphnia are less

sensitive than plants and algae. Sediment-dwelling organisms were slightly less sensitive than Daphnia and therefore not relevant for the final risk assessment. Algae are the most sensitive group of organisms. The EC_{50} of 0.0045 mg/L for *S. capricornutum* should be used for the risk assessment.

The metabolite UR-50604 is not of ecotoxicological relevance.

Beflubutamid is liable for bioaccumulation. The BCF is higher than the relevant trigger of 100 but the elimination is fast. Furthermore data from an ELS-test indicate that no effects on the reproduction are to be expected under the proposed conditions of use. Therefore the bioaccumulation potential is regarded as acceptable.

The TER values for a distance of 1 m to waterbodies are below the relevant trigger value indicating an unacceptable risk to aquatic organisms. Therefore, risk mitigation measures are to be set on member state level. Depending on the maximum application rate the risk is acceptable in a distance of 5 or 10 m.

2.6.3 Effects on bees and other arthropod species

2.6.3.1 Effects on bees

Two laboratory studies have been performed to determine possible side effects to honeybees, 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 indicate that beflubutamid is not toxic for bees. Hazard quotients were calculated on the basis of the LD_{50} values for oral and contact toxicity and the highest amount of active substance per ha. All quotients were below the threshold of 50. This indicates that honeybees will not be put at risk by the use of beflubutamid containing plant protection products.

2.6.3.2 Effects on other arthropod species

Non-target arthropods are likely to be exposed to formulated beflubutamid by direct spray, contact on 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 1 worst-case exposure scenario, the predicted environmental exposure of non-target arthropods is assumed to be equivalent to the maximum nominal field rate.

The field rates tested given in Table 2.6-1 compare to the intended uses outlined in this monograph. According to the data submitted a low toxicity was demonstrated in basic laboratory tests on a number of species (i.e. *A. rhopalosiphi, T. pyri, C. carnea, P. cupreus*).

Table 2.6-1: Summary of arthropod toxicity data with two formulations of beflubutamid (ASU 92530 H and ASU 95 510 H)

Test material	Species	Developmental stage	Substrate	Dosage mL/ha	Effects [%] lethal	sublethal
Predatory mites						
ASU 92530 H	*T. pyri*	Protonymphs	I	500	8	9
ASU 95 510 H	*T. pyri*	Protonymphs	I	3000	31	0
Parasitoids						
ASU 92530 H	*A. rhopalosiphi*	Adults	I	500	0	44
ASU 95 510 H	*A. rhopalosiphi*	Adults	I	3000	3	13
Plant dwelling species						
ASU 92530 H	*C. carnea*	Larvae	I	500	6	5
ASU 95 510 H	*C. carnea*	Larvae	I	6000	18	0
Soil dwelling species						
ASU 92530 H	*P. cupreus*	Adults	I	500	12	8
ASU 95 510 H	*P. cupreus*	Adults	I	6000	0	9

I = Inert substrate, N = Natural substrate

The submitted studies fulfil the requirements of Annexes II and III of the Directive. For the intended uses of beflubutamid, the risk for arthropods is acceptable and fulfils the decision criteria mentioned in Annex VI, point 2.5.2.4.

2.6.4 Effects on earthworms and other soil macro-organisms

The studies on the acute toxicity of technical beflubutamid, the metabolite UR-50604 and a formulation containing beflubutamid and isoproturon indicate that the acute risk for earthworms is low. The metabolite UR-50604 is more toxic than the active substance. The TER values are above the relevant triggers. Thus, the acute toxicity risk for earthworms is expected to be acceptable.

Five studies on reproduction have been submitted. Three studies (ARW2001-45, ARW2001-46 and ARW2001-163) are considered valid. The long-term TER for reproduction is first calculated using the results from the two-dose-reproduction test (ARW2001-45) with the formulation containing only beflubutamid. The corrected NOEC is < 0.17 mg as/kg. Compared to the PEC of about 0.34 mg/kg the TER is < 0.5. This is below the relevant trigger of 5. Using the dose-response reproduction test (ARW 2001-163) with an NOEC of 0.34 mg/kg with respect to beflubutamid, the resulting TER is 1, still below the trigger of 5. Looking at the amount of reduction in the tests, the reduction at the relevant rates of 3 l product and 0.255 kg as/ha and at the next following rates amounts to 20 to 30 %, independent of the formulation and the application rate. This is not a severe reduction and it is questionable whether this effect is detectable in the field. Nevertheless, products with this active substance have to be evaluated critical concerning the amount of beflubutamid.

Acute toxicity for earthworms:	LC_{50} 732 mg as/kg (beflubutamid)
	LC_{50} > 1000 mg/kg (formulation containing 86 g/L beflubutamid and 502 g/L isoproturon = "Herbaflex" = ASU 95 510)
	LC_{50} 229 mg/kg (metabolite UR-50604)
Reproductive toxicity to earthworms:	NOEC< 0.255 kg as/ha (formulation ASU 92530 H containing 500 g/L beflubutamid)
	NOEC < 3 L/ha (formulation ASU 95 510 H containing isoproturon 502 g/L and beflubutamid 85 g/L)
	NOEC 6 L/ha (formulation ASU 95 510 H containing isoproturon 502 g/L and beflubutamid 85 g/L)

2.6.5 Effects on soil micro-organisms

The influence of the active substance beflubutamid (0.6 kg as/ha) and the metabolite UR-50604 (0.34 kg as/ha) on carbon- and nitrogen conversion is < 25 % in comparison to the untreated control.
When applying beflubutamid 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)

Non-target plants

Pre- and post-emergence studies were not done according to a current guideline or guideline draft, but taking into account the draft EPA-guidelines OPPTS 850.4225, OPPTS 850.4250 and OECD-draft 208. Six plant species were tested. The risk assessment is based on the ED_{50} of 14.8 g as/ha of *Lactuca sativa* in the post-emergence test. The highest recommended field rate of Herbaflex will be 3 L/ha or 255 g as/ha beflubutamid. The corresponding TER_{1m} is 2.9 (taking 50 % interception into account) and the TER_{5m} is 23. These data indicate a possible risk to terrestrial non-target plants.

Pesticidal activity

The metabolite UR-50604 showed no herbicidal activity in pre- and post-emergence tests with 11 plant species at relevant transformation rates of the active substance.

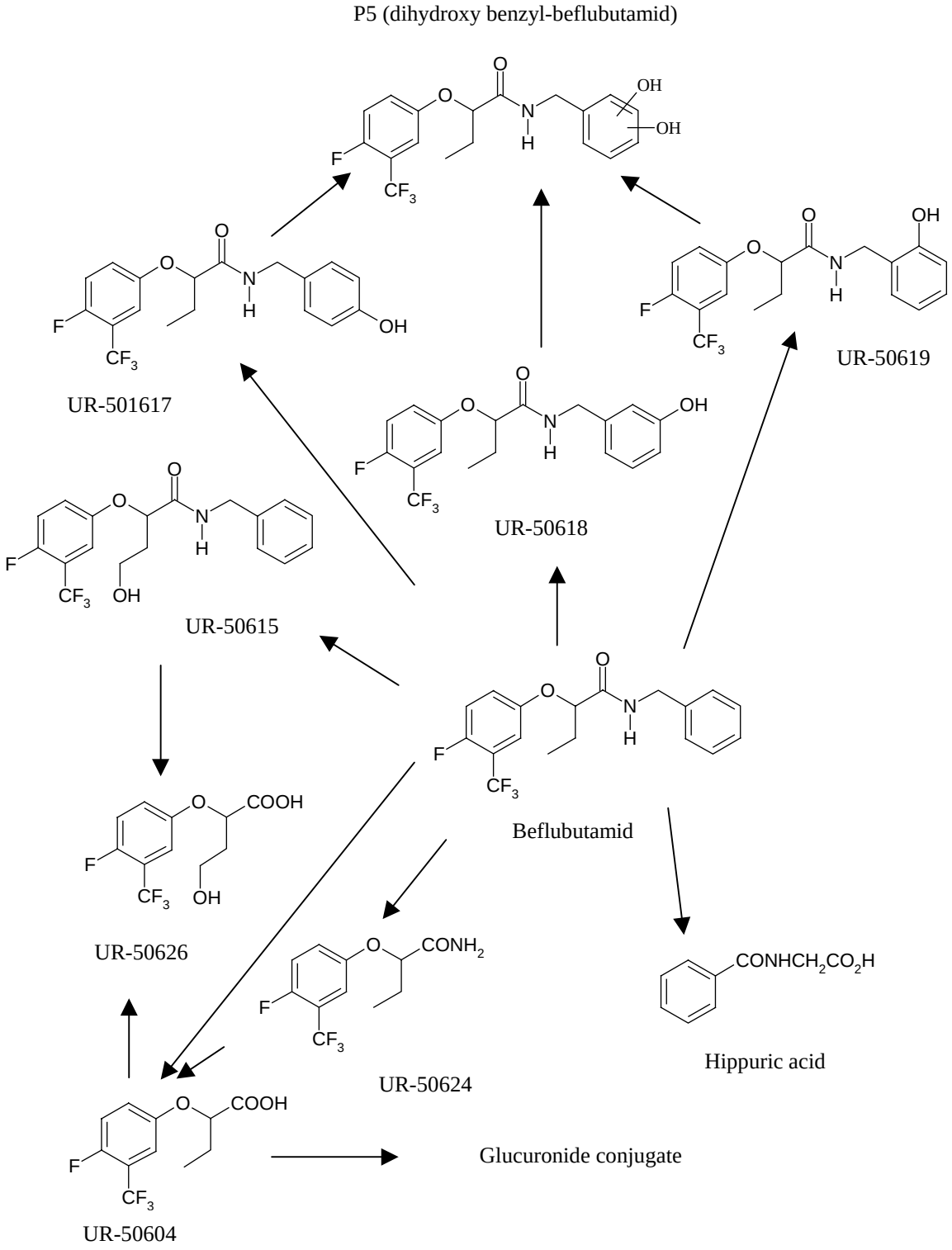
2.6.7 Effects on biological methods of sewage treatment

Data from activated sludge respiration inhibition tests show no unacceptable risk to sewage treatment plants (EC_{50} >100 mg/L).

2.7 Overall conclusion (metabolism schemes)

2.7.1 Toxicology (laboratory animals)

Figure 2.7-1: Beflubutamid (UR-50601): Proposed metabolic pathway in rats



UR-50617, UR-50618, UR-50619 eliminated in bile as glucuronide conjugates

2.7.2 Residues (plant, plant products, livestock animals)

Figure 2.7-2: Proposed metabolic pathway of beflubutamid in wheat

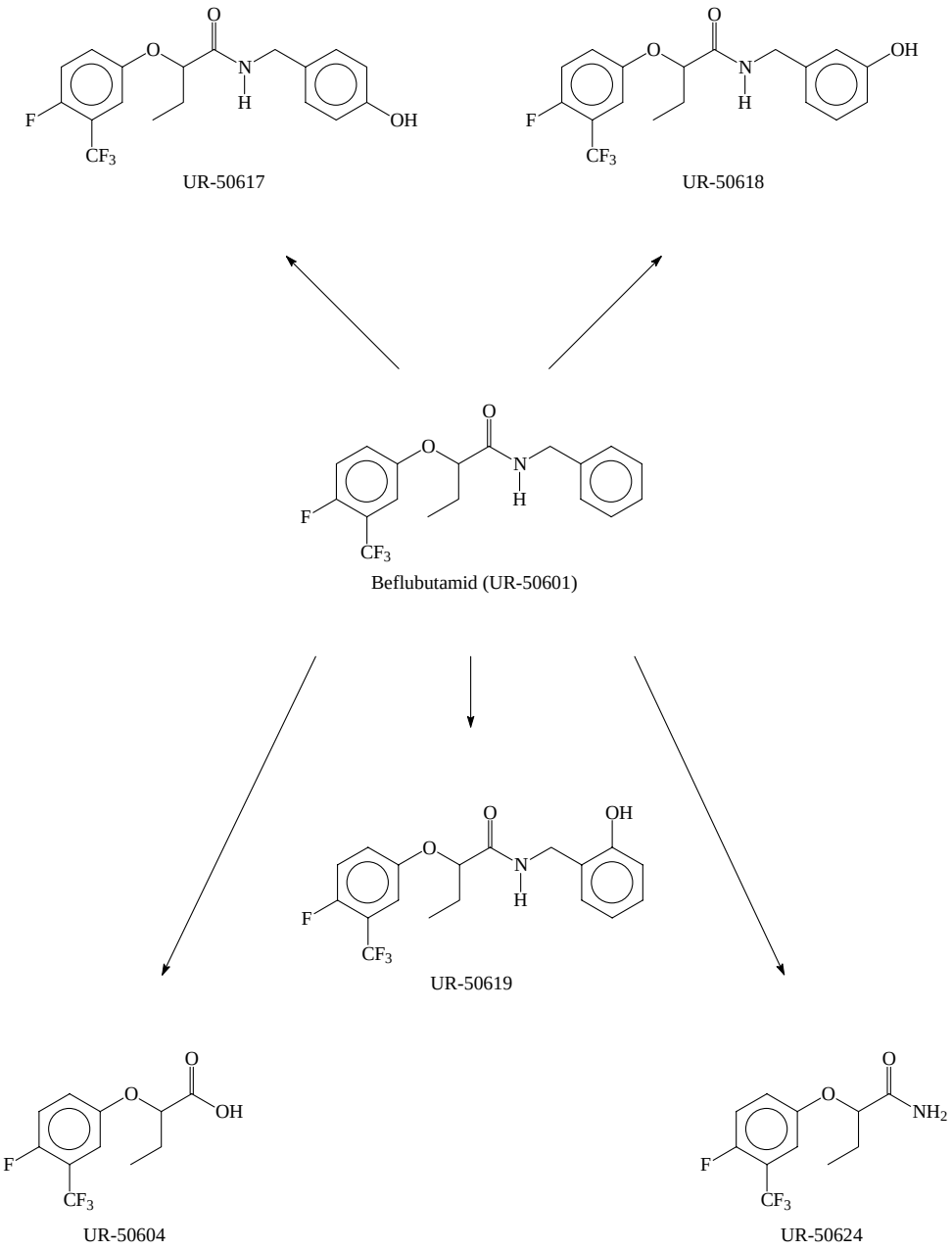
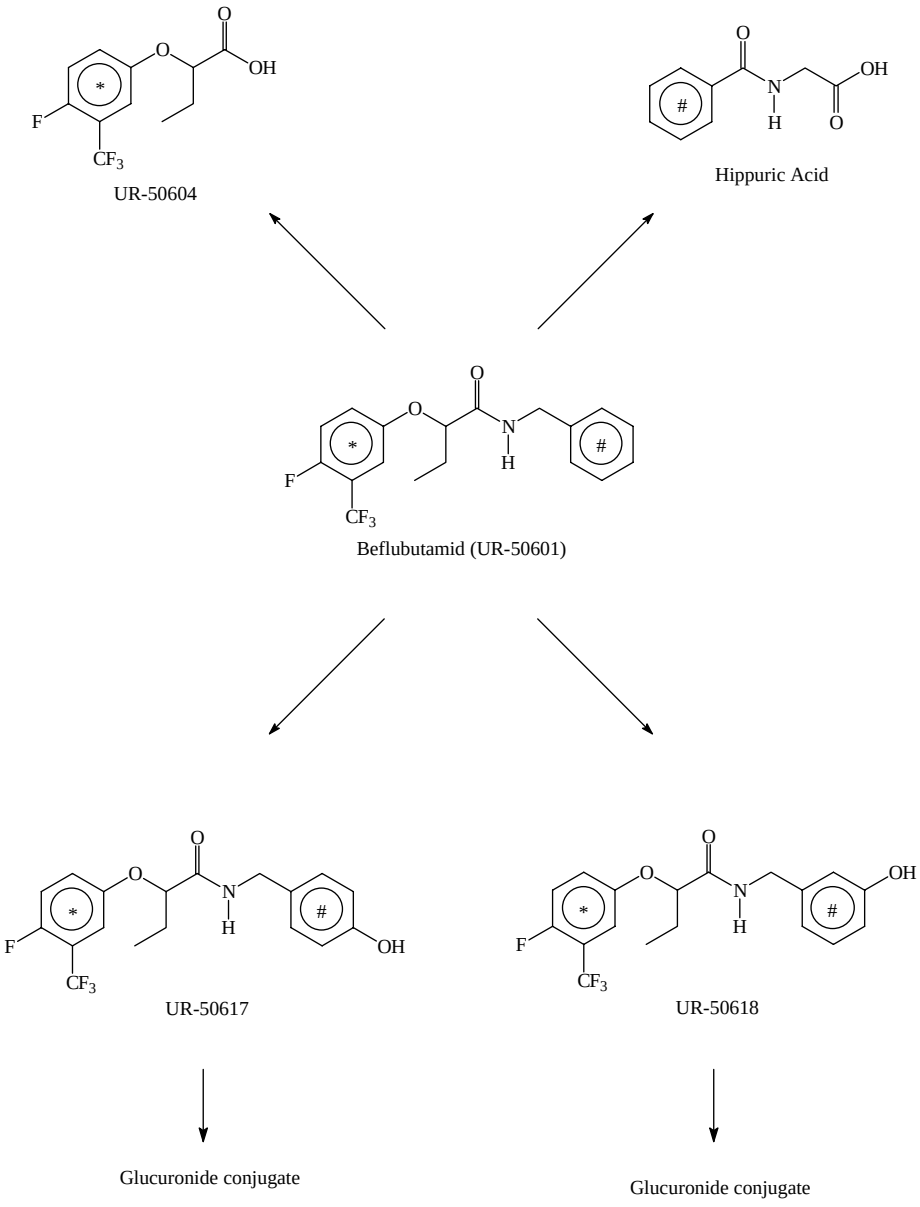


Figure 2.7-3: Proposed biotransformation pathway in the goat



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

Figure 2.7-4: Proposed degradation pathway of UR-50601 in aerobic soil

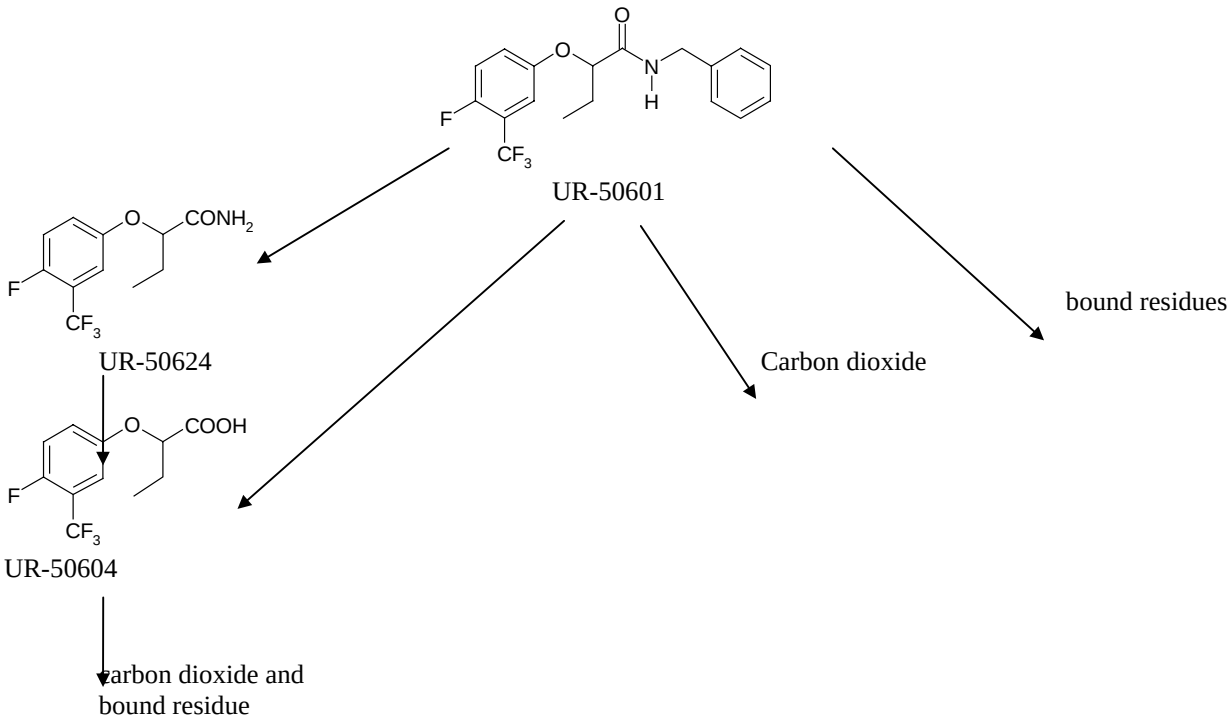


Figure 2.7-5: Proposed degradation pathway for UR-50601 in anaerobic soil

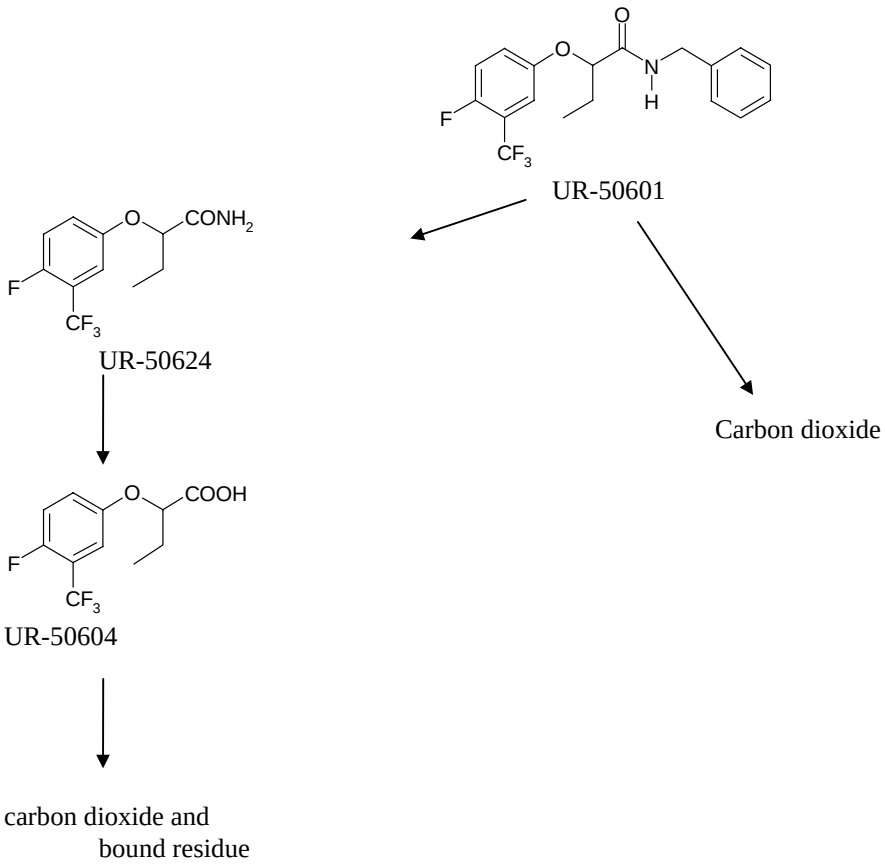


Figure 2.7-6: Proposed degradation pathway for UR-50601 by soil photolysis

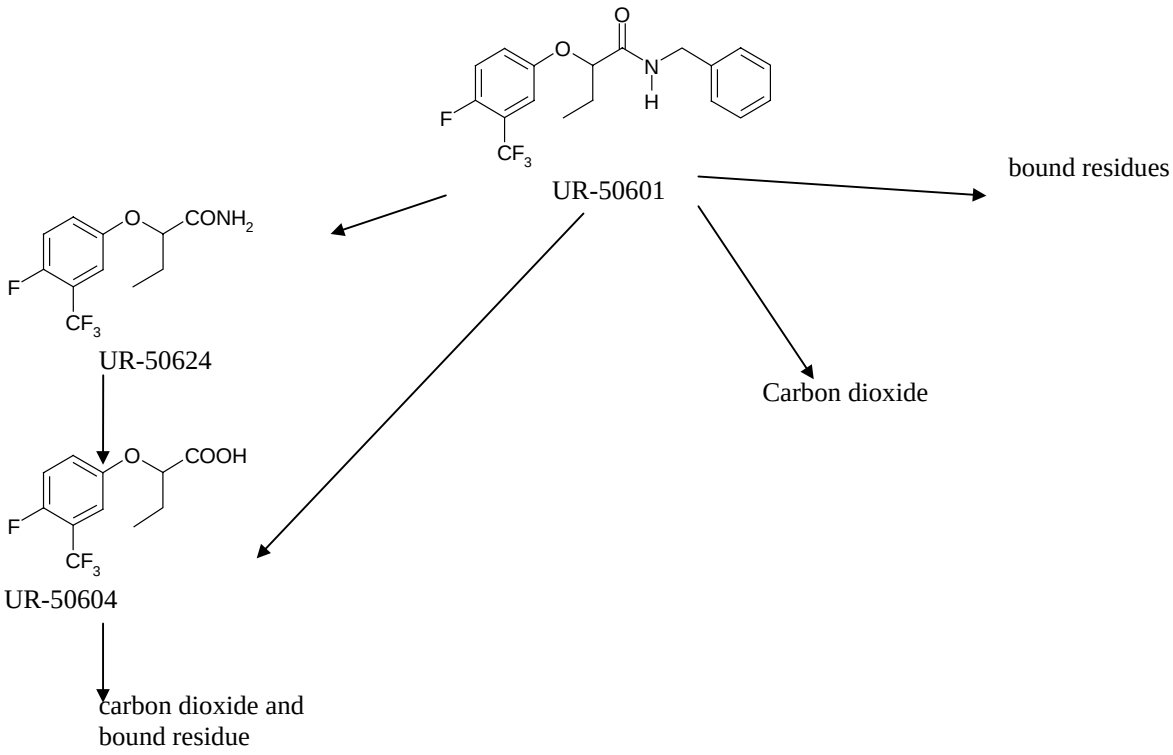
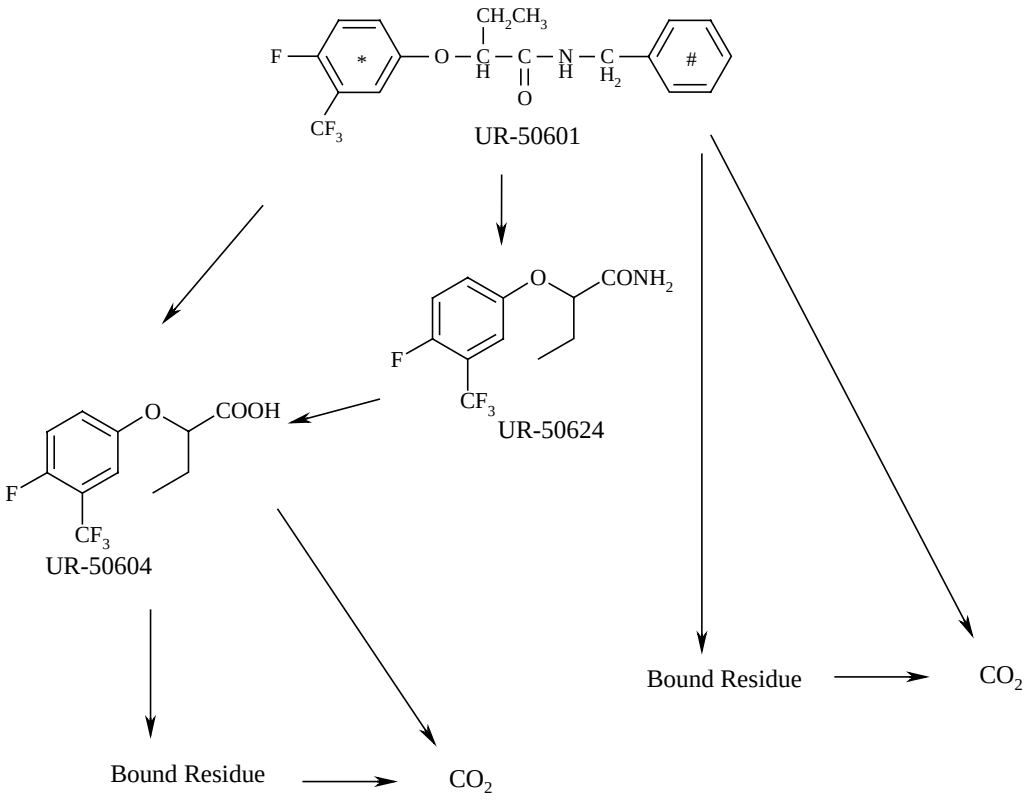


Figure 2.7-7: Proposed route of degradation of UR-50601 in aerobic water/sediment systems



Appendix 1

Beflubutamid

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	adenosin diphosphate
AE	acid equivalent
AFID	alkali flame-ionization 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 encephalopathie
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	coeficient 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 pot 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 ionization 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 ionization 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	granulosevirus
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 ionization 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 gaschromatography
Hs	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilization concentration
ICM	integrated crop management

ID	ionization 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 fertilization
k	kilo
K	Kelvin or Henry`s Law constant (in athmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsortion coefficient
K_{om}	organis 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 determination
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 concentratin
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 intend 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-detektor
pH	pH-value
PHED	pesticide handler`s exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
PIXE	proton inducted 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 acic
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 procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogene free
spp	subspecies
sq	square
SSD	sulfur 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 estimination)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily tntake
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 ration
TER_I	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration 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 riboncleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainly 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
ACTM	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	Comite 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 Organization
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 Organization 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 Monotoring 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 Commissin of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commissin for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Restistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Orginazation
ISO	International Organization for Standardization

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 Pesticdes (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 Center for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Cooperation 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 Programmme
WCP	Workd Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wide Fund for Nature

Appendix 2

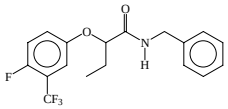
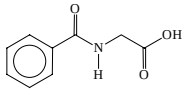
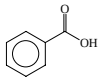
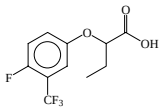
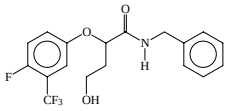
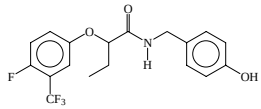
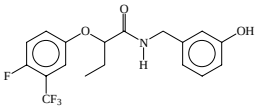
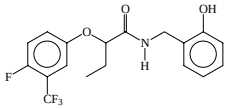
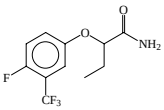
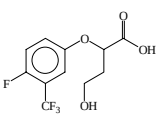
Beflubutamid

Specific Terms and Abbreviations

2.8.2 Appendix II: Specific terms and abbreviations

Abb.	Definition
DAT	Days After Treatment
PAS	Pure Active Substance
RAC	Raw Agricultural Commodity
TAS	Technical Active Substance
TRR	Total Radioactive Residue

List of metabolites of beflubutamid

Code / Name	Chemical Structure	Chemical Name	Found in Matrix
UR-50601 **Beflubutamid**		(*RS*)-N-Benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)-butanamide	Wheat, Soil, Water/ Sediment
Hippuric acid		N-Benzoylglycine	Goat, Rat
UR-50627		Benzoic acid	Wheat straw
UR-50604		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy) butanoic acid	Wheat, Rotat. Crops, Goat, Rat, Soil, Water/ Sediment
UR-50615		(*RS*)-*N*-Benzyl-2-(4-fluoro-3-trifluoromethyl-phenoxy)-4-hydroxybutanamide	Rat
UR-50617		(*RS*)-*N*-(4-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Goat, Rat
UR-50618		(*RS*)-*N*-(3-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Goat, Rat
UR-50619		(*RS*)-*N*-(2-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Rat
UR-50624		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy)butanamide	Wheat, Rotat. Crops, Rat, Soil
UR-50626		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy)-4-hydroxy butanoic acid	Rat

Appendix 3

Beflubutamid

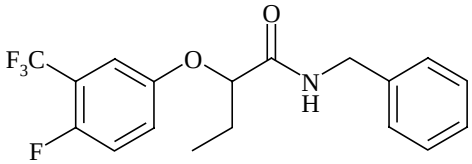
List of End-Points

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)	Beflubutamid
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	Germany

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	(*RS*)-*N*-benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide
Chemical name (CA)	2-[4-fluoro-3-(trifluoromethyl)phenoxy]-*N*-(phenylmethyl)butanamide
CIPAC No	662
CAS No	113614-08-7
EEC No (EINECS or ELINCS)	Not available
FAO Specification (including year of publication)	Not yet published
Minimum purity of the active substance as manufactured (g/kg)	970
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None
Molecular formula	$C_{18}H_{17}F_4NO_2$
Molecular mass	355.12 g/mol
Structural formula	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	75 °C (99.98 %)
Boiling point (state purity)	decomposition
Temperature of decomposition	decomposition begins from 128 °C
Appearance (state purity)	White fluffy powder (99.98 % and 97.46 %)
Relative density (state purity)	1.33 (99.98 %)
Surface tension	66.1 mN/m for a 90 % saturated aqueous solution (19.5 °C)
Vapour pressure (in Pa, state temperature)	$1.1 \cdot 10^{-5}$ Pa at 25 °C
Henry's law constant (Pa m^3 mol^{-1})	$1.1 \cdot 10^{-4}$ Pa m^3 mol^{-1}

Solubility in water (g/l or mg/l, state temperature)	$2.30 \cdot 10^{-3}$ g/l at 10 °C $3.29 \cdot 10^{-3}$ g/l at 20 °C $5.03 \cdot 10^{-3}$ g/l at 30 °C Preliminary work showed that the water solubility did not change significantly with pH.	
Solubility in organic solvents (in g/l or mg/l, state temperature)	Acetone	> 600 g/l at 20 °C
	1,2-Dichloroethane	> 544 g/l at 20 °C
	Ethylacetate	> 571 g/l at 20 °C
	Methanol	> 473 g/l at 20 °C
	n-Heptane	= 2.18 g/l at 20 °C
	Xylene	= 106 g/l at 20 °C
Partition co-efficient (log P_{OW}) (state pH and temperature)	No pH dependency. log $P_{O/W}$ = 4.28 at 21 °C	
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH : 5 no degradation (50°C)	
	pH : 7 no degradation (50°C)	
	pH : 9 no degradation (50°C)	
Dissociation constant	dissociation is unlikely	
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	281.5 nm	
Photostability (DT_{50}) (aqueous, sunlight, state pH)	DT_{50} 48 d (pH 7, 25°C)	
Quantum yield of direct phototransformation in water at λ > 290 nm	0.044 (pH 7)	
Flammability	neither highly flammable nor autoflammable	
Explosive properties	Not explosive	

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 as (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		
Winter wheat Winter barley Triticale Winter rye	Northern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-0.128 + 0.250-0.750 isoproturon Spring: 0.0425-0.085 + 0.250-0.5 isoproturon	200-400 200-400	0.170-0.255 + 1-1.5 isoproturon 0.170 + 1.0 isoproturon		Co-formulation with isoproturon
Winter wheat Winter barley Durum wheat	Southern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-0.128 + 0.250-0.750 isoproturon Spring: 0.0425-0.128 + 0.250-0.750 isoproturon	200-400 200-400	0.170-0.255 + 1-1.5 isoproturon 0.170-0.255 + 1-1.5 isoproturon		Co-formulation with isoproturon

(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	None
with regard to fate and behaviour data	None
with regard to ecotoxicological data	N, R 50/53

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; reversed phase column
Impurities in technical as (principle of method)	HPLC-UV; chiral and reversed phase columns
Plant protection product (principle of method)	HPLC-UV; reversed phase column

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	GC-PND	0.05 mg/kg (cereal grain)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	not relevant	
Soil (principle of method and LOQ)	LC-MS GC-MS	0.01 mg/kg 0.01 mg/kg
Water (principle of method and LOQ)	HPLC-UV LC-MS	0.1 µg/l (surface and drinking water) 0.1 µg/l (surface water)
Air (principle of method and LOQ)	HPLC-UV	0.6 µg/m^3
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	Nearly completely absorbed based on excretion via bile and urine
Distribution	Widely distributed
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	Completely excreted within 120 hours mainly via bile (66% - 85% in 48 hours)
Metabolism in animals	Extensively metabolised by hydroxylation, cleavage of the amide bond and conjugation as glucuronides (major metabolites: phenoxybutyric acid, hippuric acid)
Toxicologically significant compounds (animals, plants and environment)	Parent compound and metabolites

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	>5000 mg/kg bw
Rat LD_{50} dermal	>2000 mg/kg bw
Rat LC_{50} inhalation	>5 mg/l air /4h (nose only)
Skin irritation	Non-irritant
Eye irritation	Non-irritant
Skin sensitization (test method used and result)	Non-sensitising (M & K)

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect	Decreased bw; liver (rat,mouse,dog), kidney + thyroid gland (rat)
Lowest relevant oral NOAEL / NOEL	90-d oral, rat: 400 ppm (30 mg/kg bw/d)
Lowest relevant dermal NOAEL / NOEL	No data - Not required
Lowest relevant inhalation NOAEL / NOEL	No data - Not required

Genotoxicity (Annex IIA, point 5.4)

No evidence of genotoxic potential

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

Target / critical effect	Liver, kidney + thyroid gland (rat)
Lowest relevant NOAEL / NOEL	104-wk oral, rat: 50 ppm (2.2 mg/kg bw/d)
Carcinogenicity	No carcinogenic potential with relevance to humans.

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	Impairment of body weight development during lactation, delay in age for vaginal opening (F1-females) at parental toxic doses doses; offspring kidney changes at 3200 ppm.
Lowest relevant reproductive NOAEL / NOEL	2-gen. rat: 200 ppm (approx. 17 mg/kg bw/d)
Developmental target / critical effect	Developmental effects on the kidney/ureter at maternally toxic doses.
Lowest relevant developmental NOAEL / NOEL	100 mg/kg bw/d (rat, rabbit)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

No concern of neurotoxic effects from toxicity studies; no data for delayed neurotoxicity - not considered necessary

Other toxicological studies (Annex IIA, point 5.8)

No data

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 (BgVV)	0.022 mg/kg bw	104-wk, oral rat	100
AOEL systemic (BgVV)	0.3 mg/kg bw/d	90-d, rat	100
ARfD (acute reference dose)	Not necessary-	Not allocated	

Dermal absorption (Annex IIIA, point 7.3)

No studies performed; 100% assumed (worst case)

Acceptable exposure scenarios (including method of calculation)

Operator	Intended use acceptable (operator exposure < systemic AOEL; German model and UK-POEM; with PPE)
Workers	Intended use acceptable
Bystanders	Intended use acceptable

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	wheat
Rotational crops	carrot, wheat
Plant residue definition for monitoring	beflubutamid
Plant residue definition for risk assessment	beflubutamid
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	lactating goat
Animal residue definition for monitoring	none
Animal residue definition for risk assessment	none
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	yes

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

Total radioactive residues of [ring-UL-^{14}C-phenoxy] beflubutamid from soil by succeeding crops (carrot, wheat) planted 30 days after soil treatment were found in mature crop parts at levels of ~0.01 mg as-equiv/kg carrot root, ~0.03 mg as-equiv /kg carrot foliage, ~0.02 mg as-equiv /kg wheat grain, and ~0.1 mg as-equiv /kg straw. In practice no residues detectable with conventional analytical methodology are expected in rotational crops.

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

Freezer storage stability of beflubutamid and UR-50604 was proven on wheat grain, straw and forage during the course of the residue trials covering the storage conditions of the samples prior to analysis.

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 studies required / conducted		

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)
spring barley	N S	4 x <0.05 mg/kg grain 4 x <0.05 mg/kg grain		0.05 mg/kg	0
spring wheat	N S	1 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0
durum wheat	N	1 x <0.05 mg/kg grain		0.05 mg/kg	0
winter wheat	N S	4 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0

(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	0.022 mg/kg bw/d
TMDI (European Diet) (% ADI)	0.001 mg/kg bw (4.7 %)
NEDI (% ADI)	not calculated
Factors included in NEDI	not applicable
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 *
no data generated			

* 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)

cereals grain	0.05 mg/kg
other food of plant origin	0.05 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)

Mineralization after (...) days	12.2 - 46.8 % (phenoxy label; 120 or 152 d) 55.1 % (benzylamine label; 152 d)
Non-extractable residues after (...) days	31.8 - 50.5 % (phenoxy label; 120 or 152 d) 25.8 % (benzylamine label; 152 d)
Major metabolites - name and/or code, % of applied (range and maximum)	Phenoxybutyric acid /UR-50604: 9.0 – 26.1 % (phenoxy label)

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

Anaerobic degradation	CO_2 : not detected (both labels) Non-extractable residues: 4.1 % (phenoxy label; 120d); 19.4% (benzylamine label; 120 d) major metabolite: Phenoxybutyric acid /UR-50604: 23.1 %(phenoxy label)
Soil photolysis	Active substance: 73.1 – 77.9% after 10 d irradiation 91.8 – 112% after 10 d (dark control)

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

Method of calculation	Active substance: DT_{50lab}/DT_{90lab} aerobic bi-exponential DT_{50lab}/DT_{90lab} anaerobic pseudo-first order kinetic DT_{50f}/DT_{90f} first order kinetic, linear regression Metabolite UR-50604: DT_{50lab}/DT_{90lab} aerobic pseudo-first order kinetic
Laboratory studies (range or median, with n value, 0with r^2 value)	Active substance: DT_{50lab} (20°C, aerobic) (r^2= 0.99) -Arrow sandy loam 5 d -Wick 5 d -Speyer 2.2 118 d -Speyer 2.2 12 d -Evesham 3 8 d Metabolite UR-50604: DT_{50lab} (20°C, aerobic) (r^2=0.99) - Wick 6 d -Evesham 3 5 d

	Active substance: DT_{90lab} (20°C, aerobic) (r^2=0.99) Arrow sandy loam 176 d -Wick 16 d -Speyer 2.2 >365 d -Speyer 2.2 > 365 d Evesham 3 62 d
	Active substance: DT_{50lab} (10°C, aerobic) (r^2=0.99) -Evesham 3 20 d Metabolite UR-50604: DT_{50lab} (10°C, aerobic) (r^2=0.99) -Evesham 3 80 d
	Active substance: DT_{50lab} (20°C, anaerobic): - water phase 4 d (r^2=0.99) - soil 260 d (r^2=0.96) DT_{90lab} (20°C, anaerobic): - water phase 12 d (r^2=0.99)
	degradation in the saturated zone: no data
Field studies (state location, range or median with n value)	DT_{50f}: Active substance: Autumn use: Spain 103d (r^2=0.97) United Kingdom 51d (r^2=0.99) Spring use: Spain 86d(r^2=0.97) Summer use: Germany North 20d (r^2=0.86) Germany South 15d (r^2=0.79) Metabolite UR-50604: < 10 –16 µg/kg between 59 – 126 d

	DT_{90f}: Active substance: Autumn use: Spain 343d United Kingdom 169d Spring use: Spain 285d Summer use: Germany North 65d Germany South 49d
Soil accumulation and plateau concentration	No accumulation.
Soil residue studies	Laboratory studies (results expressed as mg equivalents active substance / kg soil dry weight): Active substance: carrot 0.083 mg/kg (30d); wheat 0.056 mg/kg (30d), 0.005 mg/kg (193d). Metabolite UR-50604: carrot 0.024 mg/kg (30d); wheat 0.019 (30d).

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc}	Active substance: Soil pH K_f K_{oc} 1/n Arrow 6.4 26.7 1335 0.93 Wick 5.8 8.5 1061 0.92 Speyer 2.2 6.0 43.0 1793 0.92 Evesham 3 7.1 16.2 496 0.86 Metabolite UR-50604 Wick 5.8 0.2 22 0.93 Speyer 2.2 6.0 0.2 9 0.81 Evesham 3 7.1 0.1 6 0.57
K_d	Not calculated.
pH dependence (yes / no) (if yes type of dependence)	No

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

Column leaching	Not tested; mobility assessed in adsorption/desorption studies
Aged residues leaching	Not tested; mobility assessed in adsorption/desorption studies
Lysimeter/ field leaching studies	Lysimeter or field leaching studies not performed.

PEC (soil) (Annex IIIA, point 9.1.3) **beflubutamid**

Method of calculation	First order kinetic, DT_{50f} 103 d, , no process other than degradation considered, no multiple applications because DT50 much lower than interval for next application
Application rate	0.255 g as/kg

$PEC_{(s)}$ mg/kg	Single application Actual	Single application Time weighted average
Initial	0.340	---
Short term		
24 h	0.338	0.339
2 d	0.335	0.338
4 d	0.331	0.335
Long term		
7 d	0.324	0.332
28 d	0.282	0.310
50 d	0.243	0.289
100 d	0.173	0.247

PEC (soil) (Annex IIIA, point 9.1.3) **metabolite UR-50604**

Method of calculation	Only the calculated DT50 values of 5 and 6 days in the Wick and Evesham3 soils are considered as valid although they may not represent worst case values. Therefore, no calculation was conducted but the non-relevance of this metabolite regarding toxicology, ecotoxicology and biological activity was demonstrated.
Application rate	maximum 26.1% UR-50604

$PEC_{(s)}$ mg/kg	Single application Actual	Single application Time weighted average
Initial	0.066	---

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)	Active substance: No degradation at pH 5, 7 and 9 (50°C) Metabolite UR-50604: No degradation at pH 7 (25°C, 7 days; dark control of photolytic degradation in water)
Photolytic degradation of active substance and relevant metabolites	Active substance: DT50 48 d (first order kinetics) at pH 7 (25°C) quantum yield: 0.044 (pH 7) Metabolite UR-50604: DT50 21 (pH 5), 24 (pH 7) and 20 d (pH 9) quantum yield: 8.8 x 10^{-5} at pH 9; 1.9 x 10^{-4} at pH 7, 1.8 x 10^{-4} at pH 5
Readily biodegradable (yes/no)	No (see results of water/sediment study)
Degradation in water/sediment - DT_{50} water - DT_{90} water - DT_{50} whole system - DT_{90} whole system	16 and 20 days ("Running water", "Static pond") 53 and 66 days (" , ") 49 and 64 days (" , ") 164 and 212 days(" , ") Remark: First order kinetics , data from mean values of different labelling.
Mineralization (100 days)	7.6 and 10.7 %(phenoxy-label) 32.1 and 41.6 % (benzylamine-label)
Non-extractable residues (100 days)	11.9 and 12.4 % (phenoxy label) 28.8 and 19.7 % (benzylamine label)
Distribution in water / sediment systems (active substance) (100 days)	Water: 3.2 and 1.0 % (phenoxy label) 1.3 and 0.8 % (benzylamine label) Sediment: 23.3 and 13.7 % (phenoxy label) 29.5 and 27.0 % (benzylamine label)
Distribution in water / sediment systems (metabolites)(maximum)	Metabolite UR-50604: Water: 36.1 (100d) and 34.6% (100d) (phenoxy label) Sediment: 9.4 (100d) and 20.3% (100d)(phenoxy label)

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

Method of calculation	First order kinetic; DT50 20 d; spray drift values (Ganzelmeier 1995), drift to a static ditch of 1m width and 30 cm depth; 1m drift distance
Application rate	0.255 kg as/ha
Main routes of entry	spray drift (limited potential for drainflow and runoff/erosion)

$PEC_{(sw)}$ µg/l	Single application Actual	Single Application Time weighted average
Initial	3.40	3.40
Short term		
24 h	3.28	3.34
2 d	3.17	3.28
4 d	2.96	3.17
Long term		
7 d	2.66	3.02
14 d	2.09	2.69
21 d	1.64	2.41
28 d	1.28	2.17
42 d	0.79	1.79

PEC (surface water) (Annex IIIA, point 9.2.3) **metabolite UR-50604**

Method of calculation	In two aerobic water/sediment studies the metabolite UR-50604 accumulated to a maximum of 45.5-54.9%. Therefore, there is no absolute maximum level of accumulation nor the rate of subsequent dissipation. Spray drift values (Ganzelmeier 1995), drift to a static ditch of 1m width and 30 cm depth; 1m drift distance
Application rate	0.255 kg as/ha ; 100% conversion to metabolite UR-50604.
Main routes of entry	spray drift (limited potential for drainflow and runoff/erosion)

PEC$_{(sw)}$ µg/l	Single application Actual	Single application Time weighted average
Initial	2.55 µg/l	2.55 µg/l

PEC (sediment) beflubutamid

Method of calculation	Drift to a static ditch of 1 m width and 1 m length; drift from 1 m distance with drift value of 4% (Ganzelmeier 1995); Sediment depth 5 cm; sediment bulk density 1.5 g/cm3; one application per year. Maximum accumulation of UR-50601 in sediment 57.5% of applied radioactivity.
Application rate	0.255 kg as/ha

PEC$_{(sed)}$	Single application Actual	Single application Time weighted average
Initial	0.0078 mg/kg	0.0078 mg/kg

PEC (sediment) metabolite UR-50604

Method of calculation	Drift to a static ditch of 1 m width and 1 m length; drift from 1 m distance with drift value of 4% (Ganzelmeier 1995); Sediment depth 5 cm; sediment bulk density 1.5 g/cm^3; one application per year. Maximum accumulation of UR-50604 in sediment 40% of applied radioactivity.
Application rate	0.255 kg as/ha; 100% conversion to metabolite UR-50604

PEC$_{(sed)}$	Single application Actual	Single application Time weighted average
Initial	0.0041 mg/kg	0.0041 mg/kg

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

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	**Calculation of the Rapporteur:** FOCUS-PELMO active substance: DT_{50}: 12 d K_{oc}: 1260 (average); 1/n: 0.9200 metabolite UR-50604: DT50 5 d Koc: 12.3; 1/n: 0.8700
Application rate	0.255 kg as/ha every season in 20 years
$PEC_{(gw)}$	
Maximum concentration	----
Average annual concentration	< 0.001 µg/L Hamburg, Piacenza

PEC (ground water) (Annex IIIA, point 9.2.1) **metabolite UR-50604**

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	see above
Application rate	
$PEC_{(gw)}$	
Maximum concentration	----
Average annual concentration	Scenario: Hamburg 0.113 µg/L; Piacenza 0.224 µg/L

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

Direct photolysis in air	**Model: Aqueous solution** Active substance: DT_{50} 48 d (first order kinetics) at pH 7 (25°C) Metabolite UR-50604: DT_{50} 21 (pH 5), 24 (pH 7) and 20 d (pH 9)
Quantum yield of direct phototransformation	**Model: Aqueous solution** Active substance: 0.044 (pH 7) Metabolite UR-50604: 8.8×10^{-5} at pH 9 1.9×10^{-4} at pH 7 1.8×10^{-4} at pH 5
Photochemical oxidative degradation in air	DT_{50} = 3.5 hours (12 h day) and 15.7 hours (24h day), respectively (according to Atkinson calculation)
Volatilization	from plant surfaces: no data
	from soil: no data

PEC (air)

Method of calculation	Not relevant

$PEC_{(a)}$

Maximum concentration	Not relevant

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	Beflubutamid and the major metabolite phenoxybutyric acid (UR50604) (soil (aerobic, anaerobic), water/sediment, groundwater). In soil the metabolite is consired as ecotoxicological relevant, but has no potential for accumulation. For groundwater, the metabolite is not relevant regarding ecotoxicology and biological activity. The evaluation of the toxicological relevance of the major metabolite is not yet finished due to missing data.

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

Soil (indicate location and type of study)	New active substance; no data available
Surface water (indicate location and type of study)	New active substance; no data available
Ground water (indicate location and type of study)	New active substance; no data available
Air (indicate location and type of study)	New active substance; no data available

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} >5000 mg/kg (rat)
Long-term toxicity to mammals	NOAEL 200 ppm (for reproductive effects in rat multi-generation study)
Acute toxicity to birds	LD_{50} >2000 mg/kg (bobwhite quail)
Dietary toxicity to birds	LC_{50} >5200 ppm (bobwhite quail)
Reproductive toxicity to birds	NOEL 1000 ppm (bobwhite quail)

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
0.255	Cereals	Herbivorous bird	acute	>285	10
0.255	Cereals	Herbivorous bird	short-term	>185	10
0.255	Cereals	Herbivorous bird	long-term	36	5
0.255	Cereals	Insectivorous bird	acute	>660	10
0.255	Cereals	Insectivorous bird	short-term	>650	10
0.255	Cereals	Insectivorous bird	long-term	125	5
0.255	Cereals	Insectivorous mammal	acute	>710	10
0.255	Cereals	Insectivorous mammal	long-term	114	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				
O. mykiss	Active substance	acute	Mortality EC_{50}	1.86
P. promelas	"	long-term	Growth NOEC	0.11
D. magna	"	acute	Immobilization EC_{50}	1.64
"	"	chronic	Reproduction NOEC	0.455
S. capricornutum	"	chronic	Biomass EC_{50}	0.00455
A. flos-aquae	"	chronic	Biomass EC_{50}	>6.01
C. riparius	"	long-term	Emergence NOEC	1.8
L. gibba	"	long-term	Fronds	0.02
O. mykiss	Metab. UR-50604	acute	Mortality EC_{50}	>93
D. magna	"	"	Immobilization EC_{50}	>91
S. capricornutum	"	chronic	Biomass EC_{50}	69.2
O. mykiss	ASU 95 510 H	acute	Mortality EC_{50}	39.1
D. magna	"	"	Immobilization EC_{50}	17.3
S. capricornutum	"	chronic	Biomass EC_{50}	0.052
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
0.255	Field crop	*S. capricornutum*	chronic	1	1.3	10
"	"	"	"	5	8.8	10
"	"	"	"	10	13	10

Bioconcentration

Bioconcentration factor (BCF)	230
Annex VI Trigger for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	
Level of residues (%) in organisms after the 14 day depuration phase	< 5

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

Acute oral toxicity	LD_{50} > 200 µg/bee
Acute contact toxicity	LD_{50} > 200 µg/bee

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

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.255	Cereals	oral	1.275	50
0.255	Cereals	contact	1.275	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 g as/ha	Endpoint	Effect %	Annex VI Trigger
Laboratory tests						
T. pyri	Protonymphs	ASU 92530 H	250	Mortality Fecundity	8 9	30
T. pyri	Protonymphs	ASU 95 510 H	255	Mortality Fecundity	31 0	30
A. rhopalosiphi	Adults	ASU 92530 H	250	Mortality Fecundity	0 44	30
A. rhopalosiphi	Adults	ASU 95 510 H	255	Mortality Fecundity	3 13	30
C. carnea	Larvae	ASU 92530 H	250	Mortality Fecundity	6 5	30
C. carnea	Larvae	ASU 95 510 H	510	Mortality Fecundity	18 0	30
P. cupreus	Adults	ASU 92530 H	250	Mortality Food uptake	12 8	30
P. cupreus	Adults	ASU 95 510 H	510	Mortality Food uptake	0 9	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} 732 mg as/kg (beflubutamid) (corrected to 366 mg as/kg)
Acute toxicity (Metabolite UR-50604)	LC_{50} 229 mg/kg (corrected to 115 mg)
Reproductive toxicity	NOEC < 0.255 kg as/ha (form. ASU 92 530 H containing 500 g/L beflubutamid), equivalent to < 0.34 mg as/kg, corrected to < 0.17 mg as/kg NOEC 6 l product/ha (form. ASU 95 510 H containing Isoproturon 500 g/L and 85 g/L beflubutamid), equivalent to 0.68 mg as/kg, corrected to 0.34 mg as/kg

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

Application rate (kg as/ha)	test substance	Crop	Time-scale	TER	Annex VI Trigger
0.255	active substance	Cereals	acute	1076	10
0.255	ASU 92530 H	Cereals	long-term	< 0.5	5
0.255	ASU 95510 H	Cereals	long-term	1	5

*PEC 0.34 mg as/kg (see chapter B.8.3)

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

Nitrogen mineralisation	Active substance beflubutamid: Effects <25 % up to 0.6 kg/ha Metabolite UR-50604 : Effects <25 % up to 0.34 kg/ha
Carbon mineralisation	Active substance beflubutamid: Effects <25 % up to 0.6 kg/ha Metabolite UR-50604 : Effects <25 % up to 0.34 kg/ha

Effects on biological methods of sewage treatments (Annex IIA, point 8.7)

Acute toxicity	EC_{50} > 100 mg as/L

Level 3

Beflubutamid

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

Beflubutamid (ISO common name proposed), *(RS)*-*N*-benzyl-2-(4-fluoro-3-trifluoromethyl-phenoxy) butanamide (IUPAC), as a phenoxybutamid is a herbicidally active substance. The formulated product Herbaflex [ASU 95 510 H (UBH-820/isoproturon)] is a suspension concentrate (SC) containing 85 g/L beflubutamid and 500 g/L isoproturon.

Beflubutamid is intended to be used as a selective post-emergence herbicide in winter cereals [winter wheat (TRZAW), winter barley (HORVW), triticale (TTLSS) and rye (SECCW)] in the Northern European countries and in winter wheat (TRZAW), winter barley (HORVW) and durum wheat (TRZDU) in the Southern European countries.

Limitations in the choice of succeeding crops in regular rotations or in the case of crop failure subsequent to beflubutamid application can not be assessed as the only experiment run on this issue was invalid.

The resistance risk of weeds to the active substance beflubutamid can be considered as to be low.

Residues of beflubutamid can be determined by gas chromatography with EC-, PN- or MS-detection (plant material, soil) as well as by HPLC with UV- or MS-detection (plant material, soil, water, air).

The residue behaviour of beflubutamid has been investigated in metabolism studies on wheat plants. The residue situation in forage, grain and straw was investigated in a sufficient number of supervised residue trials in growing areas in the northern and southern part of Europe. Different SC formulations containing the active substances beflubutamid and isoproturon representing the product to be commercialised were used in these trials. Based on the results of these trials residues in grain and straw above the LOQ at normal harvest are not expected under practical conditions. Analytical methodology also appropriate for monitoring has been applied in these trials. The residue situation in small grain cereals based on the known data is regarded to be acceptable if the plant protection products containing beflubutamid will be used properly. Health risks for consumers possibly caused by residues in food of plant origin following treatment with the active substance are therefore not expected.

The available data on mammalian toxicology, mutagenicity and animal metabolism for the active substance are considered to adequately support the risk evaluation of beflubutamid 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.
The data for beflubutamid do not support evidence of genotoxic, carcinogenic and the fertility or development disturbing properties of the active substance. 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.
UR-50604 was found as major metabolite in the metabolism studies in rats, i.e. urinary excretion of UR-50604 accounted for 23-31% of the administered dose. No further toxicological studies with UR-50604 have been submitted. Because the concentration of the

main metabolite of beflubutamid (UR-50604) exceeds 0.1 µg/l in groundwater, the toxicological relevance of this metabolite is to evaluate before an inclusion of beflubutamid in Annex I of Directive 91/414/EEC is possible (see level 4).

The environmental fate and behaviour of beflubutamid and the major metabolite UR-50604 in soil shows no persistence potential based on results of dissipation studies in Spain (spring/autumn), United Kingdom (autumn) and Germany (spring/summer). Beflubutamid can be classified as a low mobile substance whereas the major metabolite UR-50604 is a very high mobile substance. There is no concern of groundwater contamination due to modelling results of < 0.1 µg/L for the active substance. Regarding the metabolite UR-50604, the Rapporteur conducted FOCUS-PELMO calculations for the scenarios "Hamburg" and "Piacenza" with concentrations of 0.113 and 0.224 µg/L, respectively. Therefore, groundwater contamination of the major metabolite UR-50604 can not be excluded.
The metabolite UR-50604 is non-relevant regarding its herbicidal activity, however, it is ecotoxicological relevant because of its acute effects on earthworms. Otherwise, there is no potential for accumulation of the metabolite UR-50604 in soil. For groundwater, the evaluation of the toxicological relevance of the major metabolite is not yet finished due to missing data.

Based on the results of different investigations concerning the degradation behaviour of beflubutamid in the aquatic environment, it can be concluded that the active substance and the major metabolite UR-50604 have to be regarded as the relevant residue in surface water and sediment. The relevant residue for quantification in air is the active substance only.

From the ecotoxicological point of view the effects on terrestrial vertebrates (birds and mammals), bees, other non-target arthropods, earthworms, soil micro-organisms and the biological methods of sewage treatments are acceptable.

An unrestricted use of beflubutamid is considered unacceptable because of the effects on aquatic plants. Therefore, risk mitigation measures are to be set on Member State level.

A risk for non-target higher terrestrial plants can not be excluded.

3.2 Proposed decision concerning inclusion in Annex I

Concerning the submitted data a postponement of the inclusion of the active substance beflubutamid in Annex I of Directive 91/414/EEC is recommended pending submission and evaluation of further information.

An inclusion of beflubutamid in Annex I of Directive 91/414/EEC is only possible if the main metabolite of beflubutamid UR-50604 is not considered to be relevant.

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

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), the submission of further studies for the evaluation of the toxicological relevance of the metabolite UR-50604 is required.

Depending on results of metabolite UR-50604's toxicological relevance in groundwater, further testing - especially regarding leaching behaviour - may be necessary.

Level 4

Beflubutamid

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

Physical and chemical properties of the active substance

None.

Data on application and further information

None.

Classification, packaging 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 metabolite UR-50604, the following studies are required in addition to the already submitted studies:

- Acute oral toxicity in rats
- Reverse mutation test for bacteria (Salmonella typhimurium/Escherichia coli)
- Gene mutation test on mammalian cells
- Chromosome aberration test on mammalian cells
- Repeat-dose oral toxicity study in rats of at least 28 days of duration 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

AIIA 7.1.3.3
Based on the results of metabolite UR-50604's toxicological relevance, further studies regarding leaching behaviour, e.g. lysimeter oder field leaching studies, may be necessary.

AIIIA 9.2.1
The notifier has to submitt a new FOCUS-PELMO calculation.
Justification:
The DT_{50} values from "Arrow" soil are also to be taken into account because the microbial biomass is in the same order as for the other soils and these values are not evaluated as outliers. The Rapporteur conducted a new simulation taking into account all these results for the scenario "Hamburg" and "Piacenza" which resulted in concentrations for the metabolite UR-50604 of 0.113 and 0.224 µg/L (DT_{50} 12 d (active substance) and 5d (metabolite UR-50604)).

Furthermore, it is unclear why different intervalls (Speyer 2.2. 0-30 days, Wick and Evesham 0-120 days) were selected for the determination of DT_{50} values.

Ecotoxicology

None.

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

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
Annex IIIA, point 4.1.2:
The suitability of the packaging, including closures, in terms of its strength, leakproofness and resistance to normal transport an handling must be determined and reported according to ADR Methods 3552, 3553, 3560, 3555, 3556, 3558, or appropriate ADR Methods for intermediate bulk containers and where for the preparation child-resistant closures are required, according to ISO standards 8317.

Classification, packaging and labelling

None.

Methods of analysis

Analytical methods for formulation analysis

None.

Analytical methods for residue analysis

Annex IIA, point 4.2.2:
A statement as to the suitability of the submitted method for the quantification of phytotoxic concentration in soil.

Annex IIA, point 4.2.3:
The sampling site and the characteristics of the surface water (pH, DOC, total hardness) must be reported.
Justification:
No data were given in the submitted methods.

Toxicology and metabolism

None.

Residue data

None.

Environmental fate and behaviour

None.

Ecotoxicology

None.

Monograph

02 August 2002

Beflubutamid

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]
Anonym	AIIA-1.8; AIIA-1.9; AIIA-1.10; AIIA-1.11; AIIA-2.5	1998	UR-50601: Identity (Tier II - Doc. J). GLP, unpublished CHE2000-1158	Y	UBE
Anonym	AIIIA-1.4	1996	Safety Data Sheet for PROXEL GXL. not GLP, unpublished BEI2000-416	Y	ASU
Anonym	AIIIA-1.4	1996	Safety Data Sheet for KELZAN. ESD 021GB 14 not GLP, unpublished BEI2000-415	Y	ASU
Anonym	AIIIA-1.4	1996	Safety Data Sheet for 1,2-PROPYLENE GLYCOL TECHN. ES 00804-B (D/E) not GLP, unpublished BEI2000-414	Y	ASU
Anonym	AIIIA-1.4	1997	Safety Data Sheet for RHODORSIL ANTISCHAUMMITTEL 426 R. not GLP, unpublished BEI2000-413	Y	ASU
Anonym	AIIIA-1.4	1997	Safety Data Sheet for SYNPERONIC 91/6. not GLP, unpublished BEI2000-412	Y	ASU
Anonym	AIIIA-1.4	1996	Safety Data Sheet for ATLOX 4913. not GLP, unpublished BEI2000-411	Y	ASU
Betteley, J.M.T.	AIIA-1.10; AIIA-1.11	1999	Determination of Active Ingredient, Isomeric Ratio and the Level of Twelve Impurities three Batches. UBE 102/993155 GLP, unpublished CHE2000-1297	Y	UBE
Betteley, J.M.T.	AIIA-1.10	2000	UR-50601 Purity and impurity determination. UBE 116/004021 GLP, unpublished CHE2000-1391	Y	UBE

[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]
Betteley, J.M.T.	AIIA-1.10	2000	UR-50601 Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 117/004022 GLP, unpublished CHE2000-1392	Y	UBE
Betteley, J.M.T.	AIIA-1.10	1999	Determination of Active Ingredient, Isomeric Ratio and the Level of Twelve Impurities. UBE 093/984738 GLP, unpublished CHE2000-1296	Y	UBE
Betteley, J.M.T.	AIIA-1.10; AIIA-1.11; AIIA-4.1	1999	UR-50601: Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 32/994457 GLP, unpublished CHE2000-1132	Y	UBE
Orgwa, T., Hase, H.	AIIA-1.10; AIIA-1.11	1999	Determination of Active Ingredient,and the level of twelve impurities in Lot. 950427. USA-R-96113 GLP, unpublished CHE2000-1298	Y	UBE
Orgwa, T., Hase, H.	AIIA-1.11	1999	Purity analysis of the active substance UR-50601 (Lot. 960725). USA-R-96175 GLP, unpublished CHE2000-1301	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

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]
Anonym	AIIA-1.8; AIIA-1.9; AIIA-1.10; AIIA-1.11; AIIA-2.5	1998	UR-50601: Identity (Tier II - Doc. J). GLP, unpublished CHE2000-1158	Y	UBE
Betteley, J.	AIIA-2.1.3	2001	UR-50601: Boiling point UBE 123/0113654. not GLP, unpublished CHE2001-558	Y	TSU
Betteley, J.	AIIA-2.3.1	2000	UR-50604: Vapour pressure. UBE 120/004101 GLP, unpublished LUF2001-17	Y	UBE
Brielbeck, B. Marx, D.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8	2000	Revision of the final report AB 95510-FO-012 Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at room temperature and after storage at 35 °C and 0 °C. AB 95510-FO-012rev GLP, unpublished PHY2001-66	Y	ASU
Brielbeck, B. Marx, D.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8; AIIIA-5.1	1999	Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at Room Temperature and after Storage at 35 °C and 0 °C. AB 95510-FO-012 GLP, unpublished PHY2000-572	Y	ASU
Brielbeck, B. Marx, D.	AIIIA-2.7	1999	Determination of the two years storage stability of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820) at ambient temperature. PP 95510-PC-032 GLP, unpublished PHY2000-574	Y	ASU

[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]
Chalker, M.H. et al.	AIIA-2.9; AIIA-7.2.1.1	1997	Hydrolysis under laboratory conditions. UBE 58/971769 GLP, unpublished WAS2000-554	Y	UBE
Elsom, L.F. et al.	AIIA-2.9; AIIA-7.2.1.2	1998	Photolytic degradation in water. UBE 57/973942 GLP, unpublished LUF2000-464	Y	UBE
Flack, I.	AIIA-2.1; AIIA-2.2; AIIA-2.4; AIIA-2.5; AIIA-2.6; AIIA-2.7; AIIA-2.8; AIIA-2.11; AIIA-2.13; AIIA-2.14; AIIA-2.15	1998	UR-50601: Physical and chemical properties. UBE 047/972099 GLP, unpublished CHE2000-1160	Y	UBE
Flack, I.	AIIIA-2.2; AIIIA-2.3	1999	ASU 95 510 H (UBH-820/IPU); Physical and chemical properties (explosive properties, flash point and autoflammability). STJ 017/993827 GLP, unpublished PHY2000-573	Y	ASU
Frauen, M. Stähler, O.	AIIIA-2.7	2001	Final Report of the two Years' Storage Stability of ASU 95 510 H (500 g/l Isoproturon + 85 g/l UBH-820) at ambient Temperature. AB 95510-PC-032 GLP, unpublished PHY2001-257	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

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]
Anderl	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2,5 l/ha). MZ99HO15401.03BI not GLP, unpublished BIO2001-111	Y	ASU
Anderl	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3 l/ha). MZ99HO15401.04BI not GLP, unpublished BIO2001-110	Y	ASU
Anderl	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3 l/ha). MZ99HO15501.03OP not GLP, unpublished BIO2001-105	Y	ASU
Anderl	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in W.-Gerste (3l/ha). MZ97H015201.04 BI not GLP, unpublished BIO2001-57	Y	ASU
Anderl	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2l/ha). MZ97H015801.05MT not GLP, unpublished BIO2001-63	Y	ASU
Anderl	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2 l/ha). MZ987H016691.03MT not GLP, unpublished BIO2001-86	Y	ASU
Anderl	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3l/ha). MZ97H016901.03KL not GLP, unpublished BIO2001-70	Y	ASU
Anderl	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). MZ97H015401.03AZ not GLP, unpublished BIO2001-61	Y	ASU

[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]
Anderl	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3 l/ha). MZ99HO15501.04OP not GLP, unpublished BIO2001-104	Y	ASU
anonym	AIIIA-6.0	2002	NL: Herbicidal activity of the metabolite UR-50604. not GLP, unpublished BIO2002-678	Y	TSU
Anonym	AIIA-3.7	1997	Safety Data Sheet for ISOPROTORON TECHNICAL MICRONIZED. 1393 not GLP, unpublished CHE2000-1230	Y	ASU
Anonym	AIIA-3.7	2000	Material Safety Data Sheet for UBH-820, Beflubutamid (proposed). H-98-10 not GLP, unpublished CHE2000-1229	Y	UBE
Anonym	AIIIA-3.7	1997	Material Safety Data Sheet for ASU 95 510 H. not GLP, unpublished CHE2000-1225	Y	ASU
Anonym	AIIIA-4.4; AIIIA-4.5; AIIIA-4.6	1999	Material Safety Data Sheet - Herbaflex. not GLP, unpublished CHE2000-1130	Y	ASU
Anonym	AIIIA-6.0	2000	Report Herbicidal activity of the metabolite UR-50604. not GLP, unpublished BIO2000-432	Y	ASU
Anonym	AIIIA-6.0	2000	Wirksamkeitsunterlagen zum Mittel Herbaflex. not GLP, unpublished BIO2000-333	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3 l/ha). HA-HW 1999-012 not GLP, unpublished BIO2001-107	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2 l/ha). OL/HA 99/1-030 not GLP, unpublished BIO2001-121	Y	ASU

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Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (2 l/ha). OL/HA 99/1-029 not GLP, unpublished BIO2001-122	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Barley. FSTA 994899 99 H CP ST 29 not GLP, unpublished BIO2001-126	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Barley. FSTA 993735 99 H CP ST 30 not GLP, unpublished BIO2001-128	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Soft Wheat. FSTA 994906 99 HCP ST 32 not GLP, unpublished BIO2001-129	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Soft Wheat. FSTA 993722 99 H CP ST 33 not GLP, unpublished BIO2001-130	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Wheat. 99 H TR ST 09 not GLP, unpublished BIO2001-131	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Wheat. 99 H TR ST 10 not GLP, unpublished BIO2001-132	Y	ASU
Anonym	AIIIA-6.2	1998	Herbicide Trial on Winter Barley. FSTA 904028 98 H CP ST 05 not GLP, unpublished BIO2001-143	Y	ASU
Anonym	AIIIA-6.2	1998	Herbicide Trial on Winter Barley. FSTA 983913 98 H CP ST 08 not GLP, unpublished BIO2001-144	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Soft Wheat. FSTA 993714 99 H CP ST 02 not GLP, unpublished BIO2001-145	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Soft Wheat. FSTA 993728 99 H CP ST 27 not GLP, unpublished BIO2001-146	Y	ASU

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]
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Soft Wheat. FSTA 994913 99 H CP ST 28 not GLP, unpublished BIO2001-147	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Soft Wheat. FSTA 996269 99 H CP ST 31 not GLP, unpublished BIO2001-148	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Soft Wheat. 99 H CP ST 13 not GLP, unpublished BIO2001-151	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Soft Wheat. 99 H CP ST 14 not GLP, unpublished BIO2001-152	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Soft Wheat. 99 H CP ST 15 not GLP, unpublished BIO2001-153	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Soft Wheat. 99 H CP ST 16 not GLP, unpublished BIO2001-154	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Barley. 99 H CP ST 17 not GLP, unpublished BIO2001-155	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Barley. 99 H CP ST 18 not GLP, unpublished BIO2001-156	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Barley. 99 H CP ST 19 not GLP, unpublished BIO2001-157	Y	ASU
Anonym	AIIIA-6.2	1999	Post-Emergence Herbicide Trial on Barley. 99 H CP ST 20 not GLP, unpublished BIO2001-158	Y	ASU

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]
Anonym	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in W.-Gerste (3l/ha). OL/HA 96/1-002 not GLP, unpublished BIO2001-56	Y	ASU
Anonym	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). OL/HA 96/1-003 not GLP, unpublished BIO2001-60	Y	ASU
Anonym	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). OL/HA 97/1-039 not GLP, unpublished BIO2001-68	Y	ASU
Anonym	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3l/ha). OL/HA 97/1-038 not GLP, unpublished BIO2001-71	Y	ASU
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2l/ha). HA03/98D/321 not GLP, unpublished BIO2001-75	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Soft Wheat. FSTA 995992 98 H CP ST 03 not GLP, unpublished BIO2001-78	Y	ASU
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2l/ha). HA03/98C/231 not GLP, unpublished BIO2001-79	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Soft Wheat. FSTA 984041 98 H CP ST 04 not GLP, unpublished BIO2001-80	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficasy oh Winter Barley. FSTA 995999 98 H CP ST 06 not GLP, unpublished BIO2001-81	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Efficacy on Winter Barley. FSTA 984037 98 H CP ST 07 not GLP, unpublished BIO2001-82	Y	ASU

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]
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2 l/ha). HR-5-ASU-103-9835HGZ200 not GLP, unpublished BIO2001-89	Y	ASU
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2 l/ha). HA-HW 1998-024 not GLP, unpublished BIO2001-90	Y	ASU
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2 l/ha). HA 12/98D/321 not GLP, unpublished BIO2001-91	Y	ASU
Anonym	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (2 l/ha). OL/HA 98/1-021 not GLP, unpublished BIO2001-93	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (3 l/ha). HA-HW 1999-013 not GLP, unpublished BIO2001-94	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (2 l/ha). OL/HA 98/1-013 not GLP, unpublished BIO2001-95	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (3 l/ha). HA-HW 1999-010 not GLP, unpublished BIO2001-97	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Wheat. 99 H CP ST 21 not GLP, unpublished BIO2001-133	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Wheat. 99 H CP ST 22 not GLP, unpublished BIO2001-134	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Barley. 99 H CP ST 23 not GLP, unpublished BIO2001-135	Y	ASU

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]
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Barley. 99 H CP ST 11 not GLP, unpublished BIO2001-136	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Barley. 99 H CP ST 12 not GLP, unpublished BIO2001-137	Y	ASU
Anonym	AIIIA-6.2	1999	Herbicide Trial on Winter Barley. 99 H CP ST 24 not GLP, unpublished BIO2001-138	Y	ASU
Anonym	AIIIA-6.2	1998	Herbicide Trial on Winter Soft Wheat. FSTA 984022 98 H CP ST 01 not GLP, unpublished BIO2001-140	Y	ASU
Anonym	AIIIA-6.2	1998	Herbicide Trial on Winter Soft Wheat. FSTA 983920 98 H CP ST 25 not GLP, unpublished BIO2001-141	Y	ASU
Anonym	AIIIA-6.2	1998	Herbicide Trial on Winter Soft Wheat. FSTA 983928 98 H CP ST 26 not GLP, unpublished BIO2001-142	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2,5 l/ha). HA-HW 1999-014 not GLP, unpublished BIO2001-101	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2,5 l/ha). HA-HW 1999-012 not GLP, unpublished BIO2001-106	Y	ASU
Anonym	AIIIA-6.2	1999	Prüfbericht zuw Wirksamkeit von ASU 95510 H in Winterweizen (3 l/ha). HA-HW 1999-014 not GLP, unpublished BIO2001-100	Y	ASU
Anonym	AIIIA-6.7	2001	Appendix II, Preliminary user's Instruction for Herbaflex. not GLP, unpublished BIO2001-169	Y	ASU
Anonym	AIIIA-6.7	2000	Vorläufige Gebrauchsanleitung Herbaflex. not GLP, unpublished BIO2001-165	Y	ASU

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]
Bär, H.	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2 l/ha). HA 11/98/1 L not GLP, unpublished BIO2001-85	Y	ASU
Böttger	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2 l/ha). HR-H-99-ASU-23 not GLP, unpublished BIO2001-120	Y	ASU
Böttger	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2 l/ha). HR-H-99-ASU-24 not GLP, unpublished BIO2001-119	Y	ASU
Broschewitz	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2l/ha). HRo-WRo-H-1-98-1 not GLP, unpublished BIO2001-74	Y	ASU
Broschewitz	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2l/ha). HRo-WG-H-1-98-1 not GLP, unpublished BIO2001-76	Y	ASU
Broschewitz	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (2 l/ha). HRo-Triticale-H-1-98-5 not GLP, unpublished BIO2001-92	Y	ASU
Broschewitz	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2l/ha). HRo-WW-H-1-98-2 not GLP, unpublished BIO2001-84	Y	ASU
Broschewitz	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Triticale (2l/ha). Hro-Triticale H-1-98-1 not GLP, unpublished BIO2001-72	Y	ASU
Ceynowa	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2l/ha). 97.H.W.L.003-3 not GLP, unpublished BIO2001-59	Y	ASU

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]
Ceynowa	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). 97.H.W.L.003-5 not GLP, unpublished BIO2001-66	Y	ASU
Ceynowa	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 955510 H in W.- Gerste (2 l/ha). 97.H.W.L.004-3 not GLP, unpublished BIO2001-55	Y	ASU
Dexheimer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterroggen (2 l/ha). FO/HA 99030 not GLP, unpublished BIO2001-98	Y	ASU
Dexheimer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintertriticale (2 l/ha). FO/HA 99029 not GLP, unpublished BIO2001-96	Y	ASU
Fiebig, S.	AIIIA-6.1; AIIIA-6.6.1	2002	NL: ASU 92530 H: Standardized Bioassay for the Determination of ED-10 and ED-50-values for Herbicides an Following Crops in Soil. GLP, unpublished BIO2002-347	Y	TSU
Frosch	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 in Winterweizen (2 l/ha). 9912-17 not GLP, unpublished BIO2001-99	Y	ASU
Funaki, E., Okada, T.	AIIA-3.5	2001	Herbicidal Activity of the metabolite UR-50604. not GLP, unpublished BIO2001-53	Y	UBE
Gleser	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2 l/ha). 99.H.G.K.303-14 not GLP, unpublished BIO2001-109	Y	ASU
Gleser	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2,5 l/ha). 99 H.W.H.118-4 not GLP, unpublished BIO2001-103	Y	ASU

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]
Gleser	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3 l/ha). 99 H.W.H.118-4 not GLP, unpublished BIO2001-102	Y	ASU
Günnigmann, A.	AIIIA-6.7	2000	Appendix I-2, Preliminary screening trial to test phytotoxicity to oil seed rape as a succeeding crop with ASU 95510 H (85 g/l beflubutamid + 500 g/l isoproturon) and ASU 92530 H (500 g/l beflubutamid). not GLP, unpublished BIO2001-161	Y	ASU
Häussler, W.	AIIIA-6.7	1993	Appendix I-1, Field trials using UBH820 for pre- and post-emergence control of weeds in cereals and oilseed rape. 93/501 not GLP, unpublished BIO2001-160	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Roggen (3 l/ha). H99BIR01 not GLP, unpublished BIO2001-118	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Roggen (3 l/ha). H99CVR07 not GLP, unpublished BIO2001-115	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Roggen (3 l/ha). H99CVR04 not GLP, unpublished BIO2001-116	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Roggen (3 l/ha). H99BIR02 not GLP, unpublished BIO2001-117	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Weizen (3 l/ha). H99FRW01 not GLP, unpublished BIO2001-114	Y	ASU

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]
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3 l/ha). H99SEG01 not GLP, unpublished BIO2001-113	Y	ASU
Meierhofer	AIIIA-6.2	1999	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (3 l/ha). H99SEG02 not GLP, unpublished BIO2001-112	Y	ASU
Meierhofer	AIIIA-6.7	1999	Appendix I-5, Individual trial assessment report on herbicide trials, Report No. H99FRW01, H99SEG01, H99SEG02, H99BIR01, H99BIR02, H99CVR04, H99CVR07. H99FRW01, H99SEG01, H99SEG02, H99BIR01, not GLP, unpublished BIO2001-164	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1998	Determination of Efficacy for Control of Broadleaf Weeds in Cereals. 98003/FI-EHCE not GLP, unpublished BIO2001-77	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1998	Efficacy against Grass Weeds and Broadleaf Weeds in Winter Cereals (Winter Wheat and Winter Barley) in France, (2 Sites in Southern France and 2 Sites in Northern France), Trial No. F97025E, F97026E, F97027E, F97028E. 97222/F1-EHCE not GLP, unpublished BIO2001-139	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1997	ASU 95510 H - Efficacy against Weeds in Winter Cereals (including Durum) in Italy (4 Sites) with Regards to Grass Weeds and Broadleaf Weeds, Trial No. I97001E, I97002E, I97003E, I97004E. 97005/I1-EHCE not GLP, unpublished BIO2001-149	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1998	ASU 95510 H - Determination of Efficacy for Control of Broadleaf Weeds in Cereals, 4 Sites in Italy 1998, Trial No. I98010E, I98011E, I98012E, I98013E. 98003/I1-EHCE not GLP, unpublished BIO2001-150	Y	ASU

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]
Oberwalder, Chr.	AIIIA-6.2	1998	Determination of Efficacy for Control of Broadleaf Weeds in Cereals, Four Sites in France 1998, Trial No. F989012E, F98013E, F98014E, F98015E. 98003/F1-EHCE not GLP, unpublished BIO2001-125	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1998	Efficacy against Grass Weeds and Broadleaf Weeds in Winter Cereals (Winter Wheat and Winter Barley) in France (2 Sites in Southern France, 2 Sites in Northern France), Trial No. F97025E, F97026E, F97027E, F97028E. 97222/F1-EHCE not GLP, unpublished BIO2001-124	Y	ASU
Oberwalder, Chr.	AIIIA-6.2	1998	Determination of Efficacy for Control of Broadleaf Weeds in Cereals, Four Sites in Great Britain 1998. 98003/GB1-EHCE not GLP, unpublished BIO2001-123	Y	ASU
Okada, T., Funaki, E.	AIIIA-6.7	1999	Appendix I-3, Report - The terrestrial plant toxicity study of UR -50601. not GLP, unpublished BIO2001-162	Y	UBE
Pfeifer	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintertriticale (2l/ha). HA4/98C/231 not GLP, unpublished BIO2001-73	Y	ASU
Pfeifer	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). HA3/97C/231 not GLP, unpublished BIO2001-67	Y	ASU
Stähler- anonym	AIIIA-6.3	2002	NL: Information on the occurence or possible occurence of the developement of resistance. not GLP, unpublished BIO2002-348	Y	TSU
Stähler, G., Günnigmann, A.	AIIIA-6.7	2000	Efficacy of the herbicide Herbaflex used for control of weeds in winter cereals in Southern Europe (Italy, Spain, Southern France). not GLP, unpublished BIO2001-166	Y	ASU

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]
Stähler, G., Günnigmann, A.	AIIIA-6.7	2000	Efficacy of the herbicide HERBAFLEX used for control of weeds in winter cereals in Northern Europe (Germany, UK, Northern France). not GLP, unpublished BIO2001-159	Y	ASU
Steck	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (2 l/ha). MN/HA 98 142 not GLP, unpublished BIO2001-87	Y	ASU
Steck	AIIIA-6.2	1998	Prüfbericht zur Wirksamkeit von ASU 95510 H in Wintergerste (2 l/ha). MN/HA 98076 not GLP, unpublished BIO2001-88	Y	ASU
Steck	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Winterweizen (3l/ha). MN/HA 97 159 not GLP, unpublished BIO2001-62	Y	ASU
Steck	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in Sommergerste (2l/ha). MN/HA 97 152 not GLP, unpublished BIO2001-69	Y	ASU
Steck	AIIIA-6.2	1997	Prüfbericht zur Wirksamkeit von ASU 95510 H in W.-Gerste (4l/ha). MN/HA 97 071 not GLP, unpublished BIO2001-58	Y	ASU
Takamura, S., Obata, T.	AIIIA-6.7	1999	Appendix I-4, The pesticidal evaluation study of UR - 50601 -The result of first screening test. not GLP, unpublished BIO2001-163	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

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]
Betteley, J. M. T.	AIIA-4.2.3; AIIIA-5.2	1997	Development and Validation of a Method of Analysis for the Determination of UR-50601 in Water (including Drinking Water, Surface Water and Ground Water) UBE 054/972311. not GLP, unpublished MET2000-484	Y	ASU
Betteley, J.M.T.	AIIA-1.10; AIIA-1.11; AIIA-4.1	1999	UR-50601: Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 32/994457 GLP, unpublished CHE2000-1132	Y	UBE
Brielbeck, B. and Marx, D.	AIIA-4.2.1; AIIIA-5.2	1999	Validation of the Analytical Method for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Cereal (Green Plant, Grain and Straw) Study No. RU798, Analytical Method No. AM-RU-6998 Final Report AB 95510-GM-002A. not GLP, unpublished MET2000-473	Y	ASU
Brielbeck, B. and Marx, D.	AIIA-4.2.1; AIIIA-5.2	1998	Validation of the Analytical Method for the Determination of UBH-820 in Cereals (harvest values) Study No. RU0497, Analytical Method No. AM-RU-3997 Final Report AB 95510-GM-002A. not GLP, unpublished MET2000-467	Y	ASU
Brielbeck, B. and Marx, D.	AIIIA-5.1	1999	Validation of the Analytical Method for the Determination of IPU and UBH-820 in ASU 95 510 H. not GLP, unpublished CHE2000-1131	Y	ASU

[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]
Brielbeck, B. Marx, D.	AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8; AIIIA-5.1	1999	Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at Room Temperature and after Storage at 35 °C and 0 °C. AB 95510-FO-012 GLP, unpublished PHY2000-572	Y	ASU
Flack, I.	AIIA-4.2.4; AIIIA-5.2	2000	Development and Validation of a Method of Analysis in Air UBE 104/994126. not GLP, unpublished MET2000-486	Y	ASU
Harper, H.	AIIA-4.2.1; AIIIA-5.2	2000	UR-50601: An Independent Laboratory Validation of Analytical Method AB 955510-GM-002B, Developed by Stähler Agrochemie, for the Determination of Residues in Cereal (Grain, Green Plant and Straw) Report No. STJ 019/002981. not GLP, unpublished MET2000-474	Y	ASU
Todd, M.	AIIA-4.2.3; AIIIA-5.2	2001	UR-50601 - Validation of a Confirmatory Method of Analysis for the Determination of UR-50601 in Surface Water Report Amendment 1, UBE 119/004365. not GLP, unpublished MET2001-167	Y	ASU
Todd, M. A.	AIIA-4.2.2; AIIIA-5.2	2000	UR-50601: The Validation of Analysis for the Determination of Residues of UR-50601 and UR-50604 in Soil Report No. UBE 100/994745. not GLP, unpublished MET2000-483	Y	ASU UBE
Todd, M. A.	AIIA-4.2.3; AIIIA-5.2	2000	UR-50601 - Validation of a Confirmatory Method of Analysis for the Determination of UR-60601 in Surface Water Report No. UBE 119/004365. not GLP, unpublished MET2001-46	Y	ASU

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]
Wittig, A.	AIIA-4.2.2; AIIIA-5.2	2000	UR-50601 (Beflubutamid): Validation of an Analytical Method for the Determination of Residues in Soil Final Report PR00/014-2. not GLP, unpublished MET2001-45	Y	ASU
Wittig, A.	AIIA-4.2.2; AIIIA-5.2	2001	UR-50601 (Beflubutamid): Validation of an Analytical Method for the Determination of Residues in Soil - Storage Stability - Final Report PR00/014, Part 2. not GLP, unpublished MET2001-205	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

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]
Adams, K.	AIIA-5.4.1	1998	UR-50601: Mammalian cell mutation assay. UBE 046/971304 GLP, unpublished TOX2000-1555	Y	UBE
Allan, S.A.	AIIA-5.2.6	1996	UR-50601: Skin sensitisation in the guinea-pig (incorporating a positive control using formalin). UBE 3/951150/SS GLP, unpublished TOX2000-1545	Y	UBE
Anonym	AIIA-5.9	1999	Manufacturing health report. not GLP, unpublished TOX2000-1865	Y	UBE
Barker, M.H.	AIIA-5.3.1	1996	UR-50601: Toxicity to rats by repeated dietary administration for 4 weeks. UBE 11/952715 GLP, unpublished TOX2000-1546	Y	UBE
Barker, M.H.	AIIA-5.3.2	1997	UR-50601: Preliminary toxicity study in dogs by repeated oral administration for 2 weeks. UBE 39/971150 GLP, unpublished TOX2000-1551	Y	UBE
Barker, M.H.	AIIA-5.3.2	1997	UR-50601: Toxicity to dogs by repeated oral administration for 13 weeks. UBE 40/973046 GLP, unpublished TOX2000-1550	Y	UBE
Barker, M.H.	AIIA-5.3.2	1997	UR-50601: Palatability study in mice by dietary administration for 2 weeks. UBE 33/963913 GLP, unpublished TOX2000-1549	Y	UBE
Barker, M.H.	AIIA-5.3.2	1997	UR-50601: Toxicity to mice by dietary administration for 13 weeks. UBE 34/971905 GLP, unpublished TOX2000-1548	Y	UBE

[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]
Barker, M.H.	AIIA-5.3.2	1999	UR-50601: Toxicity study by oral capsule administration to beagle dogs for 52 weeks. UBE 072/992120 GLP, unpublished TOX2000-1552	Y	UBE
Barker, M.H.	AIIA-5.3.2	1997	UR-50601: Toxicity to rats by dietary administration for 13 weeks. UBE 31/963207 GLP, unpublished TOX2000-1547	Y	UBE
Barker, M.H.	AIIA-5.5	2000	UR-50601: Carcinogenicity study by dietary administration to CD-1 mice for 80 weeks. UBE 070/993289 GLP, unpublished TOX2000-1558	Y	UBE
Barker, M.H.	AIIA-5.5	2000	UR-50601: Potential tumorigenic and toxic effects in prolonged dietary administration to rats. UBE 044/993288 GLP, unpublished TOX2000-1557	Y	UBE
Blagden, S.M.	AIIA-5.2.3	1995	UR-50601: Acute inhalation toxicity (nose only) study in the rat. 512/028 GLP, unpublished TOX2000-1542	Y	UBE
Coleman, D.G.	AIIIA-7.1.6	1999	ASU 95 510 H: Skin sensitization to the guinea-pig (Magnusson & Kligman Method). STJ 013/984395/SS GLP, unpublished TOX2000-1572	Y	ASU
Dean, G.M.	AIIA-5.1	2000	UR-50601: Metabolism in the rat (main study). UBE 079/984961 GLP, unpublished TOX2000-1538	Y	UBE
Funaki, E.	AIIA-5.5	2002	UR-50601: Carcinogenicity study by dietary administration to CD-1 mice for 80 weeks (UBE 070/993289). not GLP, unpublished TOX2002-702	Y	TSU
Johnson, A.L.	AIIA-5.4.1	1995	UR-50601: An in vitro test for induction of chromosome damage: Cytogenetic study in cultured human peripheral lymphocytes. 95/UED001/0580 GLP, unpublished TOX2000-1554	Y	UBE

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]
Jones, E.	AIIA-5.4.1	1995	UR-50601: Bacterial mutation assay. UBE 4/951063 GLP, unpublished TOX2000-1553	Y	UBE
Mason, Ch.E.	AIIA-5.4.2	1998	UR-50601: Mouse micronucleus test. UBE 084/983640 GLP, unpublished TOX2000-1556	Y	UBE
Mason, St.J.	AIIIA-7.1.1	1999	ASU 95 510 H: Acute oral toxicity to the rat. STJ 009/984079/AC GLP, unpublished TOX2000-1567	Y	ASU
Mason, St.J.	AIIIA-7.1.2	1999	ASU 95 510 H: Acute dermal toxicity to the rat. STJ 010/984078/AC GLP, unpublished TOX2000-1568	Y	ASU
McEwen, A.B.	AIIA-5.1	1998	UR-50601: Metabolism in the rat (pilot study). UBE 35/971187 GLP, unpublished TOX2000-1539	Y	UBE
Myers, D.P.	AIIA-5.6.1	1997	UR-50601: Preliminary study of effects on reproductive performance in CD rats treated by dietary administration. UED 008/973099 GLP, unpublished TOX2000-1561	Y	UBE
Myers, D.P.	AIIA-5.6.1	1999	UR-50601: Study of reproductive performance in CD rats treated continuously through two successive generations by dietary administration. UBE 073/992298 GLP, unpublished TOX2000-1559	Y	UBE
Myers, D.P.	AIIA-5.6.2	1998	UR-50601: A pilot study of the effect on the female rabbit (gavage administration). UBE 9/951721 GLP, unpublished TOX2000-1566	Y	UBE
Myers, D.P.	AIIA-5.6.2	1996	UR-50601: A preliminary study of the effect on pregnancy of the rabbit (gavage administration). UBE 10/952279 GLP, unpublished TOX2000-1565	Y	UBE

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]
Myers, D.P.	AIIA-5.6.2	1995	UR-50601: A preliminary study of the effect on pregnancy of the rat (gavage administration). UBE 8/951331 GLP, unpublished TOX2000-1563	Y	UBE
Parcell, B.I.	AIIA-5.2.4	1995	UR-50601: Skin irritation to the rabbit. UBE 1/950843/SE GLP, unpublished TOX2000-1543	Y	UBE
Parcell, B.I.	AIIA-5.2.5	1995	UR-50601: Eye irritation to the rabbit. UBE 2/951189/SE GLP, unpublished TOX2000-1544	Y	UBE
Parcell, B.I.	AIIIA-7.1.4	1999	UR-50601/UBH-820 + IPU: Skin irritation to the rabbit. STJ 011/984119/SE GLP, unpublished TOX2000-1570	Y	ASU
Parcell, B.I.	AIIIA-7.1.5	1999	ASU 95 510 H: Eye irritation to the rabbit. STJ 012/984105/SE GLP, unpublished TOX2000-1571	Y	ASU
Paul, G.R.	AIIIA-7.1.3	1999	UR-50601/UBH-820 + IPU: Acute inhalation study in rats (4-hour exposure). STJ 008/984506 GLP, unpublished TOX2000-1569	Y	ASU
Snell, K.	AIIA-5.2.1	1995	UR-50601: Acute oral toxicity (Limit Test) in the rat. 512/26 GLP, unpublished TOX2000-1540	Y	UBE
Snell, K.	AIIA-5.2.2	1995	UR-50601: Acute dermal toxicity (Limit Test) in the rat. 512/27 GLP, unpublished TOX2000-1541	Y	UBE
Waterson, L.A.	AIIA-5.6.2	1997	UR-50601: A study of the effects on pregnancy of the rabbit (gavage administration). UBE 43/971457 GLP, unpublished TOX2000-1564	Y	UBE

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]
Waterson, L.A.	AIIA-5.6.2	1997	UR-50601: A study of the effect on pregnancy of the rat (gavage administration). UBE 038/971422 GLP, unpublished TOX2000-1562	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

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]
Brielbeck, B., Marx, D.	AIIA-6.3; AIIIA-8.2	2000	Final Report AB 95510-RU-010D Residue Analysis for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Spring cereals (Green plants, Grain and Straw) after Treatment with 3 l/ha ASU 95510 (85 g/l UBH-820 (UR-50601) + 500 g/l Isoproturon) at Spring 1999 Protocol No.: 95510-RU-010D Study No.: RU0798. AB 95510-RU-010D GLP, unpublished RIP2000-1895	Y	ASU
Brielbeck, B., Marx, D.	AIIA-6.3; AIIIA-8.2	1999	Final Report AB 95510-RU-010C Residue Analysis for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Summer cereal (Green plant, Grain and Straw) and Winter cereal (Green plant, Grain and Straw) after Treatment with 3 l/ha ASU 95510 H (85 g/l UBH-820 (UR-50601) + 500 g/l Isoproturon) at Spring 1998 Protocol No.: 95510-RU-010C Study No.: RU0789. AB 95510-RU-010C GLP, unpublished RIP2000-1894	Y	ASU
Brielbeck, B., Marx, D.	AIIA-6.3; AIIIA-8.2	1998	Final Report AB 95510-RU-010 Residue Analysis of UBH-820 in Cereals (Harvest Values) Protocol No.: 95510-RU-010 Study No.: RU0497. AB 95510-RU-010 GLP, unpublished RIP2000-1893	Y	ASU
Elsom, L.F.	AIIA-6.2; AIIIA-8.1	1998	C14-UR-50601 Metabolism in the lactating goat. UBE 55/973900 GLP, unpublished RIP2000-1892	Y	UBE

[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]
Haynes, L.M., Knight, L.J.L., Mayo, B.C.	AIIA-6.1; AIIIA-8.1	2000	UR-50601 Metabolism in wheat (main study). UBE 66/974473 GLP, unpublished RIP2000-1890	Y	UBE
McEwen, A.B., Mellor, S.J., Knight, L.J.L., Mayo, B.C.	AIIA-6.1; AIIIA-8.1	1998	UR-50601 Metabolism in wheat (pilot study). UBE 037/973537 GLP, unpublished RIP2000-1891	Y	UBE
Mellor, S.J., Mayo, B.C.	AIIA-6.6; AIIIA-8.5	2000	UR-50601 Confined accumulation in rotational crops. UBE 083/992872 GLP, unpublished RIP2000-1897	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

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]
Aikens, P.J. et al.	AIIA-7.1.2	1999	Adsorption/desorption on soil. UBE 086/992243 GLP, unpublished BOD2000-1130	Y	UBE
Aikens, P.J. et al.	AIIA-7.1.2	1997	Adsorption/desorption on soil. UBE 42/971616 GLP, unpublished BOD2000-1129	Y	UBE
Beulke, S. and Brown, C.D.	AIIIA-9.2.1	2000	Estimation with PELMO-3.00 of expected concentrations of UR-50601 and UR-50604 in the groundwater (PECgw). - not GLP, unpublished BOD2000-1137	Y	ASU
Beulke, S. and Brown, C.D.	AIIIA-9.2.3	2000	Estimation with PRZM-3.12 of expected concentrations of UR-50601 in surface waters (PECsw) arising from losses via surface runoff and erosion. - not GLP, unpublished WAS2000-561	Y	ASU
Chalker, M.H. et al.	AIIA-2.9; AIIA-7.2.1.1	1997	Hydrolysis under laboratory conditions. UBE 58/971769 GLP, unpublished WAS2000-554	Y	UBE
Dean, G.M. and Mayo, B.C.	AIIA-7.1.1.1.1; AIIA-7.1.1.2.1; AIIIA-9.1	1997	Aerobic soil metabolism (Pilot study). UBE 036/97729 GLP, unpublished BOD2000-1131	Y	UBE
Dean, G.M. and Mayo, B.C.	AIIA-7.1.1.2.1; AIIIA-9.1	1999	Rate of degradation in three soils. UBE 071/982852 GLP, unpublished BOD2000-1135	Y	UBE
Dean, G.M. et al.	AIIA-7.1.1.1.1; AIIA-7.1.1.2.1; AIIIA-9.1	1999	Aerobic soil metabolism (Main study). UBE 67/983000 GLP, unpublished BOD2000-1132	Y	UBE

[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]
Dean, G.M. et al.	AIIA-7.1.1.1.2	1998	Soil photolysis. UBE 077/983818 GLP, unpublished BOD2000-1134	Y	UBE
Dean, G.M. et al.	AIIA-7.1.1.1.2; AIIA-7.1.1.2.1; AIIIA-9.1	1998	Anaerobic soil metabolism. UBE 076/982926 GLP, unpublished BOD2000-1133	Y	UBE
Elsom, L.F. et al.	AIIA-2.9; AIIA-7.2.1.2	1998	Photolytic degradation in water. UBE 57/973942 GLP, unpublished LUF2000-464	Y	UBE
Elsom, L.F. et al.	AIIA-7.2.1.3.2	1999	Aerobic aquatic degradation study. UBE 069/983037 GLP, unpublished WAS2000-555	Y	UBE
Heydkamp, I.	AIIA-7.1.1.2.2	2001	Soil dissipation study with Herbafles in Germany. Rep.No. VP00-1-35 GLP, unpublished BOD2001-325	Y	ASU
Millais, A.J. and Kirkpatrick, D.	AIIA-7.2.1.2	1999	Aqueous photolysis. UBE 087/992694 GLP, unpublished LUF2000-465	Y	UBE
Schneider, V.	AIIA-7.1.1.2.2	2001	Determination of residue od UR 50601 (Beflubutamid) in soil dissipation study with Herbaflex in Germany. Rep.No. PR00/018 GLP, unpublished BOD2001-395	Y	ASU
Takamura, S.	AIIA-7.1.1.2.2; AIIA-7.1.3.3	2002	Evaluation of groundwater contamination by the metabolite UR-50604 in soil. - not GLP, unpublished BOD2002-280	Y	TSU
Takamura, S.	AIIIA-9.1.3	2002	Evaluation of groundwater contamination by the metabolite UR-50604 in soil (Refined risk assessment) Appendix 1-3. - not GLP, unpublished BOD2002-382	Y	TSU

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]
Takamura, S.	AIIIA-9.1.3	2002	PELMO simulation of UR-50601 and UR-50604 in groundwater, detailed information. - not GLP, unpublished BOD2002-281	Y	TSU
Wilson, A.	AIIA-7.1.1.2.2	2000	Terrestrial field dissipation study with ASU 95510 H (85 g/l UR + 500 g/l Isoproturon) applied to bare soil in Spain, United Kingdom and Germany in 1998/1999. UR-50601 not GLP, unpublished BOD2000-1332	Y	UBE
Wilson, A.	AIIA-7.1.1.2.2; AIIIA-9.1	1999	Terrestrial field dissipation study with ASU 95 510 H (85 g/l UR-50601+500 g/l Isoproturon) applied to bare soil in Spain, United Kingdom and Germany in 1998/1999. UBE 099/002143 GLP, unpublished BOD2000-1136	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

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]
Bell, G.	AIIA-8.2.7	2000	UR-50601 To assess the toxicity to the sediment dwelling phase of the midge Chironomus riparius. UBE 097/993026 GLP, unpublished WAT2000-586	Y	UBE
Bell, G. and Hargreaves, T.L.	AIIA-8.2.2.1	2000	UR-50601:Fish Early Life Stage Toxicity Test for Fathead minnow (Pimephales promelas). UBE 098/994315 GLP, unpublished WAT2000-578	Y	UBE
Carter, J.N.	AIIA-8.5	2000	UR-50604: Effects on soil non-target micro-organisms. UBE 105/994202 GLP, unpublished BMF2000-130	Y	UBE
Corden, M.T.	AIIA-8.2.3	1999	UR-50601: Bioconcentration in Rainbow trout. UBE 085/992393 GLP, unpublished WAT2000-579	Y	UBE
Dias, N. A.	AIIIA-10.6.1.2	2001	Stefes Derosal Liquid: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. HLS 122/010062 GLP, unpublished ARW2001-44	Y	ASU
Funaki, E. and Okada, T.	AIIA-8.6; AIIIA-10.8	2001	Herbicidal activity of the metabolite UR-50604 by pre-emergence treatment. Ube Research Laboratory not GLP, unpublished PFL2001-36	Y	ASU
Funaki, E. and Okada, T.	AIIA-8.6; AIIIA-10.8	2001	Herbicidal activity of the metabolite UR-50604 by post-emergence treatment. Ube Research Laboratory not GLP, unpublished PFL2001-35	Y	ASU
Funaki, E. and Okada,T.	AIIA-8.6; AIIIA-10.8	1999	Herbicidal activity of the metabolite of UR-50604. UBE Industries, Ltd. not GLP, unpublished PFL2000-156	Y	UBE

[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]
Gray, A.P.	AIIA-8.3	1999	UR-50601: Acute toxicity to honey bees (Apis mellifera). UBE 59/972121 GLP, unpublished BIE2000-45	Y	UBE
Halsall, N.	AIIA-8.3.2	1999	UR-50601 Evaluation of the effects of pesticides on the carabid beetle Poecilus cupreus in the laboratory. UBE 092/992727 GLP, unpublished ANA2000-924	Y	UBE
Halsall, N.	AIIA-8.3.2	1999	UR-50601 Evaluation of the effects of pesticides on the green lacewing Chrysoperla carnea in the laboratory. UBE 091/994106 GLP, unpublished ANA2000-923	Y	UBE
Halsall, N.	AIIA-8.3.2	1999	UR-50601 Evaluation of the effects of pesticides on the predacious mite Typhlodromus pyri in the laboratory using the Louis & Ufer method. UBE 089/992726 GLP, unpublished ANA2000-922	Y	UBE
Halsall, N.	AIIA-8.3.2	1999	UR-50601 Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid Aphidius rhopalosiphi in the laboratory. UBE 090/994053 GLP, unpublished ANA2000-921	Y	UBE
Halsall, N.	AIIIA-10.5.1	1999	ASU 95 510 H Evaluation of the effects of pesticides on the carabid beetle Poecilus cupreus in the laboratory. STJ 007/985091 GLP, unpublished ANA2000-920	Y	ASU
Halsall, N.	AIIIA-10.5.1	1999	ASU 95 510 H Evaluation of the effects of pesticides on the green lacewing Chrysoperla carnea in the laboratory. STJ 006/984983 GLP, unpublished ANA2000-919	Y	ASU

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]
Halsall, N.	AIIIA-10.5.1	1999	ASU 95 510 H Evaluation of the effects of pesticides on the predacious mite Typhlodromus pyri in the laboratory using the Louis & Ufer method. STJ 004/992728 GLP, unpublished ANA2000-918	Y	ASU
Halsall, N.	AIIIA-10.5.1	1999	ASU 95 510 H Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid Aphidius rhopalosiphi in the laboratory. STJ 005/993424 GLP, unpublished ANA2000-917	Y	ASU
Halsall,N.	AIIIA-10.4	1999	ASU 95 510 H: Acute toxicity to honey bees (Apis mellifera). STJ002/984619 GLP, unpublished BIE2000-44	Y	ASU
Jenkins, C.A.	AIIA-8.2.1	1999	UR-50604: Acute toxicity to Fish (Rainbow trout). UBE094/992813 GLP, unpublished WAT2000-577	Y	UBE
Jenkins, C.A.	AIIA-8.2.4	1999	UR-50604 Acute toxicity to Daphnia magna. UBE096/992814 GLP, unpublished WAT2000-581	Y	UBE
Jenkins, C.A.	AIIA-8.2.4	1999	UR-50601: Acute toxicity to Daphnia magna Determination of 48-hour EC50 under static conditions. UBE62/973063 GLP, unpublished WAT2000-580	Y	UBE
Jenkins, C.A.	AIIA-8.2.5	1999	UR-50601: Daphnia magna Reproduction Test. UBE063/98388 GLP, unpublished WAT2000-582	Y	UBE
Jenkins, C.A.	AIIA-8.2.6	1999	UR-50601: Determination of 120-hour EC50 to Anabaena. UBE74/982576 GLP, unpublished WAT2000-584	Y	UBE

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]
Jenkins, C.A.	AIIA-8.2.6	1999	UR-50604 Algal growth inhibition assay. UBE095/992458 GLP, unpublished WAT2000-585	Y	UBE
Jenkins, C.A.	AIIA-8.2.6	1999	UR-50601: Determination of 72-hour EC50 to Selenastrum capricornutum. UBE64/973064 GLP, unpublished WAT2000-583	Y	UBE
Jenkins, C.A.	AIIIA-10.2.1	1999	UR-50601: Acute toxicity to Bluegill sunfish Determination of 96-hour LC50. UBE61/973904 GLP, unpublished WAT2000-576	Y	UBE
Jenkins, C.A.	AIIIA-10.2.1	1999	UR-50601: Acute toxicity to Rainbow trout Determination of 96-hour LC50. UBE60/982140 GLP, unpublished WAT2000-575	Y	UBE
Jenkins, C.A.	AIIIA-10.2.1	1999	ASU 95 510 H (UBH-820-IPU Formulation) Acute Toxicity to Fish (Rainbow trout). STJ015/994269 GLP, unpublished WAT2000-574	Y	ASU UBE
Jenkins, W.R.	AIIA-8.2.4	1999	ASU 95 510 H (UBH-820-IPU Formulation) Acute toxicity to Daphnia magna. STJ016/994270 GLP, unpublished WAT2000-589	Y	ASU UBE
Jenkins, W.R.	AIIA-8.2.6	1999	ASU 95 510 H (UBH-820-IPU Formulation) Algal growth inhibition assay (Selenastrum capricornutum). STJ014/994268 GLP, unpublished WAT2000-590	Y	ASU UBE
Jenkins, W.R.	AIIA-8.7	1998	UR-50601 Activated sludge - Respiration inhibition test. UBE065/970432 GLP, unpublished WAT2000-588	Y	UBE

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]
Johnson, A. J. and Cameron, D. M.	AIIA-8.4.1	1997	UR-50601 Acute toxicity to the earthworm. UBE 51/971234 GLP, unpublished ARW2000-147	Y	UBE
Johnson, A. J. and Cameron, D. M.	AIIIA-10.6.1.1	1998	ASU 95 510 H Acute toxicity (LC50) to the earthworm (Eisenia foetida). STJ 003/983507 GLP, unpublished ARW2000-150	Y	ASU
Johnson, A.J. and Cameron, D.M.	AIIA-8.1.3	1998	UR-50601: Effects on reproduction in bobwhite quail. UBE 50/972155 GLP, unpublished AVS2000-119	Y	UBE
Johnson, A.J., Cameron, D.M. and Dawe, I.S.	AIIA-8.1.1	1997	UR-50601: Acute toxicity (LD50) to the bobwhite quail. UBE 48/971672 GLP, unpublished AVS2000-117	Y	UBE
Kelly, C.	AIIA-8.2.8	1998	UR-50601 Higher Plant (LEMNA) Growth inhibition Test. UBE 075/982375 GLP, unpublished WAT2000-587	Y	UBE
Noack, M.	AIIIA-10.6.1.2	2001	Herbaflex: Earthworm (Eisenia fetida), effects on reproduction. Study-No.: RRR79852 GLP, unpublished ARW2001-163	Y	TSU
Okada, T. and Funaki, E.	AIIA-8.6; AIIIA-10.8	1999	The terrestrial plant toxicity study of UR-50601. UBE Industries, Ltd. not GLP, unpublished PFL2000-155	Y	UBE
Redgrave, V. A., Dias, N. A. and Cameron, D. M.	AIIIA-10.6.1.2	2000	ASU 95 510 H To determine the effects on reproduction and growth of the earthworm, Eisenia foetida. STJ 018/994008 GLP, unpublished ARW2000-151	Y	ASU

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]
Rodgers, M. H.	AIIIA-10.6.1.2	2000	ASU 95 510 H: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. STJ 020/003115 GLP, unpublished ARW2001-46	Y	ASU
Rodgers, M. H.	AIIIA-10.6.1.2	2000	UR-50601: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. UBE 115/003229 GLP, unpublished ARW2001-45	Y	ASU
Rodgers, M. H. and Cameron, D. M.	AIIA-8.4.1	2000	UR-50604 Acute toxicity (LC50) to the earthworm (Eisenia foetida). UBE 107/994388 GLP, unpublished ARW2000-148	Y	UBE
Rodgers, M. H., Dias, N. A. and Cameron, D. M.	AIIIA-10.6.1.2	2000	UR-50601 To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. UBE 106/002043 GLP, unpublished ARW2000-149	Y	UBE
Rodgers, M.H., Cameron, D.M. and Dawe, I.S.	AIIA-8.1.2	1997	UR-50601: Dietary LC50 to the bobwhite quail. UBE 49/971079 GLP, unpublished AVS2000-118	Y	UBE
Takamura, S. and Obata, T.	AIIA-8.6; AIIIA-10.8	1999	The pesticidal evaluation study of UR-50601 -The result of first screening test-. UBE Industries, Ltd. not GLP, unpublished PFL2000-154	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

Monograph

02 August 2002

Beflubutamid

Volume 3

Annex B

Summary, Scientific Evaluation and Assessment

Rapporteur Member State: Germany

Contents

Annex B

Beflubutamid

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)

TASK FORCE

Applicant:	**Contact:**
Stähler Agrochemie GmbH & Co. KG PO Box 2047 21660 Stade Germany	Ms. G. Stähler Telephone: +49 (0) 4141 920441 Telefax: +49 (0) 4141 920410 e-mail: Staehler-agro@staehler.com
UBE Industries, Ltd, Ube Building, 2-3-11, Higashi-Shinagawa, Shinagawa-Ku, Tokyo 140-8633, Japan	Mr. Seiji Takamura Telephone: +81-3-5460-3234 Telefax: +81-3-5460-3394 E-mail: 14566u@ube-ind.co.jp
Local representative UBE Europe GmbH, Immermannstrasse 65B, 40210 Düsseldorf, Germany	Mr. Yuki Nishida Telephone: +49-211-178830 Telefax: +49-211-3613297

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

Beflubutamid (ISO, proposed)

B.1.1.3 Chemical name (Annex IIA 1.4)

IUPAC: (*RS*)-*N*-benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide

CAS: 2-[4-fluoro-3-(trifluoromethyl)phenoxy]-*N*-(phenylmethyl)butanamide

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

a.s.: UR-50601, UBH-820
formulation: ASU 95 510 H (Beflubutamid/Isoproturon)

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

CAS: 113614-08-7
CIPAC: 662

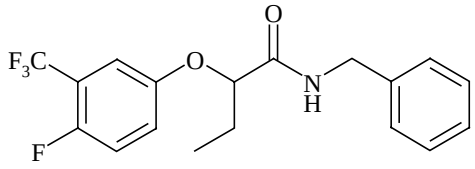
EEC: not assigned
EINECS: not assigned

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

Molecular formular: $C_{18}H_{17}F_4NO_2$ (racemate)

Molecular mass: 355.12 g/mol

Structural formula:



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

Manufacuturer:
UBE Industries, Ltd,
UBE building, 2-3-11,
Higashi-shinagawa, Shinagawa-ku,
Tokyo 140-8633,
Japan

Person to contact: as applicant (see B.1.1.1)

Manufacturing sites: Confidential information, see Annex C.

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)

≥ 970 g/kg (based on the analysis of material produced in a pilot plant)

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: Herbaflex

Code number: Plant protection product: ASU 95 510 H

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

Stähler Agrochemie
GmbH & Co. KG
P.O. Box 20 47
21660 Stade
Germany

Contact person: Gisela Stähler
Tel. No.: +49 (0) 4141 92 04 41
Fax No.: +49 (0) 4141 92 04 10

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

Suspension Concentrate (SC)

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; AIIA-1.9; AIIA-1.10; AIIA-1.11; AIIA-2.5	Anonym	1998	UR-50601: Identity (Tier II - Doc. J). GLP, unpublished CHE2000-1158	Y	UBE
AIIA-1.10; AIIA-1.11	Betteley, J.M.T.	1999	Determination of Active Ingredient, Isomeric Ratio and the Level of Twelve Impurities three Batches. UBE 102/993155 GLP, unpublished CHE2000-1297	Y	UBE
AIIA-1.10	Betteley, J.M.T.	2000	UR-50601 Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 117/004022 GLP, unpublished CHE2000-1392	Y	UBE
AIIA-1.10	Betteley, J.M.T.	2000	UR-50601 Purity and impurity determination. UBE 116/004021 GLP, unpublished CHE2000-1391	Y	UBE
AIIA-1.10	Betteley, J.M.T.	1999	Determination of Active Ingredient, Isomeric Ratio and the Level of Twelve Impurities. UBE 093/984738 GLP, unpublished CHE2000-1296	Y	UBE
AIIA-1.10; AIIA-1.11; AIIA-4.1	Betteley, J.M.T.	1999	UR-50601: Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 32/994457 GLP, unpublished CHE2000-1132	Y	UBE
AIIA-1.10; AIIA-1.11	Orgwa, T., Hase, H.	1999	Determination of Active Ingredient,and the level of twelve impurities in Lot. 950427. USA-R-96113 GLP, unpublished CHE2000-1298	Y	UBE

[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	Orgwa, T., Hase, H.	1999	Purity analysis of the active substance UR-50601 (Lot. 960725). USA-R-96175 GLP, unpublished CHE2000-1301	Y	UBE
AIIIA-1.4	Anonym	1996	Safety Data Sheet for PROXEL GXL. not GLP, unpublished BEI2000-416	Y	ASU
AIIIA-1.4	Anonym	1996	Safety Data Sheet for KELZAN. ESD 021GB 14 not GLP, unpublished BEI2000-415	Y	ASU
AIIIA-1.4	Anonym	1996	Safety Data Sheet for 1,2-PROPYLENE GLYCOL TECHN. ES 00804-B (D/E) not GLP, unpublished BEI2000-414	Y	ASU
AIIIA-1.4	Anonym	1997	Safety Data Sheet for RHODORSIL ANTISCHAUMMITTEL 426 R. not GLP, unpublished BEI2000-413	Y	ASU
AIIIA-1.4	Anonym	1997	Safety Data Sheet for SYNPERONIC 91/6. not GLP, unpublished BEI2000-412	Y	ASU
AIIIA-1.4	Anonym	1996	Safety Data Sheet for ATLOX 4913. not GLP, unpublished BEI2000-411	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

Annex B

Beflubutamid

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 beflubutamid

PAS: Pure active substance (purity: 99.98 %)
TAS: Technical active substance (purity: 97.46 %)

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	EEC A 1	Y	Melting point: 75 °C	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.1.2 (IIA 2.1)	Boiling point of purified active substance	PAS			No boiling point was observed. The as decomposes.		
B.2.1.1.3 (IIA 2.1)	Temperature of decomposition or sublimation	PAS	EEC A 2 differential scanning calorimetry	Y	Decomposition begins from 128 °C	Acceptable	Betteley, 2000 (CHE2001-558)
B.2.1.2 (IIA 2.2)	Relative density of purified active substance	PAS	EEC A 3	Y	$D_4^{20} = 1.33$	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.3.1 (IIA 2.3)	Vapour pressure of purified active substance	PAS	EEC A 4	Y	1.1×10^{-5} Pa (25°C)	Acceptable	Flack, 1998 (CHE2000-1160)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.3.1 (IIA 2.3)	Vapour pressure of metabolite UR-50604	99.92%	EEC A 4	Y	$7.38 \cdot 10^{-3}$ Pa(25°C)	Acceptable	Betteley, 2000 (LUF2001-17)
B.2.1.3.2 (IIA 2.3)	Volatility, Henry's law constant of purified active substance	n.a.	Calculation using bond contribution and group contribution	N	$1.1 \cdot 10^{-4}$ Pa m³ mol^{-1}	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.4.1 (IIA 2.4)	Appearance: physical state	PAS TAS	Visual assessment	Y	PAS: white TAS: white	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.4.2 (IIA 2.4)	Appearance: colour	PAS TAS	Visual assessment	Y	PAS: fluffy powder TAS: fluffy powder	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.4.3 (IIA 2.4)	Appearance: odour	PAS TAS	Olfactory assessment	Y	PAS: damp earth TAS: damp earth	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.5.1 (IIA 2.5)	Spectra of purified active substance	PAS	UV-VIS	Y	λ_{max} [nm] ε 281.5 2621 (neutral) 281.5 2645 (acidic) 281.5 2621 (basic)	Acceptable	Flack, 1998 (CHE2000-1160)
		PAS	IR NMR MS	Y	IR, NMR and MS spectra are consistent with the given structure of the active substance.	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.5.2 (IIA 2.5)	Spectra for impurities of toxicological, ecotoxicological or environmental concern		UV-VIS IR NMR MS		None of the impurities present in the active substance as manufactured is of toxicological, ecotoxicological or environmental significance.	Acceptable	

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.6 (IIA 2.6)	Solubility in water of purified active substance	PAS	EEC A 6	Y	The water solubility does not change significantly with pH (preliminary tests). pH 4: 3.56 µg/mL pH 7: 3.54 µg/mL pH 10: 3.45 µg/mL The solubility at different temperatures is: 10 °C: $2.30 \cdot 10^{-3}$ g/L 20 °C: $3.29 \cdot 10^{-3}$ g/L 30 °C: $5.03 \cdot 10^{-3}$ g/L	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.7 (IIA 2.7)	Solubility in organic solvents of the active substance as manufactured	TAS	EEC A 6	Y	**Solvent — Solubility (20 °C)** Acetone > 600 g/L 1,2-Dichloroethane > 544 g/L Ethyl acetate > 571 g/L Methanol > 473 g/L n-Heptane = 2.18 g/L Xylene = 106 g/L	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.8 (IIA 2.8)	Partition coefficient of purified active substance	PAS	EEC A 8 (flask method)	Y	log $P_{O/W}$ = 4.28 (21 °C)	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.9.1 (IIA 2.9)	Hydrolysis rate of purified active substance	purity > 98%	EEC C 7 [ring-U-^{14}C-phenoxy]labelling	Y	No degradation at pH 5, 7 and 9 (50°C)	Acceptable	Chalker, 1997 (WAS2000-554)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.9.2 (IIA 2.9)	Direct phototrans-formation in purified water of purified active substance	purity > 98%	SETAC [ring-U-^{14}C-phenoxy] [ring-U-^{14}C-benzylamine] labellling	Y	DT_{50} 48 d (pH 7, 25°C)	Acceptable	Elsom, 1998 (LUF2000-464)
B.2.1.9.3 (IIA 2.9)	Quantum yield of direct photodegradation	purity > 98%	SETAC [ring-U-^{14}C-phenoxy] [ring-U-^{14}C-benzylamine] labelling	Y	0.044 (pH 7)	Acceptable	Elsom, 1998 (LUF2000-464)
B.2.1.9.4 (IIA 2.9)	Dissociation constant (pK_a) of purified active substance	–	OECD 112	N	No significant dissociation expected (amide)	Acceptable	---
B.2.1.10 (IIA 2.10)	Stability in air, indirect photo-transformation	n.a.	Atkinson calculation	N	DT_{50} 3.5 hours (12 hr-day)	Acceptable	
B.2.1.11.1 (IIA 2.11)	Flammability of active substance as manufactured	TAS	EEC A 10	Y	Not highly flammable	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.11.2 (IIA 2.11)	Auto-flammability of active substance as manufactured	TAS	EEC A 16	Y	Not autoflammable	Acceptable	Flack, 1998 (CHE2000-1160)

Section (Annex point)	Study	Purity (w/w)	Method	GLP	Results	Comment / Conclusion	Reference
B.2.1.12 (IIA 2.12)	Flash point of the active substance as manufactured			Y	Not applicable		
B.2.1.13 (IIA 2.13)	Explosive properties of active substance as manufactured	TAS	EEC A 14 Koenen test fall hammer friction test	Y	There was no observable or audible reaction during the tests of mechanical sensitivity. During the thermal sensitivity test, the as ignited with a yellow to orange flame. However, no explosion or deformation of any tube was observed.	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.14 (IIA 2.14)	Surface tension	TAS	EEC A 5	Y	66.1 mN/m for a 90 % saturated aqueous solution at 20 °C	Acceptable	Flack, 1998 (CHE2000-1160)
B.2.1.15 (IIA 2.15)	Oxidising properties of active substance as manufactured	TAS	EEC A 17	Y	Not oxidising	Acceptable	Flack, 1998 (CHE2000-1160)

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

Beflubutamid (pure and technical active substance) is a white solid with damp earth odour. A melting point of 75 °C was determined for PAS. The as decomposes from 128 °C. The relative density determined at 20 °C is 1.33. The vapour pressures value is $1.1 \cdot 10^{-5}$ Pa (25 °C). The Henry´s constant at 20 °C was calculated to be $K_H = 1.1 \cdot 10^{-4}$ Pa m³ mol^{-1}. Solubility in water is about 3.5 mg/L without pH dependency. The test substance is soluble (>473 g/L) in acetone, dichloroethane, ethyl acetate and methanol. Lowest solubilities are observed in *n*-heptane (2.18 g/L) and xylene (106 g/L). The log P_{OW} is 4.28. According to the structure of the a.s. dissociation is unlikely. 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: Herbaflex (containing 85 g/l beflubutamid and 500 g/l isoproturon, SC)

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	Signal white	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.1.2 (IIIA 2.1)	Appearance: Odour	Olfactory assessment	Musty	Acceptable.	
B.2.2.1.3 (IIIA 2.1)	Appearance: Physical state	Visual assessment	Liquid	Acceptable.	
B.2.2.2.1 (IIIA 2.2)	Explosive properties	EEC A 14	Not explosive (1. mechanically, 2. thermally).	Acceptable.	Flack, I. (1999) PHY2000-573
B.2.2.2.2 (IIIA 2.2)	Oxidising properties		No method for liquids available. Since neither isoproturon nor beflubutamid have oxidising properties the aqueous SC formulation should be the same.	Acceptable.	
B.2.2.3.1 (IIIA 2.3)	Flash point	EEC A 9 ASTM D93-80	Up to 64 °C no flash point determined. > 64 °C sticky liquid.	Acceptable.	Flack, I. (1999) PHY2000-573
B.2.2.3.2 (IIIA 2.3)	Flammability		Not applicable.	Acceptable.	
B.2.2.3.3 (IIIA 2.3)	Auto-flammability	EEC A 15 ASTM E659-78	Up to 400 °C no auto-flammability observed.	Acceptable.	Flack, I. (1999) PHY2000-573
B.2.2.4.1 (IIIA 2.4)	Acidity/alkalinity		Not necessary due to pH-value.	Acceptable.	

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.4.2 (IIIA 2.4)	pH of a 1 % aqueous suspension	CIPAC MT 75.2	7.89 at 1 % concentration in distilled water; After accelerated storage for 12 weeks at 35 °C: 7.90 at 1 % concentration in distilled water	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.5.1 (IIIA 2.5)	Kinematic viscosity		Not applicable. Ultra low volume use is not intended for Herbaflex.	Acceptable.	
B.2.2.5.2 (IIIA 2.5)	Dynamic viscosity	OECD 114 Rotational viscometer	65.9 mPa·s at D = 439 s^{-1} and T = 20 °C After accelerated storage for 12 weeks at 35 °C: 74.4 mPa·s at D = 431 s^{-1} and T = 20 °C	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.5.3 (IIIA 2.5)	Surface tension	OECD 115 Ringtensiometer	50.3 mN/m	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.6.1 (IIIA 2.6)	Relative density	EEC A 3 Oscillating density meter	D_4^{20} = 1.1018 After accelerated storage for 12 weeks at 35 °C: D_4^{20} = 1.0973	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.6.2 (IIIA 2.6)	Bulk (tap) density		Not applicable.	Acceptable.	
B.2.2.7.1 (IIIA 2.7)	Storage stability	CIPAC MT 46	Physically and chemically stable after storage for 12 weeks at 35 °C. There is less than 2 % decrease in the active substance content. The alteration of the observed physical properties (pH range, viscosity, density, persistant foaming, suspensibility) are negligible.	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.7.2 (IIIA 2.7)	Low temperature stability	CIPAC MT 39 Visual examination	No separation or crystallisation after 7 days at 0 °C detectable.	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.7.3 (IIIA 2.7)	Shelf-life	GIFAP Monograph 17	Physically and chemically stable for 2 years. There is less than 2 % decrease in the active substance content. The alteration of the observed physical properties (pH range, density, emulsion stability) are negligible.	Acceptable.	Flack, I. (1999) PHY2000-573, Frauen, M.; Stähler, O. (2001) PHY2001-257
B.2.2.8.1 (IIIA 2.8.1)	Wettability		Not applicable.	Acceptable.	
B.2.2.8.2 (IIIA 2.8.2)	Persistant foaming	CIPAC MT 47.2	Foam after 1 min: 7 ml After accelerated storage for 12 weeks at 35 °C: Foam after 1 min: 7 ml	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.8.3.1 (IIIA 2.8.3)	Suspensibility	CIPAC MT 161	102 % After accelerated storage for 12 weeks at 35 °C: 102 %	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.8.3.2 (IIIA 2.8.3)	Spontaneity of dispersion	CIPAC MT 160	Isoproturon: 99 % Beflubutamid: 108 % After accelerated storage for 12 weeks at 35 °C: Isoproturon: 100 % Beflubutamid: 101 %	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
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 59.3	0.25 % > 10 µm 0.16 % > 50 µm 0.13 % > 75 µm	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.8.6.1 (IIIA 2.8.6)	Particle size distribution	CIPAC MT 59.3	> 99 % < 10 µm	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.8.6.2 (IIIA 2.8.6)	Dust content		Not applicable.	Acceptable.	

Section (Annex point)	Study	Method	Results	Comment/Conclusion	Reference
B.2.2.8.6.3 (IIIA 2.8.6)	Friability and attrition		Not applicable.	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		Not applicable.	Acceptable.	
B.2.2.8.8.2 (IIIA 2.8.8)	Pourability (rinsability)	CIPAC MT 148	2.23 % residue 0.17 % residue after rinsing	Acceptable.	Brielbeck, B.; Marx, D. (1999) PHY2000-572
B.2.2.8.8.3 (IIIA 2.8.8)	Dustability		Not applicable.	Acceptable.	
B.2.2.9.1 (IIIA 2.9)	Physical compatibility with other products		No tank mixtures are recommended.	Acceptable.	
B.2.2.9.2 (IIIA 2.9)	Chemical compability with other products		No tank mixtures are recommended.	Acceptable.	
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)

Herbaflex is a signalwhite suspension concentrate. It has neither explosive nor oxidising properties. There is no flash point up to 64 °C. Above 64 °C Herbaflex thickened to a paste and there has been observed no auto-flammability below 400 °C. Its pH-value of 7.9 lies within the naturally occurring 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.

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; AIIA-2.2; AIIA-2.4; AIIA-2.5; AIIA-2.6; AIIA-2.7; AIIA-2.8; AIIA-2.11; AIIA-2.13; AIIA-2.14; AIIA-2.15	Flack, I.	1998	UR-50601: Physical and chemical properties. UBE 047/972099 GLP, unpublished CHE2000-1160	Y	UBE
AIIA-2.1.3	Betteley, J.	2001	UR-50601: Boiling point UBE 123/0113654. not GLP, unpublished CHE2001-558	Y	TSU
AIIA-2.3.1	Betteley, J.	2000	UR-50604: Vapour pressure. UBE 120/004101 GLP, unpublished LUF2001-17	Y	UBE
AIIA-1.8; AIIA-1.9; AIIA-1.10; AIIA-1.11; AIIA-2.5	Anonym	1998	UR-50601: Identity (Tier II - Doc. J). GLP, unpublished CHE2000-1158	Y	UBE
AIIA-2.9; AIIA-7.2.1.1	Chalker, M.H. et al.	1997	Hydrolysis under laboratory conditions. UBE 58/971769 GLP, unpublished WAS2000-554	Y	UBE

[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-2.9; AIIA-7.2.1.2	Elsom, L.F. et al.	1998	Photolytic degradation in water. UBE 57/973942 GLP, unpublished LUF2000-464	Y	UBE
AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8	Brielbeck, B. Marx, D.	2000	Revision of the final report AB 95510-FO-012 Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at room temperature and after storage at 35 °C and 0 °C. AB 95510-FO-012rev GLP, unpublished PHY2001-66	Y	ASU
AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8; AIIIA-5.1	Brielbeck, B. Marx, D.	1999	Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at Room Temperature and after Storage at 35 °C and 0 °C. AB 95510-FO-012 GLP, unpublished PHY2000-572	Y	ASU
AIIIA-2.2; AIIIA-2.3	Flack, I.	1999	ASU 95 510 H (UBH-820/IPU); Physical and chemical properties (explosive properties, flash point and autoflammability). STJ 017/993827 GLP, unpublished PHY2000-573	Y	ASU
AIIIA-2.7	Brielbeck, B. Marx, D.	1999	Determination of the two years storage stability of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820) at ambient temperature. PP 95510-PC-032 GLP, unpublished PHY2000-574	Y	ASU
AIIIA-2.7	Frauen, M. Stähler, O.	2001	Final Report of the two Years' Storage Stability of ASU 95 510 H (500 g/l Isoproturon + 85 g/l UBH-820) at ambient Temperature. AB 95510-PC-032 GLP, unpublished PHY2001-257	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE

UBE: UBE Industries

Annex B

Beflubutamid

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

UR-50601 or beflubutamid (ISO common name proposed) as a phenoxybutamid is a herbicidally active novel substance for control of annual dicotyledonous weed species after germination of the weeds.

B.3.1.2 Effects on harmful organisms and translocation in plants

Beflubutamid is taken up mainly by the seedlings and to a lesser extent by roots and leaves. Limited translocation occurs, mainly by the symplast. UR-50601 inhibits the plant enzyme phytoene desaturase (PDS) of the carotenoid biosynthetic pathway leading to the photooxidation of chlorophyll, thus inducing typical bleaching symptoms.

Beflubutamid induces strong chlorosis of the new developing plant tissues. Subsequent to application the entire plant (costae, intercostal area and stem) starts whitening. As soon as the vegetation point is affected, the young plant ceases growing and further development is suppressed. The treated weeds decay or remain that small, that they are overgrown by the developing cereals.

B.3.1.3 Field of use

Beflubutamid will be used in order to control annual dicotyledonous weed species occuring in winter cereals [winter wheat (TRZAW), winter barley (HORVW), triticale (TTLSS) and rye (SECCW)] in the Northern European countries and in winter wheat (TRZAW), winter barley (HORVW) and durum wheat (TRZDU) in the Southern European countries.

B.3.1.4 Harmful organisms

The harmful dicotyledonous organisms which are indicated to be controlled by beflubutamid are as follows:

Degree of control	Northern Europe	Southern Europe
Good control	*Capsella bursa-pastoris* *Lamium purpureum* *Matricaria chamomilla* *Matricaria species* *Myosotis arvensis* *Stellaria media* *Viola arvensis* *Viola tricolor*	*Capsella bursa-pastoris* *Fumaria officinalis* *Lamium amplexicaule* *Matricaria chamomilla* *Papaver rhoeas* *Stellaria media* *Veronica hederaefolia* *Veronica persicaria* *Viola arvensis*
less satisfactory	*Veronica hederifolia*	--

control	*Veronica persicaria*	
no assessment due to insufficient data	*Lamium amplexicaule*	--

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

According to the HRAC (Herbicide Resistance Action Committee) classification beflubutamid as a phenoxybutamid belongs to the mode of action group F1. UR-50601 inhibits the plant enzyme phytoene desaturase (PDS) of the carotenoid biosynthetic pathway leading to the photooxidation of chlorophyll, thus inducing typical bleaching symptoms. No information neither studies were submitted to elucidate the mechanism of selectivity.

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

As an PDS-inhibitor, beflubutamid belongs to the mode of action group F1 according to the HRAC (Herbicide Resistance Action Committee) classification. During the period of field testing of beflubutamid, no development of resistant weed species to the active substance has been observed. No resistance of weeds to diflufenican, a pyridinecarboxamide, which belongs to the same mode of action group as beflubutamid, has been reported. Diflufenican has been using in agriculture since more than 10 years. Because of the similarity of diflufenican and beflubutamid together with the fact that the latter is a new substance not being authorized in any of the EU-member states up to now, the resistance risk of weeds to the active substance beflubutamid can be considered as to be low.

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 Herbaflex [ASU 95 510 H (UBH-820/isoproturon)] is a suspension concentrate (SC) containing 85 g/L beflubutamid and 500 g/L isoproturon. The product is intended to be used in agriculture.

B.3.2.2 Effects on harmful organisms

Herbaflex is translocated by both apo- and symplastic mechanisms. Beflubutamid inhibits the enzyme phytoene desaturase involved in carotenoid biosynthesis thereby causing chlorophyll photooxidation (bleaching). Isoproturon is taken up via the roots and leaves of the weeds and is inhibiting photosynthesis.

The product is most effective if applied on young growing dicotyledonous weeds.

Limitations in the choice of succeeding crops in regular rotations or in the case of crop failure subsequent to Herbaflex application can not be assessed for the single experiment run on this issue was invalid.

B.3.2.3 Details of intended uses

The product is intended for postemergence use in winter cereals in Northern Europe and in winter cereals [winter wheat (TRZAW), winter barley (HORVW), triticale (TTLSS) and rye (SECCW)] in the Northern European countries and in winter wheat (TRZAW), winter barley (HORVW) and durum wheat (TRZDU) in the Southern European countries. Herbaflex is applied at dose rates of 2.0 to 3.0 L/ha. Protection is achieved against dicotyledonous weeds and also some grass species due to addition of IPU.

B.3.2.4 Application rate per unit treated

The maximum recommended field rate of the product is 3.0 L/ha, corresponding to 255 g/ha beflubutamid and 1500 g/ha isoproturon.

B.3.2.5 Concentration of active substances

Herbaflex is applied at water volumes of 200 to 400 L/ha. At the maximum field rate of 3.0 L/ha (255 g/ha beflubutamid and 1500 g/ha isoproturon), the maximum concentration of beflubutamid is between 0.64 to 1.275 g/L beflubutamid and 3.75 to 7.5 g isoproturon/L in the spray liquid.

B.3.2.6 Method of application

The product Herbaflex is applied with standard tractor mounted/drawn field crop sprayers with hydraulic nozzles at water volumes of 200 to 400 L/ha.

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

Herbaflex is applied as single application with 2.0 to 3.0 L/ha in autumn or spring at BBCH 11-13 (autumn) or BBCH 11-29 (spring) of the weeds and at BBCH 11-29 (autumn) or BBCH 13-29 (spring) of the crop.

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

As the product is applied as a single application of an early post emergence herbicide on cereals, there is no necessary waiting period between the application and the planting of succeeding crops.

Limitations in the choice of succeeding crops in regular rotations or in the case of crop failure subsequent to beflubutamid application can not be assessed for the only experiment run on this issue was invalid.

B.3.2.9 Proposed instructions for use

The herbicide Herbaflex [ASU 95 510 H (UBH-820/isoproturon)] is a suspension concentrate (SC) containing 85 g/L beflubutamid and 500 g/L isoproturon. The product is intended to be used as a selective post-emergence herbicide in winter cereals in the Northern and Southern European countries and in Durum wheat in the Southern European countries. The herbicide Herbaflex is meant to control annual dicotyledonous and grass weed species.

Herbaflex is applied as single application with 2.0 to 3.0 L/ha in autumn or spring at BBCH 11-13 (autumn) or BBCH 11-29 (spring) of the weeds and at BBCH 11-29 (autumn) or BBCH 13-29 (spring) of the crop.

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 as (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		
Winter wheat Winter barley Triticale Winter rye	Northern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-0.128 + 0.250-0.750 isoproturon Spring: 0.0425-0.085 + 0.250-0.5 isoproturon	200-400 200-400	0.170-0.255 + 1-1.5 isoproturon 0.170 + 1.0 isoproturon		Co-formulation with isoproturon
Winter wheat Winter barley Durum wheat	Southern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-0.128 + 0.250-0.750 isoproturon Spring: 0.0425-0.128 + 0.250-0.750 isoproturon	200-400 200-400	0.170-0.255 + 1-1.5 isoproturon 0.170-0.255 + 1-1.5 isoproturon		Co-formulation with isoproturon

(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.: Anonym, 2000 (CHE2000-1229, Material safety data sheet)

B.3.4.1.1 Handling

Information on safe handling:
Handling in accordance with good industrial hygiene and safety procedures. After handling this material, personnel should shower and change work clothing.

Exposure controls / personal protection:
Eye/face protection: Chemical safety goggles or face shield with safety glasses.
Skin protection: Protective PVC clothing, boots and gloves.
Respiratory protection: Respirator or dust mask is recommended.

B.3.4.1.2 Storage

Store in a dry, cool, well-ventilated area.

B.3.4.1.3 Transport

Based on the measured physical/chemical properties and observed ecotoxicological properties standard classifications for transport and labelling requirements according to IMO, IATA and ARD/RDI were assigned for each product. Beflubutamid is not dangerous. Therefore, a classification is not necessary.

GGVSee/IMDG code: -- UN No.: -- MFAG: -- EmS: --
PG: -- MPO: --
GGVE/GGVS: Class -- No. -- RID/ADR: Class -- No. --
ADNR: Class -- No. -- Cat -- ICAO/IATA-DGR: not restr.
Declaration for land shipment: --
Declaration for sea shipment: --
Declaration for shipment by air: --

B.3.4.1.4 Fire fighting measures

Flammable properties
The active substance is not highly flammable, not autoflammable, not explosive and not oxidising.

Extinguishing media
Suitable extinguishing agents include water spray, alcohol foam or polymer foam, carbon dioxide.

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

Controlled incineration
Information on the pyrolytic behaviour of the active substance under controlled conditions at 800° C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis is not applicable as the halogen content of the active substance is less than 60 %.

The recommended means of safe disposal is via controlled incineration at an approved chemical waste facility according to official regulations. This is a standard process and no further detailed instructions are required.

Other methods
No other means of disposal are proposed.

B.3.4.3 Emergency measures in the case of an accident (Annex IIA 3.9)

Fire
Remove personnel in a upwind direction of the fire. Fire fighters should wear full protective suit and a self-contained breathing apparatus. Keep fire exposed container cool by spraying with water. Recommended extinguishing agents: water, alcohol foam, polymer foam or carbon dioxide.

Spillage
Evacuate the area. In cases of an accident beflubutamid should be prevented from dispersion and ladled with dippers, collect material in suitable container. Scooped materials with water should be taken to the incineration factory for disposal. Prevent spilled materials from entering the drainage system, surface or ground water.
Operators should wear chemical safety goggles or face shield with safety glasses, protective pvc clothing, boots and gloves. Respirator or dust mask provides suitable breathing protection.

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)

1 Litre Bottle	Material:	Plastic CoEx bottle with external layer of PE Lupolen 5021 D, internal layer of PA A 28 NZ alternative Ultramid C35 and middle layer of HV Admer L2100.
	Shape/size:	Round / 88.5 x 234 mm
	Opening:	42 mm diameter
	Closure:	Screw cap KS50 CAPS 6063 made of PP Novolen 2600 M and HF sealing by a Duplex target Alkosave PE-concealed 60 µm disc.
5 Litre Can	Material:	CoEx Can C95 of Hostalen GF 4750 material, ADMER 2100 adhesive material and a Grilon barrier.
	Shape/size:	Can / 190 x 140 x 313 mm
	Opening:	53 mm diameter
	Closure:	KS 63 Mauser
10 Litre Can	Material:	CoEx Can C95 of Hostalen GF 4750 material, ADMER 2100 adhesive material and a Grilon barrier.
	Shape/size:	Can / 282 x 190 x 313 mm
	Opening:	52 mm diameter
	Closure:	KS 63 Mauser

B.3.5.1.2 Suitability of packaging (Annex IIIA 4.1.2)

Suitability of the packaging according to ADR methods has not been submitted.

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

After storage of Herbaflex in 1l CoEx bottles over a period of two years at ambient temperature shows no deformation or change of colour for the used bottles.

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

Equipment and protective clothing should be cleaned by rinsing with water and with some drops of a liquid detergent. The product is formulated as an SC and easily miscible with

water, and it can therefore be easily washed away from surfaces with water. The detergent enhances this cleaning procedure.

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.3.2.8

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

Safe handling:
Do not smoke. Keep ignition source away. Ensure good ventilation/ exhaustion at the workplace and good interior ventilation. Protect against electrostatic charges.
Avoid contact with eyes and skin. Do not inhale gases/fumes/aerosols. Keep away from foodstuffs, beverages and food.

Storage:
Keep in a dry place between 0 °C and 30 °C in tightly sealed containers. Ensure good ventilation/exhaustion at the workplace. Protect from heat and direct sunlight. Provide a solvent resistant, sealed floor. Store in a way that unauthorized persons and especially children do not have access.

Transport:

Land

ADR/RID-GGVS/E class	9
Number/letter, UN-No.	11c, 3082, Dangerous to the environment, liquid

Maritime

IMDG/GGVSea class	9
Marine pollutant, UN-No.	yes, 3082, Dangerous to the environment, liquid

Air

ICAO/IATA class	9
UN-No., Page	3082, Dangerous to the environment, liquid

Protective clothing and equipment:
In the case of an accident or spillage the product may be handled and skin contact may occur: Body protection by one piece work suit (overall) with closely fitting trouser bottoms and water-resistant work boots with protective toecaps. Hand protection by protective, chemical-resistant rubber gloves. Eye protection by safety spectacles.

Fire-fighting measures:
Extinguishing media are water, foam, carbon dioxide, dry chemicals, or dry sand. Fire-fighters should wear positive pressure, full-face self-contained breathing apparatus. Cool fire-exposed containers.

Minimising generation of waste:
Only purchase and store the quantities of product which should be expected to be applied the same season. Do not mix a volume of spray-mixture which is greater than the volume necessary for the area planned to be treated. Dilute the rinsing-water of the spraying equipment in the ratio 1:10 and apply it on the previously treated area.

Combustion products generated in the event of fire:
No dangerous decomposition products have to be anticipated in the event of a fire.

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

Containment:
Do not allow product to reach sewage system or water bodies. Inform respective authorities in case product reaches water, sewage system or soil.

Decontamination:
Use adsorbent material to collect spillage (e.g. sand, diatomite, acid binders). Use a damp cloth to clean floors and other objects after removal of contaminated adsorbent. Ensure adequate ventilation.

Disposal:
Place contaminated adsorbent in closable containers. Also place used cleaning materials into closable receptables. Disposal must be made according to official regulations by landfill, incineration or recycling.

Protection:
Use the personal protective equipment proposed. Keep unprotected persons away. Ensure adequate ventilation.

First aid:
Remove victims from the danger zone. Remove soiled and impregnated clothing immediately.
Upon inhalation:
Upon intensive inhalation of fumes, contact a physician.

Following skin contact:
Wash skin immediately with plenty of water and soap. If necessary seek medical advice.
Following eye contact:
Rinse eyes thoroughly with plenty of water and immediately contact a physician.

Upon swallowing:
Call emergency doctor immediately.

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

Possibility of neutralisation
The formulation has a pH-value of approximately 7.0. A neutralisation procedure with acid or alkali needs therefore not to be recommended. Spillages should be adsorbed using sawdust, peat, or chemical binder.

Controlled incineration
Package the waste and contact the local authorities to make sure that the waste will be led to controlled incineration or safe waste disposal according to the official regulations.
The pyrolytic behaviour of the active substance does not need to be reported as the content of halogens of the active substance in the preparation is <60 %.

Disposal within Germany:
Do not re-use emptied packages. Thoroughly emptied and rinsed packages could be disposed at authorised collecting centres and will be taken to a controlled incineration using the guidelines of the IVA (Association of the German Agrochemical Producers) for safe waste disposal of agrochemical containers. Information about location/time of the collecting of the containers could be obtained from the local traders. All packaging bearing the IVA-logo are included in the waste disposal of the IVA. As the applicant is a member of the IVA, this ensures a safe waste disposal of emptied containers.

Others
No other methods (e.g. recycling) are currently available.

Ref.: Anonym, 1999 (CHE 2000-1130)

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-3.5	Funaki, E., Okada, T.	2001	Herbicidal Activity of the metabolite UR-50604. not GLP, unpublished BIO2001-53	Y	UBE

[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-3.7	Anonym	2000	Material Safety Data Sheet for UBH-820, Beflubutamid (proposed). H-98-10 not GLP, unpublished CHE2000-1229	Y	UBE
AIIIA-3.7	Anonym	1997	Material Safety Data Sheet for ASU 95 510 H. not GLP, unpublished CHE2000-1225	Y	ASU
AIIIA-4.4; AIIIA-4.5; AIIIA-4.6	Anonym	1999	Material Safety Data Sheet - Herbaflex. not GLP, unpublished CHE2000-1130	Y	ASU
AIIIA-6.0	anonym	2002	NL: Herbicidal activity of the metabolite UR-50604. not GLP, unpublished BIO2002-678	Y	TSU
AIIIA-6.0	Anonym	2000	Report Herbicidal activity of the metabolite UR-50604. not GLP, unpublished BIO2000-432	Y	ASU
AIIIA-6.0	Anonym	2000	Wirksamkeitsunterlagen zum Mittel Herbaflex. not GLP, unpublished BIO2000-333	Y	ASU
AIIIA-6.1; AIIIA-6.6.1	Fiebig, S.	2002	NL: ASU 92530 H: Standardized Bioassay for the Determination of ED-10 and ED-50-values for Herbicides an Following Crops in Soil. GLP, unpublished BIO2002-347	Y	TSU
AIIIA-6.3	Stähler- anonym	2002	NL: Information on the occurence or possible occurence of the developement of resistance. not GLP, unpublished BIO2002-348	Y	TSU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

Annex B

Beflubutamid

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):

Beflubutamid (UR-50601)

Hazard symbol:	ecotox.:	N	(Dangerous for the environment)
Indication of danger:	None		
Risk phrases:	ecotox.:	R 50/53	(Toxic to aquatic organisms / may cause long-term adverse effects in the aquatic environment)

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):

Preparation (ASU 95 510 H; product name: Herbaflex)

Hazard symbol:	Xn N	 (Dangerous for the environment)
Indication of danger:	Harmful	
Risk phrases:	R 40 R 50/53	Possible risks of irreversible effects (Toxic to aquatic organisms / may cause long-term adverse effects in the aquatic environment)

Reasons for classification
Due to the information available with respect to the second active ingredient contained in the product (isoproturon).

B.4.3 References relied on

No references submitted.

Annex B

Beflubutamid

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 Methods for the determination of pure active substance in the active substance as manufactured (Annex IIA 4.1)

Materials and Methods:
Test material: Beflubutamid; Batches 507003 and 950123; Purity: 97.79 % and 97.77 % respectively. The active ingredient content of acetonitrile dilutions of each batch was determined by reverse phase HPLC analysis with UV detection (220 nm) using biphenyl as an internal standard.

Findings (Determination of active ingredient):
Linearity:
Calibration regression coefficients greater than 0.99879 achieved.

Specificity:
The active ingredient in each chromatogram was confirmed by the retention time.

Non analyte interference:
No interference was observed at the retention time of the active ingredient.

Repeatability:
The analytical validation data for five samples of Batch 950123 gave a mean value of 97.5 % (RSD = 0.55 %).
The analytical validation data for five samples of Batch 507003 gave a mean value of 98.0 % (RSD = 0.37 %).

Active ingredient analytical data: validation and stability (results expressed as %)

	Month							
Batch	**0**				**6**	**12**	**28**	**24**
Number	**Mean**	**Range**	**SD**	**RSD**				
950123	97.5	97.0-98.3	0.54	0.55	-	-	-	-
507003	98.0	97.5-98.4	0.36	0.37	97.7	99.6	98.1	101.1

Accuracy:
The validation quality control data for Batch 950123 gave a mean recovery of 97.6 % (RSD = 0.89 %) and Batch 507003 gave a mean recovery of 99.9 % (RSD = 1.30 %).)

Active ingredient quality control data: validation and stability (results expressed as %)

Batch number	Month							
	0				6	12	28	24
	Mean	Range	SD	RSD				
950123	97.6	96.9-98.8	0.87	0.89	-	-	-	-
507003	99.9	98.0-101.0	1.30	1.30	100.9	101.6	99.6	103.7

Conclusions:
The analytical method for the determination of the active ingredient content in two batches of beflubutamid has been validated. The purity of Batch 950123 was determined to be 97.5 % and Batch 507003, 98.0, 97.7, 99.6, 98.1 and 101.1 % at t = 0, 6, 12, 18 and 24 months respectively and is considered to be stable over a two year period.

Existing CIPAC methods are not applicable.

Ref.: Betteley, 1999 (CHE2000-1132)

B.5.1.2 Methods for the determination of significant and/or relevant impurities and additives (e.g. stabilizers) in the active substance as manufactured

Confidential information, see Annex C.

B.5.1.3 Methods for formulation analysis (plant protection product) (Annex IIIA 5.1)

Materials and Methods:
The formulated product (batch 9901) was dissolved in acetonitrile. Beflubutamid and isoproturon were determined by reversed phase, high performance liquid chromatography (HPLC) with UV detection at 200 nm.

Beflubutamid

Specificity:
Peaks on the chromatograms were identified by comparison of retention times with known standards.

Linearity:
Calibration coefficients of 0.9998 were achieved.

Recovery:
Recovery efficiency at the nominal concentration of beflubutamid in the formulation (85 % w/w) was 100.7 - 101.0 % (mean 100.9 %). Recoveries over four concentrations were 96.2 – 101.0 % with a mean of 98.0 %. The overall RSD was 2.3 %.

Recovery values from method validation of beflubutamid in the formulation.

Concentration [mg/kg]	Number of tests	Mean Recovery [%]
42.8	4	97.7
64.3	4	97.9
85.7	4	100.9
171.3	4	95.3

Standard Deviation of overall mean: 2.3 %. Relative Standard Deviation of overall mean: 2.3 %

Relative Standard Deviation RSD of the overall average: ± 2.3 %

Isoproturon

Specificity:
Peaks on the chromatograms were identified by comparison of retention times with known standards.

Linearity:
Calibration coefficients of 0.9994 were achieved.

Recovery:
Recovery efficiency at the nominal concentration of isoproturon in the formulation (50 %w/w) was 97.7 - 106.7 % (mean 102.2 %). Recoveries over four concentrations were 94.9 – 106.7 % with a mean of 99.5 %. The overall RSD was 3.5 %.

Recovery values from method validation of Isoproturon in the formulation.

Concentration [mg/kg]	Number of tests	Mean Recovery [%]
306	4	96.9
408	4	97.3
510	4	102.2
765	4	101.6

Standard Deviation of overall mean: 3.5 %. Relative Standard Deviation of overall mean: 3.5 %

Relative Standard Deviation: RSD of the overall average: ± 3.5 %

Conclusion:
The analytical method is specific and accurate for the determination of beflubutamid and isoproturon in the formulation.
Existing CIPAC methods are not applicable.

B.5.1.3.1 Methods for the determination of significant and/or relevant impurities and additives (e.g. Stabilizers) in the preparation

There are no significant or relevant impurities for which a method is considered to be necessary.
It is considered that methods for additives in the formulation should not be required.

Ref.: Brielbeck and Marx, 1999 (CHE2000-1131)
Brielbeck and Marx, 2000 (PHY2000-572)

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

Residues of beflubutamid and its metabolite (2-(4-Fluoro-3-trifluoromethylphenoxy)butyric acid, UR-50604) in cereals (green plant, straw and grain) can be determined by GC and HPLC respectively according to report AB 95510-GM-002B (Brielbeck und Marx, 1999).
After extraction with methanol/water (70:30) and liquid/liquid partition into ethyl acetate the extracts were purified by silicagel chromatography. Beflubutamid and its metabolite were separated at this stage into separate eluates, with beflubutamid being eluted off first.
The metabolite was eluted into methanol/acetonitrile (10:90), the eluate was removed under reduced pressure and the residue reconstituted into acetonitrile for analysis by HPLC with UV-detection at 281 nm (column: Supelcosil ABZ, mobile phase: 0.01 M citric acid buffer/acetonitrile 50:50, isocratic).
Beflubutamid eluate underwent a second column purification, being eluted into acetone/hexane (90:10). The eluate was removed under reduced pressure and the residue reconstituted into acetonitrile for analysis by GC-PND.
For validation data see Table B.5.2-1.

Table B.5.2-1: Validation data for analytical method for the determination of beflubutamid and its metabolite in plant material

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	Recovery rate [%] range	RSD [%]	n
Brielbeck and Marx, 1999 (AB 95510-GM-002B)	**beflubutamid** grain	0.05*	100	93-107	7.0	3
		0.5	95	88-103	7.9	3
		1.0	84	79-91	7.7	3
		2.1	90	81-97	9.0	3
	cereal, green plant	0.05*	*112*	108-118	4.6	3
		0.5	90	85-91	5.6	3
		1.0	96	91-101	5.2	3
		2.1	101	93-109	8.0	3
	straw	0.05*	91	77-106	16.0	3
		0.5	91	86-97	6.3	3
		1.0	91	85-100	8.5	3
		2.1	99	93-104	5.6	3

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
	metabolite UR-50604					
	grain	0.05*	95	83-104	11.4	3
		0.1	97	92-102	5.2	3
		0.5	96	88-106	9.5	3
		1.0	99	82-108	14.9	3
	cereal, green plant	0.05*	87	75-96	12.4	3
		0.1	106	99-110	6.0	3
		0.5	95	87-101	7.7	3
		1.0	95	82-104	12.0	3
	straw	0.05*	99	94-103	4.5	3
		0.1	97	92-101	4.9	3
		0.5	92	83-108	15.4	3
		1.0	91	89-93	2.2	3

* limit of quantification

The applicability of the method (Brielbeck and Marx, 1999) was confirmed by an independent laboratory (Harper, 2000) in spring wheat (grain, green plant and straw) for beflubutamid only.
For validation data see Table B.5.2-2.

Table B.5.2-2: Validation data for analytical method for the determination of residues in plant material performed by an independent laboratory

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Harper, 2000 (STJ 019/002981)	grain	0.05*	85	74-98	14.4	3
		0.1	94	90-96	3.4	3
		0.5	82	74-86	8.2	3
		2.0	79	77-81	2.6	3
	wheat, green plant	0.05*	86	73-98	14.6	3
		0.1	97	95-99	2.1	3
		0.5	74	72-76	2.7	3
		2.0	71	70-73	2.1	3
	straw	0.05*	86	76-99	13.9	3
		0.1	80	78-83	3.3	3
		0.5	73	71-75	2.8	3
		2.0	94	88-104	9.0	3

* limit of quantification

According to report AB 95510-GM-002A (Brielbeck und Marx, 1998) residues of beflubutamid are extracted from cereals with methanol/water (9:1) and isolated by solid phase extraction using a C-18 column. After purification with gel chromatography columns (straw samples only) and/or purification with silicagel columns residues are eluted with hexane/acetone (90:10). The eluate was removed under reduced pressure and the residue reconstituted in hexane for analysis by gas chromatography with EC-detection.
For validation data see Table B.5.2-3.

Table B.5.2-3: Results of the confirmatory method

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%]		RSD	n
			mean	range	[%]	
Brielbeck and Marx, 1998 (AB 95510-GM-002A)	grain	0.01*	92	76-104	15.7	3
		0.02	82	78-84	3.9	3
		0.04	96	94-99	2.2	3
		0.1	92	91-94	1.7	3
	straw	0.01*	90	86-92	3.6	3
		0.02	91	81-98	9.6	3
		0.04	94	92-97	2.7	3
		0.1	91	90-92	1.1	3

* limit of quantification

B.5.2.2 Foodstuff of animal origin

The submission of an analytical method for the determination of residues in food of animal origin is not necessary, because no metabolism study in animals is required according to Directive 96/86/EC (see residue definition B.7.12).

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 report UBE 100/994745 (Todd, 2000) residues of beflubutamid and its major metabolite (UR-50604) in soil can be determined by liquid chromatography using mass spectroscopy (LC-MS).
Soil samples are extracted with a mixture of methanol/water (70:30) followed by clean up liquid/liquid partition with ethyl acetate. The resulting organic phases were then reduced to dryness and the residue reconstituted in acetonitrile/water (30:70) containing 0.1% acetic acid, for quantification by LC-MS (column: Phenomenex C18, mobile phase: 0.01 M ammonium acetate:acetonitrile, gradient; beflubutamid: *m/z* 414, UR-50604: *m/z* 265).
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 (LC-MS)

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Todd, 2000 (UBE 100/994745) Beflubutamid	clayey sand 1	0.01*	80	77-85	4.3	5
		0.1	96	92-100	3.4	5
		1.0	93	91-96	2.6	5
	clayey sand 2	0.01*	97	92-110	7.4	5
		0.1	98	91-102	4.6	5
		1.0	95	90-99	3.6	5
	sandy clay	0.01*	87	74-100	10.8	5
		0.1	73	70-76	3.0	5
		1.0	94	93-96	1.2	5
	loamy sand	0.01*	75	73-78	2.8	5
		0.1	73	72-74	1.1	5
		1.0	96	92-98	2.4	5
Metabolite UR-50604	clayey sand 1	0.01*	76	71-83	6.5	5
		0.1	95	91-100	3.4	5
		1.0	103	100-107	2.9	5
	clayey sand 2	0.01*	83	74-89	7.4	5
		0.1	99	93-104	4.9	5
		1.0	105	98-109	4.1	5
	sandy clay	0.01*	78	72-83	6.1	5
		0.1	75	72-77	2.4	5
		1.0	95	93-98	2.3	5
	loamy sand	0.01*	72	70-75	7.4	5
		0.1	73	70-76	3.5	5
		1.0	96	91-105	5.8	5

* limit of quantification

According to report PR00/014-2 (Wittig, 2000) soil samples are extracted with a mixture of methanol/water (70:30). After evaporation of methanol, NaCl-solution is added. The extract is acidified with hydrochloric acid and extracted two times with ethyl acetate. The organic phase is evaporated to dryness and dissolved in toluene. Residues of beflubutamid can be determined by gas chromatography using mass spectroscopy (SIM, *m/z* 176, 193, 221).
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 (GC-MS)

Reference	Matrix	Fortification level [mg/kg]	Recovery rate [%] mean	range	RSD [%]	n
Wittig, 2000 (PR00/014-2)	soil (Speyer 2.2)	0.01*	94	78-108	12.0	5
		0.1	90	79-99	9.6	5
		1.0	96	84-102	7.3	5

* limit of quantification

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

Residues of beflubutamid in water (drinking water, surface water and ground water) can be determined according to report UBE 054/972311 (Betteley, 1997). After extraction with dichloromethan, evaporation to dryness and reconstitution in methanol/water (70:30) determination is done by HPLC with UV-detection at 210 nm (column: Hypersil ODS, mobile phase: methanol:water 65:35, isocratic).
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 water

Reference	Matrix	Fortification level [µg/l]	Recovery rate [%] mean	range	RSD [%]	n
Betteley, 1997 (UBE 054/972311)	drinking water	0.1*	94	87-100	7.0	3
		0.5	95	88-105	9.4	3
		2.5	81	79-84	3.1	3
	surface water	0.1*	102	100-104	2.0	3
		0.5	83	77-88	6.7	3
		2.5	75	73-76	2.3	3
	ground water	0.1*	91	89-94	3.2	3
		0.5	91	88-95	4.2	3
		2.5	81	74-88	8.6	3

* limit of quantification

B.5.3.3 Confirmatory method

A confirmatory method is developed based on Study UBE 054/972311 (Betteley, 1997). Residues of beflubutamid in surface water can be determined according to report UBE 119/004365 (Todd, 2000). After extraction with dichloromethane and concentration determination is done by LC-MS (*m/z* 414, 354, 268).
For validation data see Table B. 5.3-4.

Table B. 5.3-4: Results of the confirmatory method

Reference	Matrix	Fortification level [µg/l]	Recovery rate [%] mean	range	RSD [%]	n

Reference	Matrix	Fortification level [µg/l]	Recovery rate [%] mean	range	RSD [%]	n
Todd, 2000	Surface water	0.1*	96	92-103	4.9	5
(UBE		1.0	87	83-90	3.5	5
119/004365)		2.5	81	79-84	3.1	3

* limit of quantification

B.5.3.4 Air

According to report UBE 104/994126 (Flack, 2000) a defined air volume is passed through Tenax adsorption tubes spiked with beflubutamid. After extraction with methanol residues are determined by HPLC with UV-detection at 220 nm (column: Apex C18, mobile phase: methanol/water 75:25, isocratic).
For validation data see Table B.5.3-5.

Table B.5.3-5: Validation data for analytical method for the determination of residues of beflubutamid in air

Reference	Matrix	Fortification level [µg/m³]	Recovery rate [%] mean	range	RSD [%]	n
Flack,	air	0.6*	88	88	-	2
2000		6.0	93	93	-	2
35 °C and 80% rel. humidity		60.0	100	99-100	-	2
20 °C and 30% rel. humidity		0.6*	93	92-94	-	2
		6.0	96	95-97	-	2
		60.0	101	101	-	2

* limit of quantification

The method is also fully validated using a sampling time of 2 hours.
Due to particular conditions for the determination of residues in air a confirmation method is not required because corresponding methods was submitted for soil and water.

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 neither the active substance beflubutamid nor its major metabolite are 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 and for the active substances in the formulation.

Beflubutamid in the technical active substance is determined by a HPLC internal standard method on a reversed phase column with UV detection.

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

Beflubutamid and isoproturon in the formulation are determined by HPLC external standard methods on a reversed phase column with UV detection.

All methods are fully validated.

B.5.5.2 Residue analysis

For the assessment of the analytical methods for the determination of beflubutamid 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	0.05	mg/kg	proposed MRL for cereals grain
soil	0.05	mg/kg	general upper limit. Depending on the outstanding phytotoxic concentration of beflubutamid to the most sensitive species, further data could be requested.
drinking water	0.1	µg/l	EU drinking water limit
surface water	4.5	µg/l	EC_{50} (algae)
air	87	µg/m³	based on a proposed $AOEL_{systemisch}$ of 0.29 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 beflubutamid in plant material, soil, drinking water, surface water and air (for a summary see Table B.5.5-1).

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

Matrix		Methode	Limit of quantification		Reference
crops	cereal grain	GC-PND	0.05	mg/kg	Brielbeck, Marx,

	Matrix	Methode	Limit of quantification		Reference
	green plant straw				1999
		HPLC-UV	0.05		(metabolite UR-50604)
	wheat grain	GC-PND	0.05	mg/kg	Harper, 2000
	green plant straw				
	cereal grain	GC-ECD	0.01	mg/kg	Brielbeck, Marx,
	straw				1998
soil		LC-MS	0.01	mg/kg	Todd, 2000
		GC-MS	0.01	mg/kg	Wittig, 2001
water	drinking-	HPLC-UV	0.1	µg/l	Betteley, 1997
	surface-				
	ground-				
	surface-	LC-MS	0.1	µg/l	Todd, 2000
air		HPLC-UV	0.6	µg/m^3	Flack, 2000

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-1.10; AIIA-1.11; AIIA-4.1	Betteley, J.M.T.	1999	UR-50601: Determination of active ingredient, isomeric ratio and the level of twelve impurities. UBE 32/994457 GLP, unpublished CHE2000-1132	Y	UBE
AIIA-4.2.1; AIIIA-5.2	Brielbeck, B. and Marx, D.	1999	Validation of the Analytical Method for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Cereal (Green Plant, Grain and Straw) Study No. RU798, Analytical Method No. AM-RU-6998 Final Report AB 95510-GM-002A. not GLP, unpublished MET2000-473	Y	ASU

[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-4.2.1; AIIIA-5.2	Brielbeck, B. and Marx, D.	1998	Validation of the Analytical Method for the Determination of UBH-820 in Cereals (harvest values) Study No. RU0497, Analytical Method No. AM-RU-3997 Final Report AB 95510-GM-002A. not GLP, unpublished MET2000-467	Y	ASU
AIIA-4.2.1; AIIIA-5.2	Harper, H.	2000	UR-50601: An Independent Laboratory Validation of Analytical Method AB 955510-GM-002B, Developed by Stähler Agrochemie, for the Determination of Residues in Cereal (Grain, Green Plant and Straw) Report No. STJ 019/002981. not GLP, unpublished MET2000-474	Y	ASU
AIIA-4.2.2; AIIIA-5.2	Todd, M. A.	2000	UR-50601: The Validation of Analysis for the Determination of Residues of UR-50601 and UR-50604 in Soil Report No. UBE 100/994745. not GLP, unpublished MET2000-483	Y	ASU UBE
AIIA-4.2.2; AIIIA-5.2	Wittig, A.	2000	UR-50601 (Beflubutamid): Validation of an Analytical Method for the Determination of Residues in Soil Final Report PR00/014-2. not GLP, unpublished MET2001-45	Y	ASU
AIIA-4.2.2; AIIIA-5.2	Wittig, A.	2001	UR-50601 (Beflubutamid): Validation of an Analytical Method for the Determination of Residues in Soil - Storage Stability - Final Report PR00/014, Part 2. not GLP, unpublished MET2001-205	Y	ASU
AIIA-4.2.3; AIIIA-5.2	Betteley, J. M. T.	1997	Development and Validation of a Method of Analysis for the Determination of UR-50601 in Water (including Drinking Water, Surface Water and Ground Water) UBE 054/972311. not GLP, unpublished MET2000-484	Y	ASU
AIIA-4.2.3; AIIIA-5.2	Todd, M.	2001	UR-50601 - Validation of a Confirmatory Method of Analysis for the Determination of UR-50601 in Surface Water Report Amendment 1, UBE 119/004365. not GLP, unpublished MET2001-167	Y	ASU

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-4.2.3; AIIIA-5.2	Todd, M. A.	2000	UR-50601 - Validation of a Confirmatory Method of Analysis for the Determination of UR-60601 in Surface Water Report No. UBE 119/004365. not GLP, unpublished MET2001-46	Y	ASU
AIIA-4.2.4; AIIIA-5.2	Flack, I.	2000	Development and Validation of a Method of Analysis in Air UBE 104/994126. not GLP, unpublished MET2000-486	Y	ASU
AIIIA-5.1	Brielbeck, B. and Marx, D.	1999	Validation of the Analytical Method for the Determination of IPU and UBH-820 in ASU 95 510 H. not GLP, unpublished CHE2000-1131	Y	ASU
AIIIA-2.1; AIIIA-2.4; AIIIA-2.5; AIIIA-2.6; AIIIA-2.7; AIIIA-2.8.2; AIIIA-2.8.3; AIIIA-2.8.5; AIIIA-2.8.8; AIIIA-5.1	Brielbeck, B. Marx, D.	1999	Determination of the physical-chemical Properties of ASU 95510 H (500 g/l Isoproturon + 85 g/l UBH-820 SC) at Room Temperature and after Storage at 35 °C and 0 °C. AB 95510-FO-012 GLP, unpublished PHY2000-572	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

Annex B

Beflubutamid

B-6: Toxicology and metabolism

B.6 Toxicology and metabolism

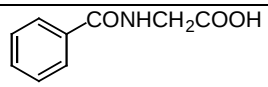
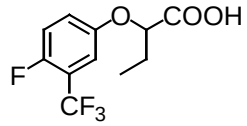
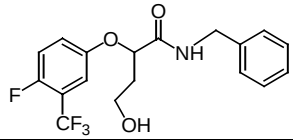
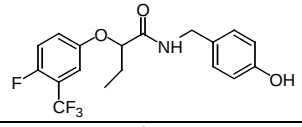
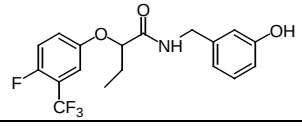
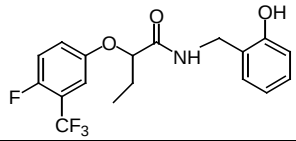
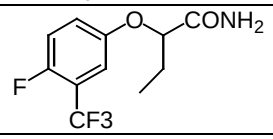
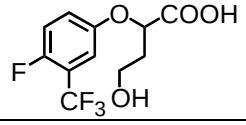
B.6.1 Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA 5.1)

Animal metabolism was studied in rats mainly after oral administration of [^{14}C-phenoxy]beflubutamid at nominal dose levels of 35 and 350 mg/kg bw. [^{14}C-benzylamine] beflubutamid was used for an additional excretion balance study. The extent of absorption was 93% (male) and 83% (female) after a 35 mg/kg bw dose, and 49% (male) and 56% (female) after a 350 mg/kg bw dose. Excretion was rapid with >90% of the dose being excreted in 48 hours rather in faeces than urine. Excretion in the bile accounted for 85% (male) and 66% (female) of a 35 mg/kg bw dose, and 42% (male) and 47% (female) of a 350 mg/kg bw dose. Whole-blood and plasma analyses indicate that the rate and extent of systemic exposure of rats to radioactivity, (as characterised by C_{max} and AUC_t), increased with increasing dose, however the observed increases in C_{max} and AUC_t were disproportionately lower than predicted from a linear relationship. After repeat dosing there was no indication of accumulation in plasma, however there was some indication of a selective up-take into blood cells.

Whole body autoradiography showed that distribution in tissues was similar for male and female rats, with radioactivity being widely distributed and present in all tissues from rats sacrificed at the time of peak plasma concentration. After a single oral dose of 35 mg/kg bw the highest concentrations (excluding gastrointestinal tract), occurred in the liver and kidney, the organs of metabolism and excretion. The concentrations in the gastrointestinal tract after 6 and 10 hours were similar suggesting that the administered radioactivity was undergoing entero-hepatic circulation. After a single oral dose of 350 mg/kg bw tissue concentrations were 2-6 times higher at 6 hours after dosing than seen at the lower level.

Beflubutamid was rapidly and extensively metabolised (see Table B.6.1-1). The major metabolite found in the plasma and excreted in the urine from rats treated with [^{14}C-phenoxy]beflubutamid was phenoxybutyric acid (UR-50604) formed by cleavage of the amide bond. Urinary excretion of this metabolite accounted for 23 – 31 % of the administered dose. In faeces the metabolites were hydroxylated derivatives of beflubutamid which were generally eliminated via the bile as glucuronide conjugates. After administration of [^{14}C-benzylamine]beflubutamid the major radiolabelled urine metabolite was hippuric acid. There was no evidence of significant stereoselective metabolism.

Table B.6.1-1: Metabolites of beflubutamid identified in rats

Code	Chemical structure	Chemical name
Hippuric acid		*N*-benzoylglycine
UR-50604		(*RS*)-2-(4-fluoro-3-trifluoromethylphenoxy)butanoic acid
UR-50615		(*RS*)-*N*-benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)-4-hyroxybutanamide
UR-50617		(*RS*)-*N*-(4-hyroxybenzyl)-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide
UR-50618		(*RS*)-*N*-(3-hyroxybenzyl)-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide
UR-50619		(*RS*)-*N*-(2-hyroxybenzyl)-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide
UR-50624		(*RS*)-2-(4-fluoro-3-trifluoromethylphenoxy)butanamide
UR-50626		(*RS*)-2-(4-fluoro-3-trifluoromethylphenoxy)-4-hyroxybutanoic acid

B.6.1.1 Rat oral single dose toxicokinetic study at multiple dose levels and oral repeat dose toxicokinetic study at single dose level

Report: G.M. Dean, E. Caldwell (2000); UR-50601: Metabolism in the rat (main study); UBE Industries, Ltd., unpublished report no. UBE 079/984961, 28 January 2000 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 26.01.1998 to 01.02.1999.

Test Material: [Ring-U^{14}C-phenoxy]beflubutamid (Label P), 1.59 GBq/mmol (4.458 MBq/mg), supplied by Amersham Life Sciencees plc, Little Chalfont, Buckinghamshire, UK, Lot number: CFQ9801, radiochemical purity ≥97%; [ring-U^{14}C-benzylamine]beflubutamid (Label B), 1.48 GBq/mmol (4.150 MBq/mg), supplied by Amersham Life Sciencees plc, Lot number: CFQ9800, ≥97%; non-radiolabelled original test-substance, supplied by UBE Industries Ltd., Lot number: CFQ507003, ≥97.46%;

Test Animals: Sprague-Dawley CD rat

GLP: Yes

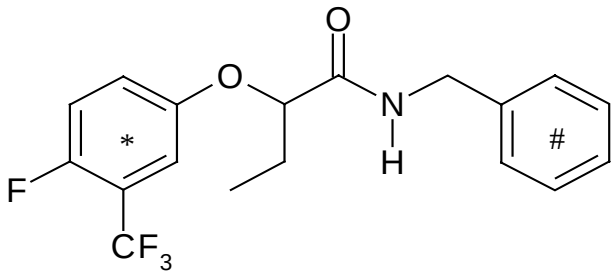
Test Method: 87/302/EEC

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Test material: Beflubutamid (UR-50601)



* Position of radiolabel in [ring-U-^{14}C-phenoxy]beflubutamid
# Position of radiolabel in [ring-U-^{14}C-benzylamine]beflubutamid

[Ring-U-^{14}C-phenoxy]beflubutamid: batch number: CFQ9801, radiochemical purity: >98%, specific activity: 1.59GBq/mmol
[Ring-U-^{14}C-benzylamine]beflubutamid: batch number: CFQ9800, radiochemical purity: >98%, specific activity: 1.48GBq/mmol

Based on a pilot study with beflubutamid [Report no. UBE 35/971187 performed at Huntingdon Life Sciences Ltd., UK, 22.09.1998] the need for extensive studies using the benzylamine label were not required, due to the nature of the metabolism. Furthermore, no detectable radioactivity was found in the expired air traps, so these were not included in the main study.

Excretion studies

Groups of 4 male and 4 female Sprague-Dawley CD rats were given a single oral dose of [ring-U-^{14}C-phenoxy]beflubutamid at 35 mg/kg bw or 350 mg/kg bw, [ring-U-^{14}C-benzylamine]beflubutamid at 35 mg/kg bw, or fourteen consecutive daily doses of 35 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid (4 males only). Cooled urine and faeces were collected at 24 hour intervals up to 120 hours after the last dose. Additionally in the multiple dosing study, urine and faeces were collected in the 24 hour periods following the 1st, 5th and 10th dose. Upon sacrifice the residual carcass and the organs were taken for analysis after blood sampling. Biliary excretion was measured in another group of 4 male and 4 female rats receiving a single dose of 35 mg/kg bw or 350 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid including bile sampling, urine and faeces collection and organ analysis.

Blood/plasma kinetics

Groups of 12 male and 12 female rats received a single oral dose of 35 mg/kg bw or 350 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid. At different time points blood samples were taken. Another group of 12 male and 12 female rats received a daily dose of 35 mg/kg bw

[ring-U-^{14}C-phenoxy]beflubutamid for 14 consecutive days. Blood samples were taken at different time points.

Tissue distribution studies

Groups of 8 male and 8 female rats received a single oral dose of 35 mg/kg bw or 350 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid or 35 mg/kg bw once daily for 14 days. Based on the results from the plasma kinetics blood samples were taken from animal groups prior to sacrifice at 6 and 10 hours after dosing. Upon sacrifice the residual carcass and the organs were taken for analysis.

Whole-body autoradiography

One male and one female rat received a single oral dose of 35 mg/kg bw or 350 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid. Six hours after dosing, to coincide with the peak plasma concentration, the animals were sacrificed and used for autoradiography.

Analysis

Blood samples were centrifuged and the plasma measured for radioactivity by LSC, replicate samples of blood from the sampling times were combusted to determine the concentrations of radioactivity in whole-blood. Tissues concentrations were determined by either combustion or solubilisation of replicate subsamples. Urine, cage washes and bile concentrations were determined by direct radioassay of aliquots. Faeces were solvent extracted and aliquots of the extract and combustion of the residue were undertaken to determine residue levels. Subsequent tissue extracts, faeces extracts, bile, plasma and urine were analysed by HPLC and TLC to assess the nature and proportion of any metabolites.

Findings:

Excretion balance: See Table B.6.1-2. After a single oral dose of 35 mg/kg bw of [ring-U-^{14}C-phenoxy]beflubutamid the urinary excretion accounted for 34-47% during 0-120 hours compared to 21-37% after the high dose level of 350 mg/kg bw. Most of this was excreted within 48 hours. The excretion in the faeces was 51-66% in the low dose level, compared to 64-80% in the high dose level, most within 72 hours. The excretion is similar for low dose levels with both radiolabels. The urinary excretion was higher in female than in male rats, while the excretion in faeces was higher in male than in female rats in both the single low and high dose level. After 5 days the recovery was 97-102%. After administration of 35 mg/kg bw for 14 days the excretion pattern was similar to that seen after single administration. Repeat administration does not result in substantial retention of radioactivity.

Biliary excretion: Rats with cannulated bile ducts excreted 66-85% in the bile during 48 hours after low dose level administration compared to 42-47% after high dose level. Absorption (urine, bile and carcass) was estimated to be 83-93% at low dose and 49-57% at high dose. It was also shown that absorption was greater in male than in female rat at low dose level (Table B.6.1-3). Recovery after 48 hours was 100-103%.

Pharmacokinetic parameters: After a single low dose, the concentration of radioactivity in whole-blood and plasma was higher in males than in females, with peak radioactivity 6 hours after dosing (Table B.6.1-4). This is comparable for the high dose level, except that peak concentrations were found at 3 (female) and 6 hours (males). The terminal half-lifes in plasma and whole-blood following single high dose was shorter than following single low dose, except for whole-blood in females. There was no evidence of accumulation in plasma over the 14-day period, although the systemic exposure in blood after repeated doses tended to be higher than after a single dose, giving some indication of a selective uptake into red blood cells. C_{max} and AUC_t increased with increasing dose, however the observed increases in C_{max} and AUC_t were disproportionately lower than that predicted from a linear relationship.

Tissue distribution: The tissue distribution was similar between males and females. Highest concentrations in tissues were found at the time of peak plasma concentration and radioactivity was present in all tissues. The highest radioactivity occurred in liver and kidneys, the organs of metabolism and excretion. Concentrations in all other tissues were lower than those measured in plasma. After repeated exposure the pattern of distribution and relative magnitude of the residue in each tissue was similar. After a single high oral dose tissue concentrations were 2-6 times higher at 6 hours after dosing than seen at the lower level. At 120 hours after a single low or high oral dose radioactivity had virtually been cleared from all tissues. The tissue distribution of beflubutamid at 6, 10 and 120 hours are shown in Table B.6.1-5, Table B.6.1-6, and Table B.6.1-7. From this it can be seen that there was no evidence of retention in tissues after repeat dosing or after a single dose.

Metabolic pathway: Beflubutamid was rapidly and extensively metabolised, which resulted in very little beflubutamid reaching the systemic circulation. Fat was the only tissue where beflubutamid was detected as a significant proportion of the tissue residue. The major metabolite found in the systemic circulation (plasma) and excreted in urine (23-31%) was phenoxybutyric acid (UR-50604) formed by cleavage of the amide bond and there was some evidence this further underwent limited conjugation prior to excretion. The major component in urine after administration of the benzylamine label was 29-36% hippuric acid. In faeces <5% unchanged beflubutamid was detected after a single or repeated low dose administration. Up to 5 hydroxylated products were found in the faeces in similar proportions for both labels used, which were generally eliminated via the bile as glucuronide conjugates. In addition a small amount of UR-50624 was found in the bile and faeces. In the bile unchanged beflubutamid accounted for <10% and UR-50604 represented 6.4-22.3% of the low dose, while UR-50624 was excreted as the free metabolite, the hydroxylated products were generally eliminated as glucuronide conjugates. (See Table B.6.1-8, Table B.6.1-9, Table B.6.1-10). A proposed metabolic pathway for beflubutamid is shown in Figure B.6.1-1.

Table B.6.1-2: Mean excretion and retention after single low or high dose and repeated (14 daily) low dose administration of beflubutamid

Dose level	**35 mg/kg bw* single**		**35 mg/kg bw# single**		**350 mg/kg bw* single**		**35 mg/kg bw* multiple**
Sample	Male	Female	Male	Female	Male	Female	Male Day 14 sampling 0-120 hours
Urine (+ cage wash)	33.77	47.02	38.88	45.18	21.42	36.55	40.10
Faeces	65.63	50.62	57.50	53.81	80.09	64.06	88.97
Carcass	0.25	0.26	0.25	0.27	0.09	0.20	1.69
Total recovery	99.62	97.93	96.62	99.26	101.6	100.8	-

Results expressed as total % dose, 120 hours after dosing stopped; *: [ring-U-^{14}C-phenoxy]beflubutamid; #: [ring-U-^{14}C-benzylamine]UR-5060

Table B.6.1-3: Mean excretion and retention in bile-duct cannulated rats after single low or high dose administration of [ring-U-^{14}C-phenoxy]beflubutamid

Dose level	35 mg/kg bw single		350 mg/kg bw single	
Sample	Male	Female	Male	Female
Urine	8.16	16.29	6.78	8.96
Faeces	9.50	19.62	53.11	41.13
Bile	84.88	66.24	42.34	47.32
Carcass	0.36	0.43	0.19	0.94
Tissues	0.32	0.25	0.19	2.04
Total recovery	103.2	102.8	102.6	100.4

Results expressed as total % dose dose, up to 48 hours after dosing

Table B.6.1-4: Mean concentrations in plasma and whole-blood after a single low or high dose and repeated low dose administration of [ring-U-^{14}C-phenoxy]beflubutamid

Dose			Pharmacokinetic parameter				
			C_{max} (µg equiv/ml)	T_{max} (hours)	AUC_t (µg equiv.h/ml)[d]	$t_{1/2}$ (hours)	C_{max} ratio (plasma/ whole blood)
35 mg/kg bw single	Plasma	Male	31.23	6	347	22	-
		Female	23.67	6	306	75a	-
	Whole blood	Male	20.79	6	245	39a	1.50
		Female	15.58	6	191	17	1.52
350 mg/kg bw single	Plasma	Male	137	6	2562	12	-
		Female	100.14	3	1997	18[a]	-
	Whole blood	Male	83.78	6	1576	10	1.64
		Female	60.52	3	1256	15	1.65
35 mg/kg bw* multiple	Plasma	Male	26.79	6	366	33[a]	-
		Female	28.75	3	341	31	-
	Whole blood	Male	17.56	6	340	63[b]	1.53
		Female	20.31	4	365	106[c]	1.42

[a]: Value is estimate only, terminal rate constant could not be adequately estimated since amount of variance accounted for by the model was <0.9 and the regression coefficient was <0.95; [b]: Value is estimate only, terminal rate constant could not be adequately estimated since period over which the half-life was estimated was less than two-fold the half life itself; [c]: Value is estimate only, terminal rate constant could not be adequately estimated since amount of variance accounted for by the model was <0.9; [d]: Whole-blood (µg equivalents/g); plasma (µg equivalents/ml); *: 14 consecutive daily doses.

Table B.6.1-5 Mean (± sd)[a] concentrations of radioactivity in tissues 6, 10 and 120 hours after: a single oral dose of [^{14}C-phenoxy]beflubutamid (35 mg/kg bw) to rats. Results are expressed as µg equivalents/g or ml

Tissues	Sacrifice time/sex					
	6 hours		10 hours		120 hours	
	Male	Female	Male	Female	Male	Female
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Adrenal glands	7.78 ± 1.96	12.90 ± 1.88	6.29 ± 2.51	9.08 ± 2.62	Nd	Nd
Blood cell	3.28 ± 0.82	4.39 ± 0.64	1.89 ± 0.46	2.16 ± 0.40	0.23 ± 0.03	0.22 ± 0.03
Bone	0.82 ± 0.20	1.18± 0.43	0.94 ± 0.36	1.31 ± 0.24	Nd	Nd
Bone marrow	2.93 ± 0.64	4.25 ± 0.40	2.54 ± 1.11	3.38 ± 1.02	Nd	Nd
Brain	1.67 ± 0.31	2.53 ± 0.23	1.25 ± 0.31	1.60 ± 0.30	Nd	Nd
Eye	1.62 ± 0.45	2.24 ± 0.73	1.30 ± 0.50	1.75 ± 0.70	Nd	Nd
Fat (abdominal)	12.06± 2.99	18.61 ± 2.97	11.48 ± 2.01	17.98 ± 3.16	0.08 ± 0.03	0.16 ± 0.01
G.I.T.	348.51 ± 0.60	277.18 ± 26.23	256.30 ± 77.95	272.11 ± 66.92	1.11 ± 1.63	0.52 ± 1.11
Heart	6.73 ± 2.11	9.50 ± 2.47	6.27 ± 2.01	6.82 ± 2.54	Nd	Nd
Kidney	36.52± 4.81	57.11 ± 5.37	31.98 ± 6.03	38.67 ± 21.08	0.17 ± 0.07	0.16 ± 0.01
Liver	58.10 ± 12.33	38.24 ± 5.56	62.08 ± 5.16	39.20 ± 3.44	1.06 ±0.59	0.84 ± 0.16
Lung	6.82 ± 1.95	10.40 ± 3.11	6.24 ± 2.08	7.76 ± 2.86	0.05 ± 0.01	0.06 ± 0.02
Lymph node (mes)	5.33 ± 1.51	9.86 ± 2.13	4.45 ± 1.59	7.16 ± 1.46	0.07 ± 0.02	0.08 ± 0.03
Muscle	2.53 ± 0.55	3.55 ± 0.64	2.18 ± 0.66	2.45 ± 0.86	Nd	Nd
Ovary	Nc	10.97 ± 1.93	Nc	9.76 ± 2.79	Nc	Nd
Pancreas	7.05 ± 2.65	11.41 ± 4.56	5.16 ± 1.61	7.27 ± 2.14	0.07 ± 0.02	0.07 ± 0.01
Plasma	20.68 ± 6.12	29.52 ± 10.98	19.21 ± 8.96	21.83 ± 8.53	0.06 ± 0.03	0.04 ± <0.01
Prostate	4.95 ± 1.81	Nc	4.47 ± 3.05	Nc	Nd	Nc
Skin	4.62 ± 1.09	7.63 ± 1.34	3.72 ± 1.06	7.71 ± 2.96	0.13 ± 0.11	0.14 ± 0.11
Spleen	2.57± 0.61	4.14 ± 0.89	2.24 ± 0.86	3.03 ± 0.92	Nd	Nd
Submaxillary gland	4.37 ± 0.95	6.25 ± 1.04	3.57 ± 1.22	4.78 ± 1.68	0.05 ± 0.01	0.04 ± 0.01
Testis	3.60 ± 0.96	Nc	3.40 ± 0.61	Nc	Nd	Nc
Thymus	2.60 ± 0.37	4.01 ± 1.18	2.17 ± 0.55	3.11 ± 0.89	0.04 ± 0.01	Nd
Thyroid	5.97 ± 1.38	9.07± 0.92	6.06 ± 1.35	6.41 ± 2.77	Nd	Nd
Uterus	Nc	9.35 ± 4.23	Nc	8.65 ± 1.84	Nc	0.04 ± 0.01
Whole-blood	11.57 ± 3.28	16.77 ± 6.44	10.80 ± 3.95	11.85 ± 4.63	0.12 ± 0.03	0.12 ± 0.02

Nd : No radioactivity detected; Nc : Not calculable; sd : Standard deviation; [a]: n = 4 males and/or females

Table B.6.1-6 Mean (± sd)[a] concentrations of radioactivity in tissues after a single oral dose of [^{14}C: -phenoxy]beflubutamid (350 mg/kg bw) to rats. Results are expressed as µg equivalents/g or ml

Tissues	Sacrifice time/sex					
	6 hours		10 hours		120 hours	
	Male	Female	Male	Female	Male	Female
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Adrenal glands	51.40 ± 11.46	51.95 ± 10.31	50.27 ± 11.00	45.79 ± 11.70	Nd	Nd
Blood cell	13.15 ± 1.79	9.01 ± 5.68	23.36 ± 2.87	7.96 ± 3.04	Nd	Nd
Bone	4.23 ± 0.54	Nd	4.97 ± 1.31	Nd	Nd	Nd
Bone marrow	9.32 ± 5.85	12.53 ± 4.52	14.09 ± 2.76	8.38 ± 3.36	Nd	Nd
Brain	11.81 ± 3.77	12.08 ± 4.50	11.57 ± 3.08	8.76 ± 2.42	Nd	Nd
Eye	7.57 ± 1.22	6.64 ± 1.49	8.70 ± 1.17	4.62 ± 1.19	Nd	Nd
Fat (abdominal)	65.35 ± 24.14	82.35 ± 31.11	78.87 ± 23.65	91.76 ± 11.63	Nd	0.92 ± 0.14
G.I.T.	2662.52 ± 286.52	3200.95 ± 347.93	1995.57 ± 433.25	2468.94 ± 606.28	1.44 ± 0.63	2.00 ± 1.48
Heart	30.50 ± 5.85	27.23 ± 7.81	36.02 ± 7.21	18.26 ± 5.38	Nd	Nd
Kidney	83.35 ± 9.99	82.72 ± 7.73	83.82 ± 3.09	57.21 ± 6.75	0.77 ± 0.12	1.04 ± 0.10
Liver	149.48 ± 19.34	93.74 ± 18.73	164.07 ± 12.00	84.47 ± 22.06	4.64 ± 1.01	5.70 ± 1.30
Lung	31.18 ± 5.58	29.32 ± 8.07	35.55 ± 6.82	21.55 ± 6.50	Nd	Nd
Lymph node (mes)	26.53 ± 10.03	44.54 ± 13.19	33.39 ± 8.37	38.95 ± 10.10	Nd	Nd
Muscle	14.97 ± 4.64	10.75 ± 1.86	14.57 ± 2.98	8.45 ± 2.24	0.26 ± 0.03	0.27 ± 0.03
Ovary	Nc	47.12 ± 19.88	Nc	32.26 ± 6.82	Nc	Nd
Pancreas	37.37 ± 7.84	29.31 ± 5.06	41.50 ± 14.94	29.24 ± 4.24	Nd	Nd
Plasma	85.25 ± 13.61	74.39 ± 25.90	105.95 ± 21.55	44.83 ± 15.78	Nd	Nd
Prostate	29.50 ± 8.32	Nc	28.38 ± 8.19	Nc	Nd	Nc
Skin	30.22 ± 10.12	32.04 ± 15.82	29.14 ± 4.73	22.17 ± 6.86	0.51 ± 0.16	0.57 ± 0.11
Spleen	15.01 ± 2.69	13.68 ± 3.68	15.50 ± 3.39	9.63 ± 2.95	Nd	Nd
Submaxillary gland	24.07 ± 3.62	22.35 ± 7.43	29.52 ± 8.51	16.49 ± 6.69	Nd	Nd
Testis	17.35 ± 3.34	Nc	20.17 ± 2.98	Nc	Nd	Nc
Thymus	15.57 ± 2.77	20.72 ± 9.29	15.82 ± 4.10	14.64 ± 2.66	Nd	Nd
Thyroid	25.87 ± 7.32	24.99 ± 9.35	33.64 ± 9.38	20.62 ± 5.97	Nd	Nd
Uterus	Nc	27.90 ± 5.30	Nc	20.91 ± 8.41	Nc	Nd
Whole-blood	50.95 ± 10.27	41.48 ± 17.35	65.34 ± 12.68	26.58 ± 8.99	Nd	Nd

Nd: No radioactivity detected; Nc: Not calculable; sd: Standard deviation; [a]: n = 4 males and/or females

Table B.6.1-7: Mean (± sd)[a] concentrations of radioactivity in tissues 6, 10 and 120 hours after the last of 14 daily oral doses of[^{14}C-phenoxy]beflubutamid (35 mg/kg bw) to rats. Results are expressed as µg equivalents/g or ml

Tissues	Sacrifice time/sex				
	6 hours		10 hours		120 hours
	Male	Female	Male	Female	Male
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
Adrenal glands	12.35 ± 3.07	18.70 ± 1.48	8.11 ± 2.29	10.31 ± 2.42	0.72 ± 0.06
Blood cell	5.89 ± 1.03	7.42 ± 0.41	5.25 ± 0.99	5.51 ± 0.79	2.64 ± 0.39
Bone	0.83 ± 0.26	1.22 ± 0.63	0.89 ± 0.54	1.13 ± 0.29	Nd
Bone marrow	4.65 ± 1.46	6.26 ± 1.56	3.05 ± 0.70	4.10 ± 1.65	0.16 ± 0.02
Brain	2.76 ± 0.55	4.00 ± 0.42	1.85 ± 0.45	2.24 ± 0.53	0.10 ± 0.02
Eye	2.52 ± 0.29	2.97 ± 0.44	1.45 ± 0.17	1.86 ± 0.31	0.08 ± 0.02
Fat (abdominal)	8.59 ± 1.82	19.25 ± 4.40	9.49 ± 1.68	18.48 ± 2.59	0.32 ± 0.03
G.I.T.	482.03 ± 71.83	341.87 ± 38.36	322.82 ± 93.16	238.61 ± 11.33	1.13 ± 0.39
Heart	9.99 ± 2.55	11.89 ± 2.67	6.32 ± 1.23	6.43 ± 1.22	0.30 ± 0.03
Kidney	48.29 ± 9.49	63.89 ± 17.51	26.78 ± 5.27	36.27 ± 7.72	0.66 ± 0.07
Liver	95.69 ± 11.15	56.45 ± 5.77	85.71 ± 17.45	38.90 ± 5.60	3.94 ± 0.89
Lung	10.78 ± 2.45	13.60 ± 2.43	7.47 ± 2.06	7.55 ± 1.51	0.33 ± 0.03
Lymph node (mes)	9.26 ± 3.61	13.67 ± 4.87	6.79 ± 1.32	9.22 ± 4.51	0.26 ± 0.03
Muscle	3.50 ± 0.84	4.11 ± 0.66	2.30 ± 0.57	2.55 ± 0.39	0.14 ± 0.02
Ovary	Nc	13.75 ± 2.66	Nc	8.90 ± 1.75	Nc
Pancreas	8.79 ± 1.44	14.01 ± 2.91	6.72 ± 1.73	7.01 ± 1.22	0.27 ± 0.04
Plasma	31.86 ± 6.67	35.99 ± 11.15	18.87 ± 5.87	17.96 ± 5.29	0.19 ± 0.04
Prostate	5.67 ± 2.17	Nc	15.00 ± 20.27	Nc	0.14 ± 0.04
Skin	7.03 ± 1.15	9.32 ± 1.61	4.63 ± 1.14	6.08 ± 0.65	0.47 ± 0.21
Spleen	4.65 ± 1.12	6.37 ± 0.89	3.32 ± 0.94	3.79 ± 0.58	0.37 ± 0.07
Submaxillary gland	6.76 ± 1.39	8.74 ± 1.11	4.52 ± 1.19	4.93 ± 1.11	0.14 ± 0.02
Testis	4.98 ± 0.88	Nc	3.76 ± 0.54	Nc	0.08 ± 0.01
Thymus	4.71 ± 1.50	6.32 ± 1.54	3.17 ± 0.32	3.92 ± 1.06	0.11 ± 0.02
Thyroid	13.25 ± 3.52	11.52 ± 2.27	6.87 ± 1.93	6.73 ± 1.08	0.58 ± 0.17
Uterus	Nc	11.61 ± 1.81	Nc	6.01 ± 1.84	Nc
Whole-blood	18.46 ± 3.66	21.25 ± 5.63	12.33 ± 3.74	12.22 ± 2.95	1.52 ± 0.19

Nd: No radioactivity detected; Nc: Not calculable; sd: Standard deviation

Table B.6.1-8: Proportions of radioactive components in urine (0-48 hours), faeces (0-72 hours) and bile* after a single low oral dose (35 mg/kg bw) of [ring-U-^{14}C-phenoxy]beflubutamid to rats

Component	Urine		Faeces		Bile*					
	M	F	M	F	M	F	Enzyme deconjugation of male rat bile			
							Untreated control	Buffer	B-glucu-ronidase	Inhibitor
Polars	5.7	8.5	4.7	2.8	55.1	46.7				
UR-50604 conjugate	1.1	2.2								
Conjugates							45.9	23.5	17.2	50.7
UR-50604	22.5	31.4	5.4	2.6	22.3	6.4	24.4	23.5	22.5	26.8
UR-50624			2.0	3.6	8.4	1.6				
P5[a]/UR-50615			7.2	9.4						
UR-50617			9.6	6.4						
UR-50618			9.3	5.8						
UR-50619			3.7	1.8			Nd	3.4	3.6	Nd
UR-50617/ 18/24							16.9	31.9	38.7	9.6
beflubutamid			3.4	2.5	5.9	9.7	1.1	5.2	7.3	1.8
Others[b]	2.1	2.7	6.8	5.3	2.8	1.9	6.3	7.3	5.3	5.9
Extracts unused[c]			1.6	1.0						
Residue[d]			11.9	9.5						

Results are expressed as % dose; *: bile from rats with cannulated bile ducts; [a]: Indicated by mass spectroscopy to be dihydroxy benzyl beflubutamid; [b]: The sum of other minor radioactive residues present in urine (including UR-50624 and UR-50626), faeces or bile; [c]: Extract containing small proportions of radioactivity that were not pooled for analysis; nd: not detected; [d]: not further analysed

Table B.6.1-9: Proportions of radioactive components in urine (0-48 hours), faeces (0-72 hours) and bile* after a single high oral dose (350 mg/kg bw) or multiple oral doses (35 mg/kg bw) of [ring-U-^{14}C-phenoxy]beflubutamid to rats

Component	350 mg/kg bw		Multiple 35 mg/kg bw* – Male			
	Male	Female	Day 1	Day 5	Day 10	Day 14
Urine (0-48 hours)						
Polars	4.3	5.1	5.2	5.4	5.4	7.3
UR-50604 conjugate	2.0	1.3	1.2	1.9	2.2	2.1
UR-50604	12.6	26.3	20.6	21.8	21.8	25.0
Other[a]	1.9	2.5	2.0	2.6	2.3	2.7
Faeces (0-72 hours)						
Polars	<0.3	0.4	3.8	6.5	4.5	2.2
UR-50604	2.9	1.0	3.6	6.4	5.4	7.8
UR-50624	1.1	<0.3	1.6	2.5	2.8	2.6
P5/UR-50615	5.4	8.5	7.8	7.9	8.6	21.7
UR-50617	14.0	17.4	4.5	5.6	10.0	13.2
UR-50618	<0.3	<0.3	3.8	10.8	5.8	10.4
UR-50619	3.2	1.5	3.0	3.2	3.5	4.5
Beflubutamid	39.9	26.6	2.4	3.0	3.1	2.6
Others[a]	3.9	1.1	3.5	5.6	7.2	2.4
Extracts unused[b]	0.5	0.9	0	0	0	4.7
Residue[c]	9.4	6.8	8.2	12.3	12.1	17.1
Bile from rats with cannulated bile ducts						
Polars	27.0	30.5				
UR-50604	8.1	8.6				
UR-50624	2.3	4.2				
Beflubutamid	4.2	2.5				
Other[a]	0.7	1.6				

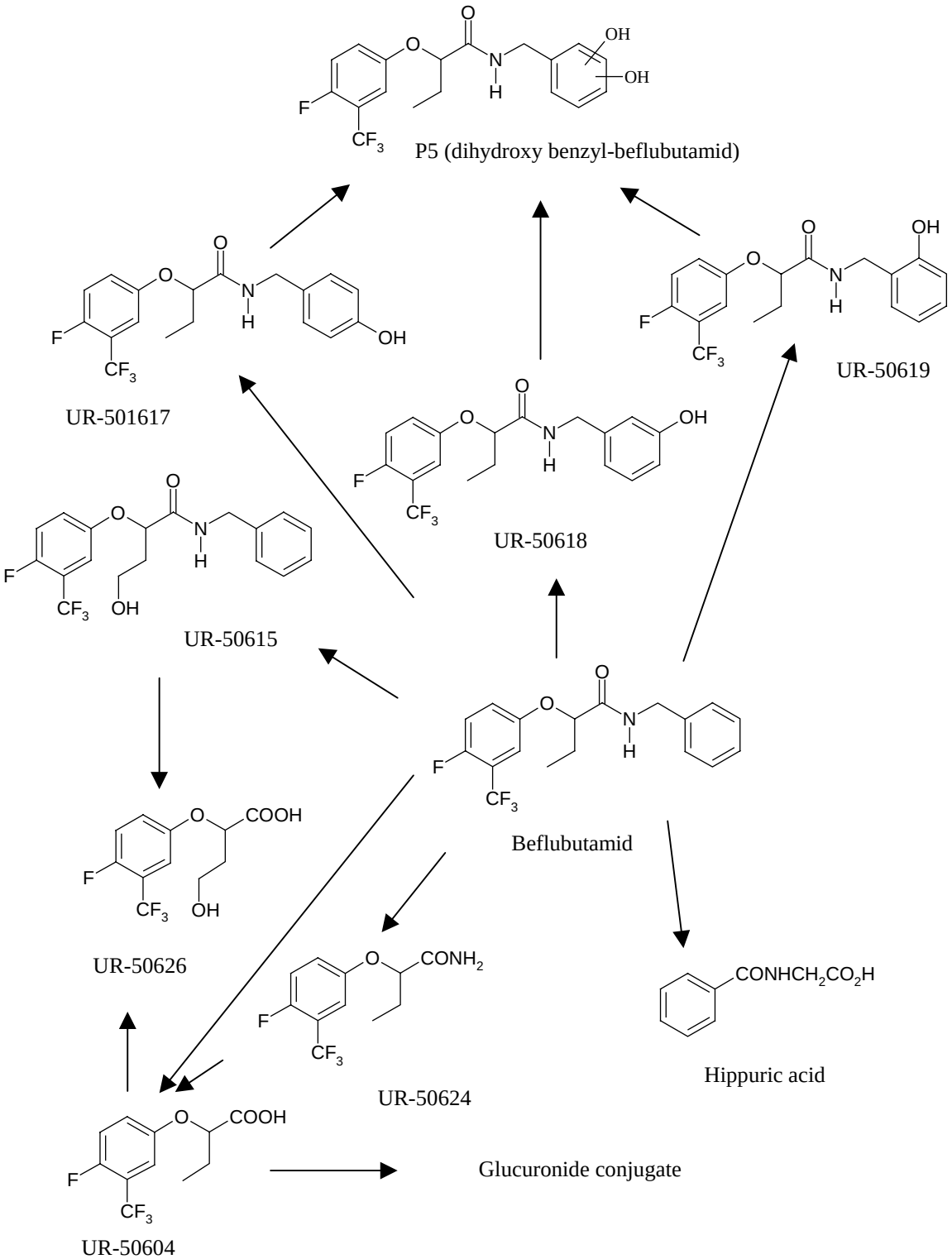
Results are expressed as % dose; *: Rats received 14 consecutive daily doses (Days 1, 5 and 10 urine or faeces extracts were for the 24 hour period following that dose); [a]: The sum of other minor radioactive residues present in urine (including UR-50624 and UR-50626), faeces or bile, but were not resolved in discrete peaks; [b]: Extracts containing small proportions of radioactivity that were not pooled for analysis; [c]: not further analysed

Table B.6.1-10: Proportions of radioactive components in urine (0-48 hours), faeces (0-72 hours) after a single oral dose (35 mg/kg bw) of [ring-U-^{14}C-benzylamine]beflubutamid to rats

Component	Male		Female	
	Urine	Faeces	Urine	Faeces
B1	6.7	4.8	5.8	3.2
Hippuric acid	29.3	Nd	36.2	Nd
B2	-	3.2	-	1.9
B3	-	2.3	-	2.1
B4	-	1.3	-	1.9
B5	-	2.7	-	4.3
B6[a]	-	6.2	-	8.1
UR-50615	-	6.2	-	4.4
UR-50617	-	10.1	-	7.5
UR-50618	-	4.6	-	3.9
UR-50619	-	3.3	-	2.4
Beflubutamid	-	2.9	-	4.6
Other[b]	1.3	0.2	1.1	1.0
Extracts unused[c]	0.92	0.78	1.31	0.58
Residue[d]	-	8.85	-	7.92

Results are expressed as total % dose; [a]: Postulated to be dihydroxy benzyl beflubutamid; [b]: Areas of no discreet radioactivity; [c]: Extract containing small proportions of radioactivity that were not pooled for analysis; [d]: not further analysed

Figure B.6.1-1: Proposed biotransformation pathway for beflubutamid in the rat



UR-50617, UR-50618, UR-50619 eliminated in bile as glucuronide conjugates

Conclusion:
The oral absorption of beflubutamid in rat was nearly complete (>90% after 120 hours). After a high dose the absorption was less. Excretion was rapid with >90% being excreted in 48 hours. Tissue distribution was similar for male and female rats and radioactivity was present in all tissues, with the highest concentrations in liver and kidneys. Retention in tissues and carcass 5 days after dosing was very low (<0.3% dose in single dose, <2% dose after multiple dosing). Beflubutamid was rapidly and extensively metabolised with the major metabolite UR-50604 excreted in urine (23-31%).

B.6.2 Acute toxicity including irritancy and skin sensitization (Annex IIA 5.2)

Beflubutamid is of low toxicity. Slight signs of toxicity (wet fur, hunched posture and pilo-erection) were observed after inhalation of the test material. After application of beflubutamid to the eye of rabbits slight transient ocular irritation was observed. No skin irritation was observed in rabbits after dermal application. In a Maximisation test according to Magnusson and Kligman, no signs of allergic skin reactions in the test animals were recorded. Based on the above shown test results (seeTable B.6.2-1), no classification is required for acute toxicity of beflubutamid according to the criteria in Council Directive 67/548/EEC.

Table B.6.2-1: Summary of acute toxicity studies

Test	Species	Results
LD_{50} oral (Limit test)	Rat	(m/f) > 5000 mg/kg bw
LD_{50} dermal (Limit test)	Rat	(m/f) > 2000 mg/kg bw
LC_{50} inhalation (Nose only)	Rat	(m/f) > 5 mg/l air
Skin irritation	Rabbit	Non irritant
Eye irritation	Rabbit	Non irritant
Skin sensitisation (Magnusson/Kligman Test)	Guinea pig	Non sensitizing

B.6.2.1 Oral

Report: K. Snell (1995a); UR-50601: Acute oral toxicity (limit test) in the rat; UBE Industries, Ltd.; unpublished report no. 512/26, 24.07.95 [Safepharm Laboratories Limited, UK]; dates of experimental work: 15.03.1995 to 06.04.1995.

Test Material: Beflubutamid (UR-50601), batch number: 950123, purity: 97.61%

Test Animals: Sprague-Dawley rat

GLP: Yes

Test Method: OECD No. 401; 92/69/EEC B.1

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Following a range finding study, the test material was suspended in arachis oil B.P. and administered to groups of 5 male and 5 female fasted Sprague-Dawley rats by oral gavage at a dose level of 5000 mg/kg (application volume 10 ml/kg). The observation period was 14 days post-exposure.

Findings:
Mortality data: No mortalities were observed (Table B.6.2-2).

Table B.6.2-2 Acute oral toxicity of beflubutamid

Dose (mg/kg)	Mortality males	Mortality females	LD_{50} (mg/kg bw)
5000	0/5	0/5	> 5000

Clinical signs: No signs were noted during the study.
Bodyweight: All animals showed expected gain in bodyweight during the study
Necropsy: No abnormalities were noted.

Conclusion:
The acute oral median lethal dose (LD_{50}) of the test compound in rats was found to be greater than 5000 mg/kg bodyweight.

B.6.2.2 Percutaneous

Report: K. Snell (1995b); UR-50601: Acute dermal toxicity (limit test) in the rat; UBE Industries, Ltd.; unpublished report no. 512/27, 24.07.95 [Safepharm Laboratories Limited, UK]; dates of experimental work: 20.04.1995 to 04.05.1995.

Test Material: Beflubutamid; batch 950123; purity 97.61%

Test Animals: Sprague-Dawley rat

GLP: Yes

Test Method: OECD No. 402; 92/69/EEC B.3

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
The test material was administered as supplied to 5 male and 5 female Sprague-Dawley rats at 2000 mg/kg body weight to the shaved skin and held in place by a semi-occlusive dressing for 24 hours. The observation period was 14 days post-exposure.

Findings:
Mortality data: No mortalities were observed (Table B.6.2-3).

Table B.6.2-3: Acute dermal toxicity of beflubutamid

Dose (mg/kg)	Mortality males	Mortality females	LD_{50} (mg/kg bw)
2000	0/5	0/5	> 2000

Dermal reactions: No dermal reactions were observed during the study.
Clinical signs: No signs were noted during the study.
Bodyweight: All animals showed expected gain in bodyweight during the study except one male which decreased in weight during the second week of the study.
Necropsy: No abnormalities were noted.

Conclusion:
The acute dermal median lethal dose (LD_{50}) of the test compound in rats was found to be greater than 2000 mg/kg bodyweight.

B.6.2.3 Inhalation

Report: S.M. Blagden (1995); UR-50601: Acute inhalation toxicity (nose only) study in the rat; UBE Industries, Ltd.; unpublished report no. 512/028, 19.10.95 [Safepharm Laboratories Limited, UK]; dates of experimental work: 17.07.1995 to 02.08.1995.

Test Material: Beflubutamid; batch 950427; purity 97.74%

Test Animals: Sprague-Dawley rat

GLP: Yes

Test Method: OECD No. 403; 92/69/EEC B.2

Deviations: Occasional deviations from the temperature and relative humidity were stated but these are considered to have had no effect on the purpose or integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
5 male and 5 female Sprague-Dawley rats were exposed to the test material in a dust atmosphere at a mean achieved atmospheric concentration of 5 mg/l in a nose-only exposure system for 4 hours.

Table B.6.2-4: The main exposure parameters of the acute inhalation study

Parameter		Value
Chamber flow rate (l/min)		16
Chamber concentration	Mean achieved ± SD	5 ± 0.93
(mg/l)	Nominal	73.6
Particle size	MMAD ± GSD	3.6 ± 0.42
(μm)	% inspirable (< 4 μm)	54.4
Chamber air temperature	During exposure	22 - 26
(°C)	During study	21 ± 2
Relative humidity	During exposure	44 - 54
(%)	During study	55 ± 15

Findings:
Mortality data: No mortalities were observed (Table B.6.2-5).

Table B.6.2-5: Acute inhalation toxicity of beflubutamid

Dose (mg/l)	Mortality males	Mortality females	LC_{50} (4 hours) mg/l
5	0/5	0/5	> 5

Clinical signs: Wet fur was commonly noted during exposure. On removal from the chamber hunched posture and pilo-erection were common, in addition there were isolated incidents of red/brown staining around the eyes and ptosis. One hour after completion of exposure wet fur, red/brown staining around the eyes and ptosis were no longer evident. All animals recovered to appear normal one or two days after exposure.
Bodyweight: All animals showed expected gain in bodyweight during the study.
Necropsy: No abnormalities were noted.

Conclusion:
The acute inhalation median lethal concentration (LC_{50}, 4 hours) in the rat was greater than 5 mg/l of air.

B.6.2.4 Skin irritation

Report: B.I. Parcell (1995a); UR-50601: Skin irritation to the rabbit; UBE Industries, Ltd.; unpublished report no. UBE 1/950843/SE, 25.09.1995 [Huntingdon Life Sciences Ltd. (formerly Huntingdon Research Centre Ltd.), UK]; dates of experimental work: 04.04.1995 to 07.04.1995.

Test Material: Beflubutamid; batch number: 950123; purity 97.61%

Test Animals: New Zealand White rabbit

GLP: Yes

Test Method: 92/69/EEC B.4

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Six New Zealand White rabbits (4 females, 2 males) received 0.5 g of test material moistened with 0.5 ml distilled water, which was applied to the shaven skin of each animal. A 2.5 x 2.5 cm gauze pad was then placed over the area and secured in place with an adhesive dressing (semi-occlusive) and left for 4 hours. The observation period was 4 days.

Findings:
Dermal responses: No dermal response to the treatment was observed in any animal throughout the observation period (Table B.6.2-6)
Clinical signs: There were no signs of toxicity in any rabbit during the observation period.

Table B.6.2-6: Individual and mean skin irritation scores

Animal no.	Erythema (E) / Oedema (O)	Days			
		0*	1	2	3
3229 (f)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
3239 (f)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
3246 (f)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
3247 (f)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
3217 (m)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
3219 (m)	E / O	0 / 0	0 / 0	0 / 0	0 / 0
Mean score 24-72 h.	E / O		0.0 / 0.0		

*: Approximately 60 minutes after removal of the dressing; f: female; m: male

Conclusion:
No reactions were observed following a single semi-occlusive application of beflubutamid to intact rabbit skin for four hours.

B.6.2.5 Eye irritation

Report: B.I. Parcell (1995b); UR-50601: Eye irritation to the rabbit; UBE Industries, Ltd.; unpublished report no. UBE 2/951189/SE, 25.09.1995 [Huntingdon Life Sciences Ltd. (formerly Huntingdon Research Centre Ltd.), UK]; dates of experimental work: 10.04.1995 to 01.05.1995.

Test Material: Beflubutamid; batch number: 950123; purity: 97.61%

Test Animals: New Zealand White rabbit

GLP: Yes

Test Method: 92/69/EEC B.5

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Following the treatment of 2 male New Zealand White rabbits ahead of the others (rinsed and unrinsed) to gauge the eye irritation potential of beflubutamid, 8 male rabbits received a single ocular dose of 70 mg in the lower everted lid of one eye. The eyes of 3 of these rabbits were rinsed with water for 30 seconds approximately 2 minutes after instillation.

Findings:
Ocular responses: A single ocular instillation of the test compound elicited transient mild conjunctival irritation in all animals. One rabbit (with rinsed eye) showed diffuse crimson colouration of the conjunctivae accompanied by obvious swelling with partial eversion of the eyelids. All reactions had resolved 4 days after instillation (Table B.6.2-7 and Table B.6.2-8). Rinsing the eye did not appear to reduce the irritation potential.
Clinical signs: There were no signs of toxicity in any rabbit during the observation period.

Table B.6.2-7: Individual and mean eye irritation scores (unrinsed eyes)

Animal no.	Region of eye	One hour	Days				
			1	2	3	4	7
686	Cornea	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	0	0	0	0	0
	chemosis	0	0	0	0	0	0
687	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	0	0	0	0
	chemosis	0	0	0	0	0	0
689	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	0	0	0	0	0
	chemosis	0	0	0	0	0	0
690	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	1	1	0	0
	chemosis	0	0	0	0	0	0
691	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	1	1	0	0
	chemosis	0	0	0	0	0	0
3223	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	1	0	0	0
	chemosis	0	0	0	0	0	0
Mean score 24-72 h.	Cornea density		0.0				
	Iris		0.0				
	Conjunctiva -						
	redness		0.5				
	chemosis		0.0				

Table B.6.2-8: Individual and mean eye irritation scores (rinsed eyes)

Animal no.	Region of eye	One hour	Days				
			1	2	3	4	7
685	Cornea	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	0	0	0	0	0
	chemosis	0	0	0	0	0	0
758	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	0	0	0	0
	chemosis	0	0	0	0	0	0
759	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	2	1	0	0	0	0
	chemosis	2	0	0	0	0	0
760	Cornea density	0	0	0	0	0	0
	Iris	0	0	0	0	0	0
	Conjunctiva -						
	redness	1	1	0	0	0	0
	chemosis	0	0	0	0	0	0
Mean score 24-72 h.	Cornea density		0.0				
	Iris		0.0				
	Conjunctiva -						
	redness		0.3				
	chemosis		0.0				

Conclusion:
Instillation of beflubutamid into the rabbit eye elicited transient mild conjunctival irritation. On the basis of the eye reactions observed (mean eye irritation scores 24-72 hours after installation of the test article are 0-0.5) and the criteria specified in Council Directive 67/548/EEC, classification is not required.

B.6.2.6 Skin sensitisation

Report: S.A. Allan (1996); UR-50601: Skin sensitisation in the guinea-pig (Incorporating a positive control using formalin); UBE Industries, Ltd.; unpublished report no. UBE 3/951150/SS, 07.02.1996 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work 29.03.1995 to 14.05.1995.

Test Material: Beflubutamid; batch number: 950123; purity: 97.61%

Test Animals: Guinea pig of the Dunkin/Hartley strain

GLP: Yes

Test Method: 92/69/EEC B.6 (Magnusson, B. and Kligman, A. M. (1970) *Allergic Contact Dermatitis in the Guinea-pig: Identification of contact allergens,* Thomas, C. C., Springfield, Illinois, USA)

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods: Sixty male albino guinea-pigs of the Dunkin/Hartley strain were allocated to four groups as follows:

1. Control for group 2; 20 animals
2. Test beflubutamid; 20 animals
3. Control for group 4; 10 animals
4. Test formalin (positive control); 10 animals

Based on the results of a preliminary study (intradermal injection 0.1-80% w/v, topical application 30-80% w/v), the following dose levels were selected:

Intradermal injection: 20% w/v in Alembicol D

Topical application: 80% w/v in Alembicol D

Challenge application: 80 and 40% w/v in Alembicol D

The Positive Control group received the following dosage schedule:

Intradermal injection: 0.1% v/v in water for irrigation

Topical application: 10% v/v in distilled water

Challenge application: 5 and 1% v/v in distilled water

Control groups (1 and 3) were treated similarly to the test groups. Topical application was conducted 6 days after the intradermal injection, and the challenge application was conducted two weeks after the topical application. The induction and challenge applications were held in place with occlusive dressing for 48 and 24 hours respectively. After removal of the patches, the challenge sites were evaluated after 24, 48 and 72 hours.

Findings:

Dermal responses: Dermal reactions were seen following the induction applications in all four groups. After challenge the test compound did not produce evidence of skin sensitisation (delayed contact hypersensitivity) in any of the twenty test animals. Evidence of skin sensitisation was produced by formalin in all of the ten test animals (Table B.6.2-9).

Clinical signs and bodyweight: There were no clinical signs or effects on bodyweight in any guinea-pig during the observation period due to treatment.

Table B.6.2-9: Number of animals exhibiting skin reactions after challenge

Group	Treatment	No. of animals	Incidence of erythema						Incidence of oedema					
			24 hr		48 hr		72 hr		24 hr		48 hr		72 hr	
			A	P	A	P	A	P	A	P	A	P	A	P
Control	Freund's treated controls	20	0	0	0	0	0	0	0	0	0	0	0	0
Test	beflubutamid	20	0	0	0	0	0	0	0	0	0	0	0	0
Control	Freund's treated controls	10	1	0	0	0	0	0	0	0	0	0	0	0
Positive control	Formalin	10	9	9	9	8	9	8	8	1	8	1	8	1

A: Anterior site, exposed to beflubutamid, 80% w/v in Alembicol D; P: Posterior site, exposed to beflubutamid, 40% in Alembicol D.

Conclusion: In this study, beflubutamid did not produce evidence of skin sensitisation (delayed contact hypersensitivity) in any of the twenty test animals, and therefore according to the criteria in Council Directive 67/548/EEC, classification is not required.

B.6.3 Short-term toxicity (Annex IIA 5.3)

The short-term toxicity studies were conducted during 1995–1998. All studies were performed and reported in accordance with OECD and EU testing guidelines with exceptions listed accordingly and were fully compliant with GLP. A summary of these results is presented in Table B.6.3-1.

Overall, in all animal species under investigation, the **liver** was the target organ identified after 90-days oral administration in rats, mice and dogs and in the one-year dog study. In addition, the **kidneys, thyroid gland** and **adrenal glands** were affected in rats, mainly evidenced by organ weight changes. All species under investigation revealed decreased body weight gains at the upper dose levels.

In the **28-day study in rats**, higher kidney weights were recorded in both sexes at 3200 ppm. A reduction in adipose tissue was noted in 1/5 rats at 400 ppm and in 5/5 rats at 3200 ppm. The NOAEL was found to be 400 ppm (39.9 mg/kg bw/d for males; 38.4 mg/kg bw/d for females).

In the **90-day study in rats** a prolongation of thrombotest clotting time, higher methaemoglobin (males), plasma cholesterol and phospholipid values, increased liver, thyroid, kidney, and adrenal weights were noted at the high dose level of 3200 ppm. Histopathological examination revealed centrilobular hypertrophy of hepatocytes and renal pelves dilatation (females). No histopathological changes were noted in the thyroid gland and adrenal glands which may have accounted for increased organ weights. The NOAEL was found to be 400 ppm (29 mg/kg bw/d in males; 35 mg/kg bw/d in females).

In the **90-day study in mice** higher liver weights and centrilobular hepatocyte hypertrophy was noted in all treated groups. The severity of this finding was increasing with increasing dose levels in male mice whereas females were affected with lower severity at higher dose levels. In addition, females of the two highest dose groups showed a generalised liver hepatocyte hypertrophy and periportal hepatocytes with cytosplasmic eosinophilia. Since the

liver is the target organ in all animal species under investigation, the lowest observed adverse effect level, LOAEL, was found to be 400 ppm (61 mg/kg bw/d for male and 87 mg/kg bw/d for female) based on centrilobular hepatocyte hypertrophy and liver weight changes at this dose level. A NOAEL of 50 ppm (6.4 mg/kg bw/d for males and 8.5 mg/kg bw/d for females) can be derived from the carcinogenicity study in mice.

In addition to the liver weight increases and hepatocyte hypertrophy, the **90-day study in dogs** showed increased activities of hepatic enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase), an activated partial thromboplastin time (APTT), delayed prothrombin time (PT) as well as degenerative changes in the liver and bile ducts (hepatocyte loss, necrosis, inflammation, bile duct proliferation, prominent major bile ducts). In dogs at 300 and 1000 mg/kg bw/d histopathological changes in the prostate (acinar atrophy/fibrosis), epididymides (absent spermatozoa, round spermatids and spermatocytes in ductules) and testes (degenerate/exfoliate round spermatids and spermatocytes) together with lower gonad weights at the high dose group are of equivocal toxicological relevance. The NOAEL was found to be 100 mg/kg bw/d.

The **12-month study in dogs**, confirmed the findings of the 90-day study with respect to changes in haematological and clinical chemistry parameters, i.e. increased clotting times and increased hepatic enzyme activities as well as lower plasma protein concentrations, liver weight increases together with a similar pattern of histopathological changes but additionally early portal to portal bridging and centrilobular collapse with hepatocyte necrosis occurred. Effects on testes and/or epididymides were not observed in this study. The NOAEL was was found to be 60 mg/kg bw/d .

Table B.6.3-1: Summary of subchronic toxicity studies

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
28-day feeding Crl:CD BR rat 0, 50, 400, 3200 ppm	39.9 / 38.4 m/f [400 ppm]	3200 ppm: Higher kidney weight, reduction in adipose tissue.
90-day feeding Crl:CD BR rat 0, 100, 400, 3200 ppm	29 / 35 m/f [400 ppm]	3200 ppm: Prolongation of thrombotest clotting time (m), higher methaemoglobin (m), plasma cholesterol and phospholipid values, higher liver, thyroid, kidney, adrenal weight, centrilobular hypertrophy of hepatocytes (m), renal pelves dilatation (f).
90-day feeding Crl:CD-1 BR mouse 0, 400, 1600, 3200, 6400 ppm	< 61 / 87 m/f [<50/< 50 ppm m/f] (ca. 6.4 / 8.5 m/f [50 ppm], carcinogenicity study	400 ppm: Centrilobular hepatocyte hypertrophy of the liver
90-day oral (gelatine capsule) Beagle dog 0, 100, 300, 1000 mg/kg bw/d	100 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin time, higher liver weights. At 1000 mg/kg bw/d: increase in prothrombin time, higher activities of liver enzymes, degenerative changes in liver and bile duct.
52-week oral (gelatine capsule) Beagle dog 0, 12, 60, 300 mg/kg bw/d	60 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin and prothrombin time, increases in alkaline phosphatase and alanine aminotransferase, reductions in plasma total protein, higher liver weight, liver enlargement, severe degenerative changes in the liver.

m: male; f: female; bw: bodyweight, d: day

B.6.3.1 Rat oral toxicity studies

B.6.3.1.1 28-day study

Report: M.H. Barker, B. Harris (1996); UR-50601: Toxicity to rats by repeated dietary administration for 4 weeks; UBE Industries, Ltd., unpublished report no UBE 11/952715, 03.06.1996 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 07.11.1995 to 05.12.1995.

Test Material: Beflubutamid (UR-50601), batch no. 950427, purity: 97.74%

Test Animals: Crl:CD Br rats; bw (Day 1): males 184-218 g; females: 136-167 g; Source: Charles River (UK) Ltd, Margate, Kent, UK

GLP: Yes

Test Method: OECD No. 407, adopted 12 May 1981; 92/69/EEC B.7 (1992)

Deviations: (1) Functional tests required in the current TG 407 (adopted 27.07.95) were not performed/reported.
(2) Sampling of Peyer's patches as required in current TG 407 was not mentioned in the report.
(3) Thymus weights as required in current TG 407 were not taken.
(4) Histopathological examination was carried out on a limited set of organs/tissues from control and high dose group only.

Acceptability: The study is considered to be acceptable.

Material and Methods:
The conduct of the study generally followed the current OECD TG 407, with the exceptions listed above. Four groups of 5 male and 5 female Crl:CD Br rats received the test material by dietary administration at concentrations of 0, 50, 400 and 3200 ppm for 4 weeks. In order of increasing doses the treated rats ingested the equivalent of 5.0, 39.9 and 350 mg/kg bw/day for males and 5.1, 38.4 and 325 mg/kg bw/day for females. Bodyweight gain, water and food consumption were measured at regular intervals. All animals were subjected to ophthalmoscopy, haematology, clinical chemistry, urinalysis, organ weights, and macropathology. Histopathological examinations were carried out on a limited set of organs/tissues from the control and high dose group and on macroscopically abnormal tissue from any animal on study.

Findings:
Mortality: No mortalities were observed.
Clinical signs: No treatment-related effects were observed.
Bodyweight gain: At 3200 ppm statistically significant lower bodyweight gains were noted in the first week and overall weight gain was lower after treatment for both sexes.
Food and water consumption: No treatment-related effects were recorded. Cumulative water intakes were variable compared to controls, but the differences were not dose-related.
Ophthalmoscopy: No treatment-related effects were recorded.
Haematology: At 3200 ppm a lower total white blood cell count (principally due to lymphocyte counts) was noted in males.
Higher values for mean cell haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) noted in females at 400 ppm and/or 3200 ppm were considered unrelated to the treatment since changes were minor, no dose-response relationship was seen and other red blood cell parameters were not affected.
Clinical chemistry: At 3200 ppm minor but statistically significantly higher total protein and globulin levels for females were noted.
Urinalysis: No treatment-related effects were recorded.
Organ weights: Higher kidney weights were recorded in both sexes at 3200 ppm, reaching statistical significance in males only.
Macroscopic pathology: A reduction in adipose tissue was noted in 1/5 rats at 400 ppm and in 5/5 rats at 3200 ppm.
Microscopic pathology: No treatment-related effects were observed.
No abnormalities were detected in the kidneys of control and high dose animals which may have accounted for organ weight changes.

Table B.6.3-2: Overview of 28-day toxicity in rats treated orally with beflubutamid (group mean values)

Sex	Male				Female			
Dose (ppm)	0	50	400	3200	0	50	400	3200
Bodyweight gain (g/rat)								
Week 0-1	57	55	61	42**	26	33	23	17*
Week 0-4	165	195	175	142	73	79	67	57
Haematology								
- WBC total (10^9/l)	14.82	13.87	12.82	10.73**	11.27	8.44	8.38	9.34
- Lymphocytes (10^9/l)	12.25	11.16	10.80	8.98**	9.64	7.06	7.05	8.11
Clinical chemistry								
- Total Protein (g/dl)	6.3	6.2	6.4	6.3	6.2	6.2	6.3	6.6*
- Globulins (g/dl)	3.3	3.1	3.3	3.2	3.1	3.1	3.1	3.4*
Organ weights/g								
- Kidney, both								
- abs. values	2.82	2.97	2.88	2.99	1.91	1.80	1.86	2.01
- rel. values	0.78	0.76	0.78	0.89**	0.85	0.80	0.85	0.93*
Macroscopic pathology – Reduction adipose tissue	0	0	1	5	0	0	0	0

Statistical significance: *p<0.05; **p<0.01 (Williams' test)

Discussion:
The toxicological relevance of certain findings in the 3200 ppm groups remained inconclusive, e.g. changes of white blood cell count, mainly lymphocyte count in male animals, higher values of plasma total protein and globulins in females.
Attention was drawn to the target organs which could be identified in course of the toxicity studies, e.g. liver, kidneys, and thyroid gland. In the present 28-day study in rats statistically significant higher kidney weights in were recorded in both sexes at 3200 ppm, although on histopathological examination no abnormalities were detected. No abnormalities were detected in the liver concerning organ weight and/or histopathological changes. The thyroid gland was not examined in this study (no organ weights taken, no histopathological examination performed).

Conclusion:
The no observed adverse effect level, NOAEL, was found to be 400 ppm (39.9 mg/kg bw/d for male and 38.4 mg/kg bw/day for female), based on lower body weight gain, a reduction in adipose tissue, higher kidney weights at the next higher dose level of 3200 ppm (350 mg/kg bw/d in males; 325 mg/kg bw/d in females).

This NOAEL is in accordance with the proposal of the notifier.

B.6.3.1.2 90-day study

Report: M.H. Barker, C. Brennan (1997); UR-50601: Toxicity to rats by dietary administration for 13 weeks; UBE Industries, Ltd., unpublished report no. UBE 31/963207, 21.05.1997; Report amendment 1, 30.07.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 31.07.1996 to 31.10.1996.

Test Material: Beflubutamid; Batch 507001; Purity: 97.46%.

Test Animals: Crl:CD Br rats; bw (Day 1): males 154-186 g; females: 154-184 g; Source: Source: Charles River (UK) Ltd, Margate, Kent, UK

GLP: Yes

Test Method: 87/302/EEC, OECD No. 408, dated 12 May 1981 (EPA FIFRA 82-1; JMAFF 59 NohSan No. 4200)

Deviations: None which are considered to affect the results or integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Groups of 10 male and 10 female Crl:CD Br rats received the test material by dietary administration at concentrations of 0, 100, 400 and 3200 ppm for 13 weeks. In order of increasing doses the treated rats ingested the equivalent of 7.2, 29.1 and 230 mg/kg bw/day for males and 8.9, 34.8 and 297 mg/kg bw/day for females. Animals were subjected to ophthalmoscopy (prior to the start of treatment, control and high dose level rats in week 13), haematology, clinical chemistry and urinalysis (all animals week 13 of treatment), necropsy including organ weights, and microscopic pathology (organs/tissues of a specified list including all macroscopically abnormal tissues from the control and high dose level groups, both kidneys, livers and lungs from animals of the remaining dose levels sacrificed in week 13, and any macroscopically abnormal tissue in any animal). Test diets were prepared at weekly intervals throughout the study. The diet was then stored at 4°C until required. Achieved concentration was measured at all dose levels in diet samples from weeks 1 and 11.

Findings:
Formulation Analysis: Mean values were within the range 102% to 102.2% of nominal concentration confirming accurate formulation. Homogeneity and stability of beflubutamid in the rodent diet formulation was confirmed at a nominal concentration of 6400 ppm.
Mortality: There were no deaths related to treatment.
Clinical signs: No treatment-related findings were recorded.
Bodyweight gain: At 3200 ppm, statistically significant lower bodyweight gain was noted for males and females throughout the study.
Food and water consumption: Food consumption was lower in Week 1 for both sexes at 3200 ppm. For the rest of the treatment period, the overall food consumption in treated groups was similar to controls. No treatment-related effects were recorded for water consumption.
Ophthalmoscopy: No treatment-related effects were recorded.
Haematology: At 3200 ppm, males showed a statistically significant increase in thrombotest clotting time (TT). At 400 ppm and 3200 ppm methaemoglobin values were higher for males, reaching statistical significance only in group 4 (3200 ppm).
The following findings were not considered treatment-related: At both 400 and 3200 ppm females showed a slight, not dose-related but statistically significant decrease in thrombotest clotting time. At 100, 400 and 3200 ppm females showed an inverse dose-related trend towards decreased methaemoglobin values (statistically significant). At 100, 400 and 3200 ppm changes in mean corpuscular haemoglobin concentration (MCHC) in males and at 400 and 3200 ppm in females.

Clinical chemistry: Statistically significant increases in cholesterol and phospholipids for both sexes were recorded in the high dose group (3200 ppm) which were considered treatment-related.
The following findings were not considered treatment-related since they occurred without dose-response and/or changes were minor: Higher inorganic phosphorus levels in all treated females, statistically significant differences for plasma creatinine, urea nitrogen, calcium and chloride.
Urinalysis: No treatment-related effects were recorded.
Organ weights: At 3200 ppm, higher liver, thyroid, adrenal and kidney weights (females) were recorded.
Macroscopic pathology: Uniform cortical scarring in the kidneys of females was recorded at 400 and 3200 ppm.
Microscopic pathology: Centrilobular hypertrophy of hepatocytes was observed in males at 3200 ppm. In females of the high dose group a slightly increased incidence of dilated renal pelves was noted.
Changes in the testes and prostate noted in males no. 38 and 39 (3200 ppm), respectively where not considered directly related to the treatment with beflubutamid because of the low incidence and taking into account the lower mean body weight of high dose animals at the end of study.
There were no histopathological changes which may have accounted conclusively for the macroscopically observed cortical scarring of the kidneys in female rats and for higher thyroid and adrenal weights.

Table B.6.3-3: Overview of 90-day toxicity in rats treated orally with beflubutamid

Sex	Male				Female			
Dose (ppm)	0	100	400	3200	0	100	400	3200
Bodyweight gain								
- Week 0-1 (g)	63	66	58	49**	35	29	29	22**
- Week 1-13 (g)	260	267	275	233	115	111	121	88**
- Week 0-13 (g)	323	333	333	281*	150	140	150	110**
Haematology								
- TT (sec)	24	23	26	32**	21	20	19**	19**
- Met Hb (% Hb)	0.41	0.37	0.54	0.58*	0.67	0.38+++	0.45++	0.50+
Clinical chemistry								
- Cholesterol (mg/dl)	69	77	72	103**	86	96	92	115**
- Phospholipids (mg/dl)	110	113	110	155**	158	161	163	187*
Organ weights								
Liver (g) absolute	0.3	20.6	21.6	22.0	12.0	11.2	12.8	13.0
relative	4.0	4.0	4.1	4.7**	3.8	3.7	4.0	4.6**
Thyroid (mg) absolute	18.1❶	19.7	18.6	20.5	16.8	17.3	18.0	19.3
relative	3.6	3.8	3.6	4.4	5.3	5.8	5.7	6.9**
Kidneys (g) absolute	3.59	3.46	3.70	3.55	2.36	2.15	2.51	2.62
relative	0.70	0.67	0.71	0.76	0.74	0.72	0.79	0.94**
Adrenal glands (mg)								
absolute	58.9	64.3	63.2	68.9	76.8	72.8	72.0	78.7
relative	11.6	12.5	12.5	14.7*	24.3	24.4	23.0	28.3**
Macroscopic pathology								
Kidneys / Uniform cortical scarring	0/10	0/10	0/10	0/9	1/10	0/10	8/10	5/10
Histopathology								
Liver / Centrilobular hepatocyte hypertrophy (minimal)	0/10	0/10	0/10	3/9	0/10	0/10	0/10	0/10
Kidney / Dilatation of renal pelves	0/10	1/10	1/10	0/9	0/10	1/10	1/10	3/10

n.d.: not determined; Statistical significance: * $p<0.05$; ** $p<0.01$ (Williams' test), + $p<0.05$, ++ $p<0.01$, +++ $p<0.001$ (Student's t test)

❶ For male no. 7 (control group) a thyroid weight of 80.1 mg was recorded which is obviously a mistake also in the view that this organ was considered normal on histopathological evaluation. Therefore, the value was excluded for the calculation of means.

Conclusion:

The no observed adverse effect level, NOAEL, was found to be 400 ppm (29 mg/kg bw/day for male and 35 mg/kg bw/d for female) based on reduced bodyweight gain and slight reduction in food consumption, increase in thrombotest clotting time and methaemoglobin levels in males, an increase in plasma cholesterol and phospholipids for both sexes, changes of organ weights (e.g. liver, thyroid, kidneys, adrenal glands), centrilobular hypertrophy of hepatocytes in the liver of males, as well as dilatation of renal pelves in the kidneys of females at the next higher dose of 3200 ppm (297 mg/kg bw/d).

This NOAEL is in accordance with the proposal of the notifier.

B.6.3.2 Mouse oral toxicity studies

B.6.3.2.1 90-day study

Report: M.H. Barker, R.G. Turner-Cain (1997); UR-50601: Toxicity to mice by dietary administration for 13 weeks; UBE Industries, Ltd., unpublished report no. UBE 34/971905, 26.11.97 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 06.02.1997 to 9.05.1997; Three protocol amendments, dated 07.02.97, 23.06.97, and 22.07.97.

Test Material: Beflubutamid; Batch: 507001; Purity: 97.46%.

Test Animals: Crl:CD-1 BR-mouse; bw (Week 0): males 28-37 g; females: 23-32 g; Source: Charles River (UK) Ltd, Margate, Kent, UK

GLP: Yes

Test Method: 87/302/EEC, OECD No. 408, dated 12 May 1981

Deviations: (1) The study was performed to assist in the selection of dose levels for a carcinogenicity study. Therefore, no ophthalmoscopy, clinical chemistry, and urinalysis were performed. Microscopic examinations were restricted to all macroscopically abnormal tissues from all groups, lungs and kidneys from control and high dose group, and liver from all groups.
(2) Haematological examinations were restricted to (differential) white blood cell count. Data on red blood cell parameters, platelets and clotting potential were not provided.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Based on a 2-week oral palatability study in mice [Report no. UBE 33/963913 performed at Huntingdon Life Sciences Ltd., UK, 20.02.97] the dose levels for the 13 weeks study were set. Groups of 10 male and 10 female Crl:CD-1 (ICR) BR mice received the test material by dietary administration at concentrations of 0, 400, 1600, 3200 and 6400 ppm for 13 weeks. In order of increasing doses the treated mice ingested the equivalent of 61, 293, 535 and 1056 mg/kg bw/day for males and 87, 348, 671 and 1421 mg/kg bw/day for females. All animals were subjected to haematology, organ weights and necropsy. Histopathology was carried out on all gross changes (all groups), lungs, kidneys (control and high dose group) and liver (all groups). Test diets were prepared at weekly intervals throughout the study. Achieved concentration was measured at all dose levels in diet samples from weeks 1 and 11.

Findings:
Formulation Analysis: Mean values were within ± 3% of nominal concentration confirming accurate formulation. Homogeneity and stability of beflubutamid in the rodent diet formulation was confirmed at a nominal concentration of 6400 ppm.
Mortality: No mortalities were observed.

Clinical signs: No treatment-related findings were observed.
Bodyweight gain: Females receiving 6400 ppm showed less body weight gain, although without statistical significance (Student's t test). Males receiving 1600, 3200, or 6400 ppm also gained less weight compared to control and low dose group (400 ppm). Since the decrease was inversely dose related this finding was considered devoid of toxicological relevance.
Food and water consumption: No treatment-related effects were observed.
Haematology: No treatment-related effects were recorded on white blood cell parameters.
At 6400 ppm female mice revealed minor but statistically significant lower values for monocytes. At this dose level lymphocyte counts were also slightly lower, though without statistical significance. Since no similar findings were noted in male mice at any dose group this finding was considered incidental in nature and unrelated to the treatment with beflubutamid.
Organ weights: At 400 ppm, liver weights were statistically significantly higher for females and at 1600 ppm, 3200 ppm and 6400 ppm for both sexes.

Table B.6.3-4: Overview of 90-day toxicity in mice treated orally with beflubutamid

Sex	Male					Female				
Dose (ppm)	0	400	1600	3200	6400	0	400	1600	3200	6400
Bodyweight gain (g) (week 0-13)	14.6	16.3	++ 9.5	++ 10.0	+ 11.2	6.3	8.6	6.4	6.1	3.3
Organ weights Liver (g) absolute	2.29	2.40	2.57	2.94	3.62	1.84	2.14	2.13	2.29	2.51
relative	5.05	5.08	6.53**	6.98**	8.39**	5.52	6.25*	6.63**	7.22**	8.26**

* p<0.05; ** p<0.01 (Williams' test)

Macroscopic pathology: The liver was enlarged in male mice at all treatment levels and in female mice at 6400 ppm with incidences shown in Table B.6.3-5.

Microscopic pathology: In the liver, centrilobular hepatocyte hypertrophy was noted in male mice of all treatment groups and in female mice at 1600, 3200, and 6400 ppm. In females the changes were graded as minimal, whereas in males the severity was increasing with increasing dose levels. Furthermore, a generalised hepatocyte hypertrophy and hepatocytes with cytoplasmic eosinophilia was observed in female mice at 3200 ppm and 6400 ppm (see Table B.6.3-5).

Table B.6.3-5: Liver pathology

Sex	Male					Female				
Dose (ppm)	0	400	1600	3200	6400	0	400	1600	3200	6400
Macropathology: Liver; enlargement	0/10	1/10	1/10	6/10	10/10	0/10	0/10	0/10	0/10	2/10
Histopathology: Liver - No. examined	10	10	10	10	10	10	10	10	10	10
Hepatocyte hypertrophy - centrilobular										
Total:	0	4	6**	9**	10**	0	0	1	3	4*
• Minimal	0	2	2	1	0	0	0	1	3	4*
• Slight	0	2	4*	5*	5*	0	0	0	0	0
• Moderate	0	0	0	3	3	0	0	0	0	0
• Marked	0	0	0	0	2	0	0	0	0	0
Hepatocyte hypertrophy - generalised										
Total:	0	0	0	0	0	0	0	0	1	2
• Minimal	0	0	0	0	0	0	0	0	1	2
Periportal hepatocytes with cytoplasmic eosinophilia	0	0	0	0	0	0	0	0	5*	5*

Statistical significance: *p<0.05; **p<0.01

Discussion:
Effects on centrilobular liver hepatocytes were already noted in the lowest dose group in males. Females were affected with lower severity at higher dose levels although organ weight changes were noted already in the low dose group of 400 ppm. Females of the two highest dose groups additionally showed a generalised liver hepatocyte hypertrophy and periportal hepatocytes with cytosplasmic eosinophilia. Since the liver is the target organ in all animal species under investigation, the proposal of the notifier to set the NOAEL at 6400 ppm with the reason given that the liver findings have arisen solely as the result of an adaptive effect and are not indicative of toxicity is not supported. Taking into consideration all available data for this species, a NOAEL of 50 ppm (6.4 mg/kg bw/d for males and 8.5 mg/kg bw/d for females) can be established for mice based on the data from the carcinogenicity study.

Conclusion:
The lowest observed adverse effect level, LOAEL, was found to be 400 ppm (61 mg/kg bw/d for male and 87 mg/kg bw/d for female) based centrilobular hepatocyte hypertrophy at this dose level. A NOAEL of 50 ppm (6.4 mg/kg bw/d for males and 8.5 mg/kg bw/d for females) can be derived from the carcinogenicity study in mice.

This NOAEL is not in accordance with the proposal of the notifier who derived a NOAEL at 6400 ppm. This was based on the consideration that the liver findings were the result of an adaptive effect solely. Agreement is reached on the assumption of the notifier that the dose level of 6400 ppm (1056 mg/kg bw/day) would not be sustainable over long-term administration due to liver changes.

B.6.3.3 Dog oral toxicity studies

B.6.3.3.1 90-day study

Report: M.H. Barker, B. Harris (1997b); UR-50601: Toxicity to dogs by repeated oral administration for 13 weeks; UBE Industries, Ltd., unpublished report no. UBE 40/973046, 03.12.1997; Report amendment 1, 05.04.2000 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 04.03.1997 to 06.06.1997.

Test Material: Beflubutamid; Batch 507001; Purity: 97.46%.

Test Animals: Beagle dog, bw (week 0) males: 8.0-9.7 kg, females: 6.4-9.0 kg
Source: Interfauna UK Ltd., Abbots Ripton Road, Wyton, Huntingdon, UK

GLP: Yes

Test Method: 87/302/EEC B.27; OECD No. 409 dated 12 May 1981
(JMAFF 59 NohSan No. 4200, EPA FIFRA)

Deviations: None which are considered to have affected the results or integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
In a preliminary study an oral MTD of > 1000 mg/kg bodyweight for dogs was derived [Report no. UBE 39/971150 performed at Huntingdon Life Sciences, UK, 24.06.97]. Groups of 4 male and 4 female Beagle dogs received the test compound at 0, 100, 300, and 1000 mg/kg/day by repeated oral administration in gelatine capsules for 13 weeks. All animals were sacrificed after week 13. All animals were subjected to ophthalmoscopy, haematology, clinical chemistry, urinalysis, bone marrow smears, organ weight, macro- and microscopic pathology.

Findings:
Storage Stability: Analysis of a batch of beflubutamid demonstrated stability for the study duration when stored at 4°C in the dark. Since for the application of beflubutamid by capsule no vehicle was used, analysis of stability in vehicle and of homogeneity in vehicle was not necessary.
Mortality: One male dog (no. 1737) from the high dose group (1000 mg/kg bw/d) was sacrificed in moribund condition on day 2 of week 11 following weight loss, poor appetite and raised liver enzyme values.
Clinical signs: The incidence of vomiting (no. of days/week sign observed) was higher in female dogs of the high dose group.
Bodyweight gain: Bodyweight gain was lower at 300 and 1000 mg/kg bw/d in both sexes, although reaching statistical significance only for male dogs. Mean final body weight was also slightly lower in dogs at 100 mg/kg bw/d but the difference was less than 10% and, therefore considered not treatment-related.

Food consumption: Food consumption for males at 1000 mg/kg bw/d was statistically significantly lower than controls. Females receiving 300 or 1000 mg/kg day showed slightly reduced food consumption. However, food consumption for some of these females was somewhat variable throughout the treatment and pre-dose periods.
Ophthalmoscopy: No treatment-related effects were observed.

Table B.6.3-6: 90-day toxicity in dogs treated orally with beflubutamid

Sex	**Male**				**Female**			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Mortality	0	0	0	1	No treatment-related effects			
Clinical signs: - Vomiting Week 1-13 (Incidence)	6	0	2	6	0	0	2	13
Bodyweight gain Week 0-13 (kg)	2.9	2.3	1.2*	0.5*	1.9	1.5	1.3	0.9
Body weight (kg) - group mean values wk 13	11.9	11.3	10.2	9.7	10.0	9.2	9.1	8.4
Food consumption Week 0-13 (g/dog/week)	2800	2798	2800	2614**	2705	2742	2513	2427

* $p < 0.05$, ** $p < 0.01$ (Williams' test)

Haematology: See also Table B.6.3-7.
At 300 and 1000 mg/kg bw/d an increase in activated partial thromboplastin time (APTT) was recorded for both sexes during weeks 6 and 13. Prothrombin time (PT) was delayed at 1000 mg/kg bw/d at week 13 in both sexes, reaching statistical significance only in male dogs. These changes were considered treatment-related.
Lower eosinophil count noted for male and female dogs at various occasions at all dose levels were not considered of toxicological relevance since no histopathological findings were noted to account for this change. Likewise, changes on certain red blood cell parameters at 300 and 1000 mg/kg bw/d did not follow a conclusive pattern and are therefore, considered incidental in nature and not related to the treatment with beflubutamid.
Clinical chemistry: See also Table B.6.3-7.
An increase in alkaline phosphatase (AP), glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) was observed for each one male and one female dog at 1000 mg/kg bw/d (nos. 1739, 1742). In the male dog of this group (no. 1739), gamma glutamyltransferase (GGT), bilirubin (Bili) and cholesterol (Chol) values were also elevated.
Statistically significant findings included a decrease in glucose, sodium and calcium (males), an increase in globulin, urea and phosphorus (females), but these were minor and are considered not to be of toxicological relevance.
Urinalysis: See also Table B.6.3-7.
One male (no. 1739) of the high dose group had an increase in proteins and a large amount of bile pigment in the urine which was considered treatment-related. This change was apparently responsible for the statistical significance reached for this finding in high dose males.
All other changes reaching statistical significance were considered to be incidental in nature since changes were minor expressing individual variability.
Bone marrow smears: No treatment-related effects were recorded.

Table B.6.3-7: Laboratory investigations

Sex		Male				Female			
Dose (mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Haematology									
APTT (s)	wk 0	19.9	18.0	19.3	18.0	19.1	17.6	17.8	17.6
	wk 6	21.6	22.7	26.4	28.3*	20.8	21.3	25.4*	27.0**
	wk 13	21.3	21.8	26.7	32.3**	18.8	21.4	25.6**	27.6**
PT (s)	wk 0	6.2	6.3	6.3	6.2	6.3	6.3	6.1	6.6
	wk 6	6.2	6.4	6.4	6.3	6.3	6.4	6.2	6.7
	wk 13	6.2	6.6	6.6	7.3*	6.5	6.5	6.4	7.2
Clinical chemistry									
AP (mU/ml)	wk 0	355	268	317	279	328	326	333	333
	wk 6	279	163	210	199	258	238	236	252
	wk 13	296	152	222	348❶	222	215	230	302❷
GPT (mU/ml)	wk 0	21	31	26	23	27	23	26	25
	wk 6	25	26	18	28	29	29	26	27
	wk 13	22	26	20	159❶	34	28	25	121❷
GOT (mU/ml)	wk 0	20	20	24+	21	21	22	20	25
	wk 6	20	19	19	19	23	22	18	21
	wk 13	24	24	22	71❶	30	28	25	46❷
Urinalysis									
Protein (mg/dl)	wk 0	41	37	35	39	37	30	45	40
	wk 6	29	27	31	44*❸	25	24	29	26
	wk 13	27	24	25	60*❸	22	24	25	29

• $p < 0.05$, ** $p < 0.01$ (Williams' test) ; + $p < 0.05$ (Student's t test)
❶ Individual values male no. 1739: AP 610 mU/ml; GPT 438 mU/ml; GOT 172 mU/ml
❷ Individual values female no. 1742: AP 479 mU/ml; GPT 401 mU/ml; GOT 107 mU/ml
❸ Individual values male no. 1739: week 0: 37 mg/dl; week 6: 50 mg/dl; week 13: 99 mg/dl

Organ weights: See also Table B.6.3-8.
Both sexes at 300 and 1000 mg/kg bw/d displayed statistically significantly higher liver weights (absolute and relative). It should be mentioned that the liver weights (absolute) of male no 1739 and female no. 1742 (1000 mg/kg bw/d) were lower compared to other dogs of this group. Additionally, dogs at 100 mg/kg bw/d also had slightly increased liver weights though without statistical significance. Kidney weights were slightly higher in male dogs at 1000 mg/kg bw/d. Furthermore, male dogs at 1000 mg/kg bw/d revealed slightly lower gonad weights.
Other statistically significant findings including a decrease in absolute weight of thyroid (males), brain and adrenals (females) were not of toxicological importance, as their relative weights were inconspicuous and histopathological changes were not observed.
Macroscopic pathology: The distended gall bladder noted in male no. 1737 (1000 mg/kg bw/d) is considered treatment-related, well matching to the histopathological diagnosis (Gall bladder: bile duct proliferation). No further treatment-related gross changes were observed.
Microscopic pathology: See also Table B.6.3-8.
At 300 and 1000 mg/kg/day centrilobular hepatocyte loss/necrosis and inflammation was seen in liver of dogs of both sexes. Generalised hepatocyte hypertrophy, haemosiderin-laden (pigmented) macrophages and single cell necrosis was observed in the liver of both sexes at

1000 mg/kg bw/d. In addition, centrilobular glycogen loss in liver hepatocytes, bile duct proliferation, and prominent major bile duct was noted in single animals of the high dose group. Furthermore, changes were noted in the prostate (acinar atrophy with fibrosis), epididymides (absent spermatozoa, round spermatids and spermatocytes in ductules) and in the testes (degenerate/exfoliate round spermatids and spermatocytes) of dogs at 300 and 1000 mg/kg bw/d. These changes were considered treatment-related.
The increased thymic involution seen in male and female dogs receiving 1000 mg/kg/day and male dogs receiving 300 mg/kg bw/d were considered to be related to the lower bodyweight gain of these animals.

Table B.6.3-8: Organ weights and pathology

Sex	Male				Female			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Organ weights								
Liver (absolute means, g)	391.0	429.1	430.6	414.5	318.4	333.2	362.8	330.6
Liver (relative means)	3.31	3.77	4.27	4.21	3.19	3.65	4.09**	4.02**
Kidney (absolute means, g)	53.1	50.2	53.2	53.4	47.6	45.1	40.8	45.5
Kidney (relative means)	0.45	0.43	0.51	0.66*	0.48	0.47	0.49	0.54
Gonads (absolute means, g)	24.62	18.94	18.64	13.23	0.96	1.30	0.78	0.78
Gonads (relative means)	0.2086	0.1661	0.1828	0.1329*	0.0097	0.0147	0.0087	0.0091
Microscopic pathology								
Gall bladder: No. examined	4	4	4	4#	4	4	4	4
- Bile duct proliferation	0	0	0	1❶	0	0	0	0
Liver: No. examined	4	4	4	4#	4	4	4	4
- Bile duct proliferation	0	0	0	0	0	0	0	1
- Prominent major bile duct	0	0	0	2	0	0	0	0
- Pigmented macrophages	0	0	0	2	0	0	0	2
- Hepatocyte hypertrophy, generalised	0	0	0	1	0	0	0	3
- Centrilobular hepatocyte loss / necrosis and inflammation	0	0	1	4	0	0	1	2
- Single cell necrosis	0	0	0	3	0	0	0	2
- Glycogen loss, centrilobular (PAS stain)	0	0	0	2	0	0	0	2
Prostate:								
- Acinar atrophy/fibrosis	0/4	0/4	2/4	3/4	-	-	-	-
Epididymides:								
- Spermatozoa absent	0/4	0/4	0/4	2/4	-	-	-	-
- Round spermatids and spermatocytes in ductules	0/4	0/4	1/4	3/4	-	-	-	-
Testes:								
- Degenerate/exfoliate round spermatids and spermatocytes	0/4	0/4	1/4	3/4	-	-	-	-

#: includes one decedent; Statistical significance: *p<0.05; **p<0.01
❶ No. 1737

Discussion:
The toxicological significance of histopathological changes noted in the prostate, epididymides and testes of dogs at 300 and 1000 mg/kg bw/d is considered equivocal. On the one hand, no effects on the gonads were observed when dosages of 300 mg/kg bw/d were administered to dogs for 52 weeks. Furthermore, fertiliy was not affected in the reproductive toxicity study in rats, which support the assumption that these effects have not arisen as a

primary testicular toxicity. On the other hand, the type of changes noted upon histopathological examination in the present study especially in the testes and epididymides (occurrence of round spermatids and spermatocytes in seminiferous tubuli and ductuli) are rather indicative of a disturbed spermatogenesis than of a secondary effect due to lower body weight development noted in these dogs. Testicular changes secondary to lower body weight gain are at the most "multinucleated giant cells", which in the present study did not occur with increased incidences in the dose groups of concern.

Conclusion:
The no observed adverse effect level, NOAEL, was found to be 100 mg/kg bw/d, based on lower bodyweight gain, an increase in activated partial thromboplastin time (APTT), higher liver weights as well as histopathological changes in the liver at the next higher dose of 300 mg/kg bw/d.

This NOAEL is in accordance with the proposal of the notifier.

B.6.3.3.2 12-month study

Report:	M.H. Barker, R.G. Turner-Cain (1999a); UR-50601: Toxicity study by oral capsule administration to beagle dogs for 52 weeks; UBE Industries, Ltd., unpublished report no. UBE 072/992120, 24.11.1999; Report amendment 1 and 2, 07.04.2000 and 24.05.2000 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 3.11.1997 to 13.11.1998.
Test Material:	Beflubutamid; Batch 507003; Purity: 97.79%.
Test Animals:	Beagle dog, bw (week 0) males: 6.1-9.7 kg, females: 6.5-9.6 kg Source: Huntingdon, UK
GLP:	Yes
Test Method:	87/302/EEC B.30, OECD No. 452 dated 12 May 1981 (JMAFF 59 NohSan No. 4200, EPA FIFRA)
Deviations:	Samples of spinal cord were not processed at three levels as required in current TG 452.
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Groups of 4 male and 4 female Beagle dogs received the test compound at 0, 12, 60, and 300 mg/kg/day by repeated oral administration in gelatine capsules for 52 weeks. The dosage used in this study was based upon the results of a previously conducted 13-week study with dogs (Report No. UBE 40/973046). All animals were subject to ophthalmoscopy, haematology, clinical chemistry, urinalysis, bone marrow smears, organ weights, macro- and microscopic pathology assessments.

Findings:
Storage Stability: Analysis of a batch of beflubutamid demonstrated stability for the study duration when stored at 4°C in the dark. Since for the application of beflubutamid by capsule no vehicle was used, analysis of stability in vehicle and of homogeneity in vehicle was not necessary.
Mortality: There were no unscheduled deaths.
Clinical signs: No dose-related effects recorded. Isolated incidents of liquid faeces and vomiting were observed in both treated and control groups.
Bodyweight gain: At 300 mg/kg/d the bodyweight gain was slightly lower for both sexes, but not statistically significant.
Food consumption: Food consumption was slightly lower for dogs treated at 300 mg/kg bw/d, reaching statistical significance only in male dogs.
Ophthalmoscopy: No treatment-related effects recorded.

Table B.6.3-9: 52-week toxicity in dogs treated orally with beflubutamid

Sex	Male				Female			
Dose (mg/kg bw/d)	0	12	60	300	0	12	60	300
Bodyweight gain (kg) Week 0-52	4.3	3.2	3.7	3.0	3.4	4.1	3.9	3.0
Food consumption Week 1-52 (g/dog/week)	2800	2795	2794	2631*	2736	2757	2774	2745

* $p<0.05$ (Williams' test)

Haematology: At 300 mg/kg bw/d both sexes showed increased activated partial thromboplastin time (APTT) during Weeks 13, 26 and 52, being statistically significant for males on all occasions and during Week 52 for females. For females a statistically significant prolongation of prothrombin time (PT) was seen during Week 52.
Minor statistically significant differences relating to reticulocyte counts and to red blood cell parameters were detected in both sexes in Weeks 13 and 26. Since lower values of certain red blood cell parameters were already detected in the predosing period in dogs of the high dose group (300 mg/kg bw/d) and at week 52 investigations all values were comparable to control and the lower dose groups, this finding is considered without toxicological relevance. Likewise, the decrease in total white cell count, basophils and eosinophils noted on different occasions in high dose dogs were apparently similar to control and lower dose groups at treatment-end (week 52).
Clinical chemistry: At 300 mg/kg/day female dogs showed statistically significant increased alkaline phosphatase (AP) in weeks 26 and 52 and glutamic-pyruvic transaminase (GPT) in week 26. The latter was still increased at week 52 investigations, although without statistical significance. Minor reductions in plasma albumin levels resulting in lower total protein values were observed in males in weeks 26 and 52 and in females in week 52 (300 mg/kg bw/d).
Other statistically significant differences were not considered to be of toxicological relevance, i.e. changes in plasma urea in males, sodium, calcium and triglycerides.
Urinalysis: No treatment-related effects recorded.
Bone marrow smears: No treatment-related effects recorded.

Table B.6.3-10: Laboratory investigations

Sex		Male				Female			
Dose (mg/kg bw/d)		0	12	60	300	0	12	60	300
Haematology									
APTT (s)	wk -2	21.3	20.6	20.2	21.4	21.8	21.6	21.0	19.8
	wk 13	23.1	23.5	25.0	29.7**	24.2	24.0	25.2	28.0
	wk 26	20.9	21.2	23.0	26.2**	21.0	21.5	22.6	26.4
	wk 52	20.6	20.0	22.6	26.0*	20.6	20.1	22.2	27.9**
PT (s)	wk -2	6.2	6.4	7.1	6.4	6.5	6.2++	6.3++	6.3+
	wk 13	6.3	6.3	7.3	6.6	6.7	6.3	6.6	6.7
	wk 26	6.2	6.4	7.1	6.5	6.4	6.2	6.3	6.6
	wk 52	6.0	6.1	6.9	6.4	6.2	6.1	6.2	6.7*
Clinical chemistry									
AP (mU/ml)	wk -2	234	210	221	193	228	225	243	199
	wk 26	119	100	109	116	106	110	109	177*
	wk 52	126	99	115	111	110	97	112	207*
GPT (mU/ml)	wk -2	24	23	29	20	22	23	23	27
	wk 26	26	28	28	23	21	22	29	41*
	wk 52	35	34	37	26	26	27	28	39
Total protein	wk -2	5.3	5.2	5.0	4.8	5.1	4.9	5.2	4.8
(g/dl)	wk 26	5.2	5.1	5.1	4.7*	5.2	5.3	5.1	4.9
	wk 52	5.7	5.4	5.3	5.0*	5.5	5.3	5.5	5.1**
Alb. (g/dl)	wk -2	2.7	2.8	2.5	2.5	2.6	2.6	2.7	2.6
	wk 26	2.9	2.7	2.8	2.5	3.0	3.0	2.9	2.8
	wk 52	3.0	2.8	2.8	2.4**	2.9	3.0	2.9	2.7

* $p < 0.05$, ** $p < 0.01$ (Williams' test) ; + $p < 0.05$ (Student's t test)

Organ weights: Relative liver weight was statistically significant higher at 300 mg/kg bw/d for both sexes.

The statistically significant increase of relative kidney weights in male dogs at 300 mg/kg bw/d was not considered treatment-related since it was minor and not observed in female dogs. Likewise, no clear cut dose-response relationship was observed for the following effects and were therefore not considered to be of toxicological relevance: Reductions in adjusted lung weight for males receiving 300 mg/kg/day and for animals receiving 60 or 300 mg/kg/day (combined data) as well as adjusted/relative adrenal weight for treated females.

Macroscopic pathology: The liver was reported enlarged in one male dog at 12 mg/kg bw/d, and in 2 males and 1 female of the high dose group (300 mg/kg bw/d). In addition, one out of these males showed pale capsular areas on the liver.

Microscopic pathology: At the high dose level of 300 mg/kg bw/d, generalised hepatocyte hypertrophy was detected in all animals with a severity ranging from minimal to moderate. This change was accompanied by centrilobular collapse and hepatocyte necrosis, bile duct

hyperplasia with/without early portal to portal bridging in some animals, nodular hyperplasia in a single female and eosinophilic inclusions in hepatocytes in a male dog.

Table B.6.3-11: Organ weights and pathology

Sex	Male				Female			
Dose (mg/kg bw/d)	0	12	60	300	0	12	60	300
Organ weights:								
Liver (absolute means, g)	463.2	453.1	429.4	486.8	406.0	406.7	457.7	457.8
Liver (relative means)	3.57	3.83	3.65	4.36*	3.57	3.36	3.87	4.30*
Macropathology								
Liver enlargement	0/4	1/4	0/4	2/4	0/4	0/4	0/4	1/4
Histopathology								
Liver: Examined	4	4	4	4	4	4	4	4
- Bile duct hyperplasia	0	0	0	1	0	0	0	2
- Centrilobular collapse with hepatocyte necrosis	0	0	0	1	0	0	0	2
- Eosinophilic inclusions in hepatocytes	0	0	0	1	0	0	0	0
-Early portal to portal bridging	0	0	0	2	0	0	0	1
-Hepatocyte hypertrophy, generalised	0	0	0	4	0	0	0	4
- Nodular hyperplasia	0	0	0	0	0	0	0	1

* $p<0.05$ **$p<0.01$ (Williams' test)

Discussion:
The liver was the main target organ of toxicity. Effects on testes and/or epididymides were not observed in this study.

Conclusion:
The no observed adverse effect level, NOAEL, was found to be 60 mg/kg bw/d, based on lower body weight gain, an increase in activated partial thromboplastin time (APTT) and prothrombin time (PT), increases in alkaline phosphatase (AP) and alanine aminotransferase (GPT), slight reductions in plasma total protein, increased liver weight, liver enlargement, histopathological changes in the liver at the next higher dose of 300 mg/kg bw/d.

This NOAEL is in accordance with the proposal of the notifier.

B.6.3.4 Other routes

Studies on inhalation or dermal routes of administration were not performed.

B.6.4 Genotoxicity (Annex IIA 5.4)

The mutagenic potential of beflubutamid was studied in bacteria and mammalian cells *in vitro* by using two gene mutation assays and a chromosome aberration assay (see Table B.6.4-1) and *in vivo* by means of a micronucleus test (see Table B.6.4-2). All tests performed showed no mutagenic effect of the test compound. In the *in vivo* micronucleus test no bone marrow toxicity was observed, but at the two highest dose levels systemic toxicity was recorded.

Table B.6.4-1: *In vitro* mutagenicity tests

Test system	Test object	Concentration	Purity (%)	Results
Gene mutation assays				
Reverse mutation test for bacteria	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 *uvrA*	Main Test -/+ S9 mix: 312.5, 625, 1250, 2500, 5000 µg/plate	97.61	Negative
Gene mutation test (to thioguanine resistance)	Mouse lymphoma L5178Y cells	Test 1 - S9 mix: 10, 25, 50, 75, 100, 125, 150, 200 µg/ml + S9 mix: 5, 10, 25, 50, 75, 100, 125, 150 µg/ml Test 2 -/+ S9 mix: 1, 5, 10, 25, 50, 75, 100 µg/ml	97.46	Negative
Chromosome aberration assays				
Cytogenetic assay	Cultured human lymphocytes	Test 1 - 21 hr sampling time - S9 mix: 2.5, 5, 10, 20, 30, 40 µg/ml. + S9 mix: 25, 50, 100, 150, 200, 250, 500, 1000 µg/ml 45 hr sampling time - S9 mix: 10, 20, 30, 40, 50, 80, 100 µg/ml + S9 mix: 125, 250, 500, 1000, 5000 µg/ml Test 2 - 21 hr sampling - S9 mix: 10, 20, 30, 40, 50, 60 µg/ml + S9 mix: 150, 200, 250, 500, 750 µg/ml	97.61	Negative

Table B.6.4-2: *In vivo* mutagenicity tests in somatic cells

Test system	Test object	Concentration (mg/kg bw)	Purity (%)	Results
Chromosome aberration assays				
Micronucleus test	Male and female CD-1 Swiss mice - bone marrow cells	125, 250, 500	97.46	Negative

B.6.4.1 *In vitro* mutagenicity tests

B.6.4.1.1 *Salmonella typhimurium* reverse mutation assay

Report: E. Jones, R.A. Gant, S.J. Ransome, S.M. Henly (1995); UR-50601: Bacterial mutation assay; UBE Industries, Ltd.; unpublished report no. UBE 4/951063, 26.07.1995 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 24.03.1995 to 18.04.1995.

Test Material: Beflubutamid; batch number: 950123, purity: 97.61%, solvent: DMSO

Test System: *Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100); *Escherichia coli (*WP2 *uvr*A)

GLP: Yes

Test Method: OECD No. 471; 472; 92/69/EEC B.13, B.14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods: Four strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) and one strain of *Escherichia coli (*WP2 *uvr*A) were dosed with a single application of 0.1 ml/plate of the test substance with and without S9 mix (rat Aroclor). From a preliminary test it was concluded that the test compound was not toxic up to 5000 µg/plate and therefore this dose level was chosen as top dose level in the main test. Dose levels in the main test:

-/+ S9: 0, 312.5, 625, 1250, 2500, 5000 µg/plate in triplicate

Positive controls were included. Revertant colonies per plate following a 72 hour incubation period were counted. The main test was repeated.

Findings: None of the bacterial strains tested with the test substance showed any significant increases in the number of revertant colonies at any dose level in the presence or absence of the S9 mix (Table B.6.4-3). Precipitation took place from dose levels 1250 µg/plate and upwards in the first main test and from 625 µg/plate and upwards in the second main test. All positive control compounds induced marked increases in the number of revertants.

Table B.6.4-3: Summary of Ames tests

Concentration (µg/plate)	TA98		TA100		TA1535		TA1537		WP2 uvrA	
	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
Without S9 mix										
DMSO	29	24	124	120	12	16	12	18	66	71
312.5	22	24	122	127	8	16	11	12	83	69
625	25	27P	141	141P	13	18P	15	14P	77	64P
1250	27P	25P	134P	137P	10P	16P	14P	11P	77P	68P
2500	25P	25P	126P	130P	12P	14P	12P	10P	80P	69P
5000	23P	27P	110P	127P	15P	12P	15P	14P	61P	75P
NF	207	402	nd	nd	nd	nd	nd	nd	nd	nd
ENNG	nd	nd	362	327	154	163	nd	nd	733	680
9-AC	nd	nd	nd	nd	nd	nd	*	*	nd	nd
With S9 mix										
DMSO	30	32	144	123	15	17	12	9	70	75
312.5	22	22	120	126	14	14	12	12	65	80
625	23	26P	145	143P	15	16P	15	15P	70	70P
1250	29P	26P	148P	147P	11P	19P	15P	16P	63P	73P
2500	26P	27P	125P	135P	14P	16P	10P	9P	68P	65P
5000	19P	25P	144P	126P	13P	19P	11P	12P	69P	74P
AA	92	90	345	437	150	149	69	59	488	262

Positive controls: NF 2-Nitrofluorene; ENNG *N*-Ethyl-*N*'-nitro-*N*-nitrosoguanidine; 9-AC 9-Aminoacridine; AA 2-Aminoanthracene; P precipitated; nd not determined; * Too many colonies to count accurately

Conclusion: The test material was found to be non-mutagenic under the conditions of this *in vitro* bacterial system.

B.6.4.1.2 *In vitro* mammalian cytogeneticity

Report: D. Appleford, A.L. Johnson (1995); UR-50601: An *in vitro* test for induction of chromosome damage: Cytogenetic study in cultured human peripheral lymphocytes; UBE Industries Limited; unpublished report no. 95/UED001/0580, 07.08.1995 [Pharmaco LSR Ltd. (now known as Huntingdon Life Sciences Ltd.)]; dates of experimental work: 20.03.1995 to 20.05.1995.

Test Material: Beflubutamid; batch 950123; purity: 97.61%; solvent: DMSO

Test System: Cultured human peripheral lymphocytes

GLP: Yes

Test Method: OECD No. 473; 92/69/EEC B.10

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods: Cultured human lymphocytes were exposed to the test substance in the presence and absence of S9 mix (rat Aroclor). Without S9 mix cells were exposed continuously for 21 or 45 hours and with S9 mix exposure was limited to three hours, cells were harvested 18 or 42 hours later. On the basis of the results of the preliminary toxicity test the following concentrations (in duplicate) were selected in order that an appropriate range of toxicity was observed:

Main test - Test 1:

21 hour sampling time:
- S9 mix: 2.5, 5, 10, 20, 30 and 40 μg/ml
+ S9 mix: 25, 50, 100, 150, 200, 250, 500 and 1000 μg/ml

45 hour sampling time:
- S9 mix: 10, 20, 30, 40, 50, 80 and 100 μg/ml
+ S9 mix: 125, 250, 500, 1000 and 5000 μg/ml

On the basis of the results of the first main test, the following concentrations were selected for use at 21 hour sampling time only:

Main test - Test 2:

21 hour sampling time only:
- S9 mix: 10, 20, 30, 40, 50, 60 μg/ml
+ S9 mix: 150, 200, 250, 500 and 750 μg/ml

Positive controls were included. From 100 metaphases with 46 centromers, chromosome number, all chromosomes normal or some aberrant, and specific types and numbers of aberrations were recorded.

Findings: Throughout the study precipitation was apparent in cultures treated at 500 μg/ml and higher. The precipitate appeared to have an effect on the bioavailability of the test material to the cells.

In the first main test, cultures treated with the test substance at 500 μg/ml in the presence of S9 mix at the 21 hour sampling time, produced a small statistically significant increase in the frequency of metaphases with chromosome aberrations compared to solvent control values, only when gaps were included in the analysis. However, only one culture showed an aberrant cell frequency (10%) outside of the historical control range (0-9%). Furthermore, in the second main test no significant increases in chromosome aberrations were observed at any concentration, and the biological significance of gap-type aberrations is questionable.

No other significant increases in chromosome aberrations, compared to solvent control values, were seen in cultures treated with the test compound (Table B.6.4-4). Both positive control compounds induced marked increases in the frequency of chromosome aberrations.

Table B.6.4-4: Summary of main cytogenetic tests

Treatment (µg/ml)	Red. in Mean MI (%) [a]	Cells with aberrations including gaps (%)			Cells with aberrations excluding gaps (%)		
		Range	Mean	S.S. [b]	Range	Mean	S.S. [b]
First main cytogenetic test							
Absence of S9 mix - 21 hour sampling time							
DMSO	-	3 4	3.5	-	1 1	1.0	-
Beflubutamid (20)	2	5 5	5.0	ns	2 2	2.0	ns
Beflubutamid (30)	34	6 2	4.0	ns	3 1	2.0	ns
Beflubutamid (40)	67	5 4	4.5	ns	3 2	2.5	ns
Chlorambucil (2)	7	45 38	41.5	***	38 34	36.0	***
Presence of S9 mix - 21 hour sampling time							
DMSO	-	4 3	3.5	-	1 0	0.5	-
Beflubutamid (200)	24	6 2	4.0	ns	2 0	1.0	ns
Beflubutamid (250)	33	4 7	5.5	ns	2 2	2.0	ns
Beflubutamid (500)	57	10 8	9.0	*	2 1	1.5	ns
Cyclophosphamide (6)	20	31 18	24.5	***	20 12	16.0	***
Absence of S9 mix - 45 hour sampling time							
DMSO	-	4 2	3.0	-	2 0	1.0	-
Beflubutamid (50)	61	4 8	6.0	ns	2 2	2.0	ns
Chlorambucil (2)	27	33 32	32.5	***	28 29	28.5	***
Presence of S9 mix - 45 hour sampling time							
DMSO	-	6 3	4.5	-	0 1	0.5	-
Beflubutamid (500)	82	4 4	4.0	ns	1 1	1.0	ns
Cyclophosphamide (12)	23	10 13	11.5	**	9 8	8.5	***
Second main cytogenetic test							
Absence of S9 mix - 21 hour sampling time							
DMSO	-	4 4	4.0	-	1 2	1.5	-
Beflubutamid (20)	Increase	3 6	4.5	ns	2 3	2.5	ns
Beflubutamid (30)	59	2 3	2.5	ns	1 1	1.0	ns
Beflubutamid (40)	80	6 3	4.5	ns	1 1	1.0	ns
Chlorambucil (2)	9	28 31	29.5	***	17 22	19.5	***
Presence of S9 mix – 21 hour sampling time							
DMSO	-	4 2	3.0	-	1 1	1.0	-
Beflubutamid (200)	31	3 5	4.0	ns	1 1	1.0	ns
Beflubutamid (250)	24	6 6	6.0	ns	1 1	1.0	ns
Beflubutamid (500)	55	6 3	4.5	ns	2 0	1.0	ns
Cyclophosphamide (6)	14	17 26	21.5	***	10 19	14.5	***

[a] Reduction in mean mitotic index compared to negative control values; [b] Statistical significance: ns not significant;
* significant, 0.05>p>0.01; ** highly significant, 0.01>p>0.001; very highly significant, p<0.001;

Conclusion: Under the conditions of this test, beflubutamid did not show any evidence of clastogenic activity.

B.6.4.1.3 *In vitro* mammalian cell gene mutation

Report: K. Adams, S.J. Ransome (1998); UR-50601: Mammalian cell mutation assay; UBE Industries, Ltd.; unpublished report no. UBE 046/971304, 16.01.98 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 17.02.1997 to 07.04.1997

Test Material: Beflubutamid; batch 507001; purity: 97.46%; solvent: DMSO

Test System: Mouse lymphoma L5178Y cells heterozygous at the thymidine kinase locus, $TK^+/-$

GLP: Yes

Test Method: OECD No. 476; EEC Directive 87/302/EEC

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods: Mouse lymphoma L5178Y cells were exposed to the test substance for 3 hours with and without S9 mix (rat Aroclor). On the basis of the results of the preliminary toxicity test in which decreased relative survival was observed, the following concentrations were used in the main tests:

Main test - Test 1:

- S9 mix: 0, 10, 25, 50, 75, 100, 125, 150, 200 µg/ml

- + S9 mix: 0, 5, 10, 25, 50, 75, 100, 125, 150 µg/ml

Main test - Test 2:

-/+ S9 mix: 0, 1, 5, 10, 25, 50, 75, 100 µg/ml

Samples were taken at 24 and 48 hours to assess growth. Then the cells were plated in 96 well plates for seven days to determine cloning efficiency and for 10-14 days to assess mutant frequency (in duplicate). Positive controls were included.

Findings: The relative survivals (Day_0) of each culture were decreased with every concentration of the test compound applied, which indicates toxicity was observed in all the tests both in the absence and the presence of S9 mix.

The cloning efficiencies (Day_2) were decreased more with higher concentrations applied, both in the absence and presence of S9 mix.

In the absence of S9 mix, there were no reproducibly significant increases in mutant frequency. In the presence of S9 mix, no statistically significant increases in mutant frequency were observed (Table B.6.4-5).

Table B.6.4-5: Summary of main mammalian cell mutation tests

Concentration (µg/ml)	Absence of S9 mix			Presence of S9 mix		
	Mean % relative survival	Mean % cloning efficiency	Mean mutant frequency	Mean % relative survival	Mean % cloning efficiency	Mean mutant frequency
First main test						
DMSO	100	100	0.000279	100	100	0.000184
5	nd	nd	nd	65	np	np
10	74	112	0.000233	48	117	0.000250
25	37	85	0.000321	33	np	np
50	18	np	np	31	112	0.000251
75	9	101	0.000335	17	106	0.000237
100	10	103	0.000325	11	87	0.000285
125	7	np	np	7	np	np
150	10	np	np	5	np	np
200	5	np	np	nd	nd	nd
MMS (10)	51	83	0.001362*	nd	nd	nd
MC (2.5)	nd	nd	nd	57	78	0.001703*
Second main test						
DMSO	100	100	0.000275	100	100	0.000331
1	83	np	np	88	np	np
5	73	np	np	57	119	0.000336
10	60	77	0.000365	38	108	0.000457
25	27	95	0.000334	19	np	np
50	14	65	0.000511*	21	91	0.000494
75	12	68	0.000509*	13	96	0.000460
100	11	np	np	8	np	np
MMS (10)	85	52	0.002338*	nd	nd	nd
MC (2.5)	nd	nd	nd	37	57	0.003378*

MMS methylmethanesulphonate; MC 20-methylcholanthrene; nd not determined; np not plated in 96 wells; * $p<0.01$

Conclusion: It was concluded that beflubutamid did not demonstrate mutagenic potential in this *in vitro* mammalian cell mutation assay.

B.6.4.2 *In vivo* studies in somatic cells

B.6.4.2.1 Micronucleus test

Report: C.E. Mason (1998); UR-50601: Mouse micronucleus test; UBE Industries, Ltd.; unpublished report no. UBE084/983640, 21.10.98 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 12.05.1998 to 11.06.1998.

Test Material: Beflubutamid; batch 507001; purity: 97.46%

Test Animals: CD-1 Swiss mice

GLP: Yes

Test Method: OECD No. 474; 92/69/EEC B.12

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Based on the results from the preliminary test, in which approximately 500 mg/kg bodyweight was the maximum tolerated dose level, single doses of 0, 125, 250, and 500 mg/kg bodyweight were used in the main test. Groups of five female and five male Swiss mice were dosed intraperitoneally and killed 24 hours after dosing. In addition five female and five male mice from the negative control and from the highest dose level tested were killed 48 hours after dosing. A positive control, administered orally by intragastric gavage, was included in the test.
After killing, stained smears were prepared to determine the incidence of micronucleated cells and the proportion of immature erythrocytes for each animal.

Findings:
Mortality data: No mortalities were observed in the test.
Clinical signs: No clinical signs were shown in mice dosed 125 mg/kg bodyweight. Clinical signs observed at 250 and 500 mg/kg included body tremors, hunched posture, piloerection, prostrate posture, slow respiration, underactive, and unstable gait. All mice were recovered 48 hours after dosing.
Erythrocyte counts: No significant increase in the frequency of micronucleated immature erythrocytes was observed at 24 or 48 hours (Table B.6.4-6). No effect was observed on the proportion of immature erythrocytes, indicating no bone marrow toxicity. The positive control did show an increased frequency of micronucleated cells.

Table B.6.4-6: Summary of micronucleus test

Dose Beflubutamid (mg/kg)		Frequency of micronucleated polychromatic cells[1]		P:M Ratio[2]
	Mean incidence	Range	Mean ratio	Range
24 hour sampling time				
MC (1%)	1.2	0-3	48	43-50
125	1.5	0-4	44	37-52
250	1.3	0-4	44	32-52
500	0.9	0-2	44	39-50
MMC (12)	50.7*	23-81	45	40-50
48 hour sampling time				
MC (1%)	1.2	0-3	46	36-51
500	0.4	0-1	42	32-48

[1] Number of micronucleated cells observed per 2000 immature erythocytes examined; [2] Proportion of immature erythrocytes to mature erythrocytes; MC methylcellulose (vehicle); MMC Mitomycin C (positive control); * $p<0.001$

Conclusion: The test compound did not show any genotoxic effect in this *in vivo* study.

B.6.4.3 *In vivo* studies in germ cells

The *in vivo* micronucleus test (point B.6.4.2.1) shows a negative result and therefore it is not considered necessary to perform an *in vivo* study in germ cells.

B.6.5 Long-term toxicity and carcinogenicity (Annex IIA 5.5)

The long-term toxicity and carcinogenicity studies were conducted during 1997-1999. All studies were performed and reported in accordance with EU testing guidelines with exceptions listed accordingly and were fully compliant with GLP. A summary of these results is presented in Table B.6.5-1.

The liver was found to be the target organ in rats and mice after prolonged dietary administration of beflubutamid. In rats the **thyroid gland** and the **kidneys** were affected as well. The treatment with beflubutamid had no effects on the survival of both animal species and did not reveal a carcinogenic potential relevant to humans.

In rats lower body weight gains (both sexes 3200 ppm), a prolongation of thrombotest clotting time (males, 400 ppm and 3200 ppm) as well as higher plasma cholesterol and phospholipid values (both sexes, 3200 ppm) were observed. Additionally, in female rats at the highest dose level (3200 ppm) higher plasma total protein levels, mainly due to a simultaneous increase of albumin and globulins were recorded. Higher amounts of proteins were noted in the urine of female rats at 3200 ppm at almost all occasions being most evident after 78 weeks of treatment onwards and at week 104 investigation also at 400 ppm. Liver and kidney weights were increased in both sexes at 3200 ppm, thyroid weights were increased in male rats (3200 ppm). At week 105, female rats at 400 and 3200 ppm also showed higher thyroid weights although without statistical significance. Both at the interim and terminal sacrifice centrilobular hepatocyte hypertrophy was noted (males, 400 ppm, both sexes 3200 ppm). In females of the high dose level (3200 ppm) progressive glomerulonephrosis in the kidney was observed with slightly higher incidence at terminal sacrifice.
The incidence of thyroid gland follicular tumours was slightly increased in male rats of the high dose group (3200 ppm) at terminal sacrifice but without reaching statistical significance and with incidences lying in the upper range of historical control data for males. In female rats each one thyroid follicular adenoma and one carcinoma was observed in the 400 ppm and 3200 ppm group, respectively. These neoplastic findings are considered to be without relevance to humans.
The NOAEL was was found to be 50 ppm (2.2 mg/kg bw/d for male and 3.0 mg/kg bw/d for female).

In mice lower body weight gain (both sexes, 5000 ppm), increased liver and adrenal gland weights (both sexes, 5000 ppm), enlarged and pale liver and liver with pale area(s) (males, 5000 ppm) were noted. Liver centrilobular hepatocyte hypertrophy and hepatocytes with granular cytoplasm was noted in males at 500 ppm, centrilobular/generalised hepatocyte hypertrophy, parenchymal inflammatory cell foci, centrilobular sinusoidal dilation/congestion with pigmented sinusoidal cells was observed in both sexes at 5000 ppm. There were no conclusive histopathological findings in the adrenal glands which may have accounted for increased organ weights.
The incidence of liver tumours was slightly increased in male mice of the high dose group (5000 ppm) but the incidences were well within the historical control data for Crl:CD-1(ICR)BR mice submitted from the performing laboratory.
The NOAEL was was found to be 50 ppm (6.4 mg/kg bw/d for male and 8.5 mg/kg bw/d for female).

Table B.6.5-1: Summary of long-term toxicity and carcinogenicity studies

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
104-week feeding (combined chronic toxicity/ carcinogenicity) Crl:CD BR rat 0, 50, 400, 3200 ppm	2.2 / 3.0 m/f [50 ppm]	400 ppm / Prolongation of thrombotest clotting time, centrilobular hypertrophy of hepatocytes (m), proteinuria at wk 104 (f)
80-week feeding Crl:CD-1 (ICR) BR mouse 0, 50, 500, 5000 ppm	6.4 / 8.5 m/f [50 ppm]	500 ppm / Centrilobular hepatocyte hypertrophy, hepatocytes with granular cytoplasm

m: males; f: females; bw: bodyweight

B.6.5.1 Rat oral 2-year chronic toxicity/carcinogenicity

Report: M.H. Barker, R.G. Turner-Cain (2000b); UR-50601: Potential tumorigenic and toxic effects in prolonged dietary administration to rats; UBE Industries, Ltd.; unpublished report no. UBE 044/993288, 15.02.2000 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 17.02.1997 to 05.03.1999.

Test Material: Beflubutamid; Batch 507003; Purity: 97.79%.

Test Animals: Crl:CD BR rats; bw (Week 0): males: 175-251 g; females 136-188 g
Source: Charles River UK Ltd., Margate, Kent, England

GLP: Yes

Test Method: 87/302/EEC B.32
(JMAFF 59 Nohsan No. 4200, EPA FIFRA)

Deviations: (1) The survival at 104 weeks is less than 50% for females (between 37% and 48%).

Acceptability: The aforementioned deviation, *i.e.*, reduced survival rates in female rats, does not adversely impact the quality or integrity of the study. According to the EPA guidelines (Federal Insecticide, Fungicide, and Rodenticide Act) the survival "in any group should not fall below 25 percent" at the termination of the experiment at 24 month; according to the OECD guidelines: "In order for a negative test to be acceptable, it should meet the following criteria:...Survival in each group is no less than 50 percent... at 24 month for rats". The study is considered acceptable because the survival of males at termination of this study at 24 months is ≥ 50%, and females of the high dose group had a higher survival rate compared to control other dose groups.

Material and Methods:
Groups of 60 male and 60 female Crl:CD BR rats received the test material by dietary administration at concentrations of 0, 50, 400 and 3200 ppm for 104 weeks. These doses were based on a previous 13-week study [Report no. UBE 31/963207 performed at Huntingdon Life Sciences Ltd., UK, 21.05.1997]. Based on the results of this study it was concluded that 3200 ppm would be tolerated over a longer-term administration and so this level was chosen for further studies. An additional 20 males and 20 females for each group were treated for 52 weeks and included in an interim kill. In order of increasing doses the treated rats ingested the equivalent of 2.2, 17.7 and 150 mg/kg bw/d for males and 3.0, 24.4 and 207 mg/kg bw/d for females. All animals were subjected to bodyweight, clinical signs, food consumption, water consumption, ophthalmoscopy, haematology, biochemistry, urinalysis, organ weights, macro- and microscopic pathology assessments.
Test diets were prepared at weekly intervals throughout the study. The diet was then stored at 4°C in the dark until required. Achieved concentration was measured at all dose levels in diet samples during the study.

Findings:
Formulation Analysis: Mean values were within the range ±4% of nominal concentration confirming accurate formulation. Homogeneity and stability of beflubutamid in the rodent diet formulation was confirmed at a nominal concentration of 25 ppm, 3500 ppm and 6400 ppm.
Mortality: Treatment was not considered to have affected the distribution or rate of mortalities.
Clinical signs: There were no clinical signs that were considered to be related to treatment. The number of animals with palpable masses during the dosing period was similar for control and treated groups, for both sexes.
Bodyweight: During week 1, male rats at 400 ppm and both sexes at 3200 ppm showed a statistical significantly lower bodyweight gain. During the remaining period up to week 52 the bodyweight gain remained statistical significantly lower for both sexes at 3200 ppm, although there was some improvement. Overall (Week 0-104), slightly lower bodyweight gain was noted for both sexes at 3200 ppm attaining statistical significance for females only.
Food and water consumption: During week 1, food consumption was lower for both sexes at 3200 ppm, the differences achieving statistical significance, but subsequently consumption was comparable to controls.
Females receiving 50 or 3200 ppm showed decreased water consumption during Week 25 and 51. Males showed a slight increase at 3200 ppm during Week 51. However in the absence of a dose-related trend and statistical significance, these were not considered to be of toxicological importance.
Efficiency of food utilisation: Overall efficiencies of food utilisation during the first 26 weeks of treatment (the period of most rapid growth) for male and females receiving 400 or 50 ppm were similar to controls. However, it is apparent that both male and females receiving 3200 ppm had slightly higher ratios when compared to controls, thus indicating a slightly lower efficiency of food utilisation.
Ophthalmoscopy: No treatment-related effects were shown.

Table B.6.5-2: Mortality, bodyweight gain and food consumption in rats treated orally with beflubutamid

Sex	Male				Female			
Dose (ppm)	0	50	400	3200	0	50	400	3200
Mortality (after 104 weeks)								
Number in each group	60	60	60	60	60	60	60	60
Incidence	28	30	29	30	36	37	38	31
% Mortality	47	50	48	50	60	62	63	52
% Survival	53	50	52	50	40	38	37	48
Bodyweight gain								
Week 0-1 (g)	58	58	54**	43**	25	26	25	20**
Week 1-52 (g)	467	487	471	432**	212	216	208	173**
Week 0-104 (g)	521	574	569	504	334	345	336	283^{+}
Food consumption								
Week 0-1 (g/rat/week)	198	200	197	175**	140	142	141	131**

*p<0.05; **p<0.01 (William's test); +p<0.05 (Student's *t* test).

Haematology: See also Table B.6.5-3**.**
At 400 ppm males showed marginally but statistically significant longer thrombotest clotting times (TT) at week 26 and 52 investigations. At 3200 ppm male rats had longer thrombotest clotting times during treatment, being most apparent at Week 26. The values for females were inconspicuous, although reaching statistical significance on week 13 and 78 investigation.
All other changes reaching statistical significance were considered devoid of toxicological relevance as they occurred without dose-reponse relationship, were minor and/or were not consistently seen on subsequent occasions, i.e. changes of methaemoglobin (week 26, both sexes), mean corpuscular hemoglobin concentration (week 52 and 78, males; week 104, females), hemoglobin concentration (week 52, males; week 26, females), packed cell volume (week 26, females), and changes of total white blood cell counts (WBC) (week 13 and 104, males; week 26, 52 and 104, females).
Biochemistry: See also Table B.6.5-3.
A trend towards higher cholesterol levels was apparent over the first 78 weeks for females at 3200 ppm. High dose males had slightly higher cholesterol values in week 26 only. In addition, a minor trend towards slightly higher phospholipid concentrations was apparent, attaining statistical significance for males at Week 26 and females at Week 13 and 78.
In females at 3200 ppm, slightly higher total plasma protein values were noted on almost all occasions except at week 104, reaching statistical significance only at week 26 and 78. The increase was mainly associated with a simultaneous increase in plasma albumin and globulins. Therefore, albumin to globulin ratio was not affected.
All other changes reaching statistical significance were considered devoid of toxicological relevance as they occurred without dose-reponse relationship, were minor and/or were not consistently seen on subsequent occasions, i.e. changes of plasma urea nitrogen (week 26 and 78, males), glucose (week 26, 78 and 104, females), albumin and albumin to globulin ratio (week 104, males), GPT, GOT, γ-GT (males) and bilirubin on different occasions (both sexes), alkaline phosphatase (week 104, females), inorganic phosphate (week 26, both sexes; week 52 females), sodium and chloride (week 52, males), calcium (week 78, both sexes), and triglyceride (week 52, females).
Urinalysis: See also Table B.6.5-3.
There was an increase in urinary protein mainly in females at 3200 ppm. At week 104 investigation females at 400 ppm were also affected. The toxicological relevance for the slight increase in pH-value in both sexes is obscure.

Table B.6.5-3 Laboratory investigations

Sex		Male				Female			
Dose (ppm)		0	50	400	3200	0	50	400	3200
Haematology									
TT (sec)	Week 13	23	24	24	26**	22	21	21	20**
	Week 26	24	25	27*	40**	20	21	21	20
	Week 52	23	23	25**	27**	19	20	19	18
	Week 78	23	22	22	24	18	18	18	18*
	Week 104	23	23	23	25*	20	19	19	19
Biochemistry									
Chol (mg/dl)	Week 13	81	85	90	98	82	84	83	106**
	Week 26	85	88	89	101	96	90	91	119*
	Week 52	107	115	104	107	127	120	117	142
	Week 78	116	114	122	123	122	127	129	170**
	Week 104	108	126	116	122	105	139^{+}	129	137^{+}
PhLipid (mg/dl)	Week 13	118	128	133	139	145	144	150	169*
	Week 26	129	136	140	154*	173	162	166	199
	Week 52	153	165	158	155	222	218	216	238
	Week 78	161	162	173	176	229	242	234	294**
	Week 104	184	201	188	210	224	274^{+}	258	274^{+}
Total Protein	Week 13	6.8	6.7	6.7	6.6	6.9	6.8	6.8	7.2
(g/dl)	Week 26	7.0	7.0	7.0	7.0	7.4	7.1	7.2	7.9**
	Week 52	7.2	7.2	7.1	7.3	7.9	7.8	7.8	8.2
	Week 78	6.7	6.5	6.9	7.0	7.4	7.6	7.5	7.9**
	Week 104	6.8	6.5	6.6	6.7	7.1	7.3	7.3	7.3
Urinalysis									
Protein (mg/dl)	Week 13	164	150	155	211	71	61	69	114**
	Week 26	153	142	144	128	87	76	88	117
	Week 52	189	156	173	186	94	59	102	209
	Week 78	213	244	314	405	123	231	134	410*
	Week 104	1043	533	948	1250	214	81	665*	666*

Statistical significance: *p<0.05; **p<0.01 (William's test); +p<0.05 (Student's *t* test)

Organ weights: See also Table B.6.5-4

Increased relative liver and kidney weights in both sexes and increased thyroid weights in male rats at 3200 ppm are considered treatment-related. At week 105, female rats at 400 and 3200 ppm also showed higher thyroid weights although without statistical significance.

Males at 400 ppm and 3200 ppm had slightly reduced spleen weight (adjusted for terminal bodyweight) during week 53 (interim kill) and at 3200 ppm during week 105 (final sacrifice), but there were no microscopic findings relating to these findings.

Table B.6.5-4: Organ weights at week 53 (Interim kill) and week 105 (Final sacrifice):

Sex	Male				Female			
Dose (ppm)	0	50	400	3200	0	50	400	3200
Relative means; Liver:								
Week 53	3.6	3.5	3.6	4.4**	3.9	3.5#	3.7	4.6##
Week 105	3.73	3.29	3.47	3.95**	3.81	3.62	3.80	4.36**
Relative means, Thyroid:								
Week 53	4.26	4.39	4.66	5.45**	7.1	6.5	7.5	7.7
Week 105	0.0062	0.0064	0.0086	0.0065	0.0080	0.0079	0.0092	0.0092
Relative means, Kidneys:								
Week 53	0.63	0.61	0.65	0.74**	0.76	0.70	0.77	0.91**
Week 105	0.78	0.70	0.73	0.83	0.70	0.71	0.71	0.88**

Statistical significance: *p<0.05; **p<0.01 (William's test)
p, 0.05, ## p<0.01 (Dunnett's Test)

Pathology: See also Table B.6.5-5
Macroscopic pathology: At the interim kill no treatment-related findings were observed. Rats dying, killed *in extremis* or at termination (Week 105) did not reveal any findings that were considered to be related to treatment.
Microscopic pathology:
Interim kill: Minimal centrilobular hepatocyte hypertrophy was noted in males at 400 ppm and at 3200 ppm in both sexes.
None of the microscopic findings were considered to be associated with the other changes recorded in organ weights.
Terminal kill - Neoplastic findings: The incidence of thyroid follicular tumours was slightly increased in male rats receiving 3200 ppm (6/60). Although, the incidence of these tumours falls within the background control range (0/50 – 6/50) they are considered related to the treatment. In female rats, each one thyroid follicular adenoma and one carcinoma was observed in the 400 ppm and 3200 ppm group, respectively, versus none in the control and low dose group.
Terminal kill - Non-neoplastic findings: Centrilobular hepatocyte hypertrophy was noted in males at 400 ppm and at 3200 ppm in both sexes. A slightly higher incidence of progressive glomerulonephrosis in kidney was seen in female rats receiving 3200 ppm.
No treatment-related microscopic findings were detected which might be associated with the dark focus/foci observed in the adrenals of a great number of treated male rats, the thickening of the uterus observed in a great number of treated female rats and the lower spleen weights recorded for male rats receiving 3200 ppm. Minor variations in the incidence and distribution of all other non-neoplastic findings were considered incidental and of no toxicological importance.
Factors contributory to death: No treatment-related effect was seen in the incidence and distribution of any findings considered to be a factor contributory to death.

Table B.6.5-5: Pathology

Sex	**Male**				**Female**			
Dose (ppm)	0	50	400	3200	0	50	400	3200
Microscopic pathology	**Interim kill**							
Liver: centrilobular hepatocyte hypertrophy, minimal	0/20	0/20	3/20	11/19**	0/18	0/19	0/18	15/17**
	Terminal kill							
Neoplastic findings: Thyroid								
Follicular cell adenoma	1/60	2/59	1/60	5/60	0/60	0/40	1/42	0/60
Follicular cell carcinoma	1/60	0/59	2/60	1/60	0/60	0/40	0/42	1/60
Incidence from background control studies	3/50 6/50 3/50 0/60 2/50 (adenoma) 0/50 0/50 0/50 0/60 2/50 (carcinoma)				2/50 1/60 0/50 0/49 1/50 (adenoma) 0/50 0/60 0/50 0/49 0/50 (carcinoma)			
Non-neoplastic findings:								
Liver: centrilobular hepatocyte hypertrophy (total)	0/60	0/60	6/60*	26/60**	0/60	0/60	0/60	31/60**
Kidneys: progressive glomerulonephrosis (total)	17/60	20/60	21/60	14/60	15/60	14/60	12/60	24/60

Statistical significance: *p<0.05; **p<0.01 (William's test, Fisher's exact test for microscopy)

Conclusion:
The no observed adverse effect level, NOAEL, was found to be 50 ppm (2.2 mg/kg bw/d for male and 3.0 mg/kg bw/d for female) based on prolongation of thrombotest clotting time, an increased incidence of centrilobular hepatocyte hypertrophy in male rats and proteinuria in female rats at the next higher dose level of 400 ppm (17.7 mg/kg bw/d for males and 24.4 mg/kg bw/d for females).

This NOAEL is not in accordance with the proposal of the notifier who derived a NOAEL of 400 ppm, considering the findings in the liver as an adaptive response solely.

B.6.5.2 Mouse carcinogenicity

Report: M.H. Barker, R.G. Turner-Cain (2000a); UR-50601: Carcinogenicity study by dietary administration to CD-1 mice for 80 weeks; UBE Industries, Ltd.; unpublished report no. UBE 070/993289, 06.01.2000 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 02.09.1997 to 26.03.1999.

Test Material: Beflubutamid; Batch 507003; Purity: 97.79%.

Test Animals: Crl:CD-1 (ICR) BR mouse; bw (Week 0): males: 27-38 g; females 20-32 g, Source: Charles River UK Ltd., Margate, Kent, England

GLP: Yes

Test Method: 87/302/EEC B, OECD No. 451
(JMAFF 59 NohSan No. 4200; EPA FIFRA)

Deviations: None which are considered to affect the results or integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Groups of 50 male and 50 female Crl:CD-1 (ICR) BR mice received the test material by dietary administration at concentrations of 0, 50, 500 and 5000 ppm for 80 weeks. These doses were based on a previous 13-week study [Report no. UBE 34/971905 performed at Huntingdon Life Sciences Ltd., UK, 26.11.1997]. Based on the results of this study it was concluded that 6400 ppm would exceed the MTD over a longer-term administration. Therefore, the highest dose used in this study was chosen to be between 3200 and 6400 ppm. In order of increasing doses the treated mice ingested the equivalent of 6.4, 67 and 723 mg/kg bw/d for males and 8.5, 78 and 835 mg/kg bw/d for females. All animals were subjected to bodyweight, clinical signs, food consumption, organ weights and macro- and microscopic pathology assessments. A visual assessment was performed on bone marrow smears for animals from groups 1 and 4 (control and 5000 ppm) and for some sporadic deaths. For haematological evaluation (differential white blood cell count) a blood smear was prepared from animals killed during the treatment period. Smears from groups 1 and 4 were examined for weeks 52 and 81. In week 78 smears from all animals were examined.

Test diets were prepared at weekly intervals throughout the study. The diet was then stored at 4°C in the dark until required. Achieved concentration was measured at all dose levels in diet samples during the study.

Findings:
Formulation Analysis: Mean values were within the range ±2% of nominal concentration confirming accurate formulation.
Mortality: Treatment was not considered to have affected the distribution or rate of mortalities.
Clinical signs: No treatment-related effects observed. The number of animals with palpable masses during the dosing period was similar for control and treated groups, for both sexes.
Bodyweight: Over the growth period (up to 52 weeks) impaired bodyweight gain was apparent for males at 5000 ppm. Overall (Week 0-80) both sexes showed lower bodyweight gain, with the difference for females achieving statistical significance. Females receiving 500 ppm gained slightly more than controls, but the difference was not statistically significant and the finding is not considered to be of toxicological importance.
Food consumption: The group mean value for females receiving 5000 ppm was slightly lower than the control value (week 1-80).
Efficiency of food utilisation: The value for males receiving 5000 ppm showed a poorer food conversion than the control.
Haematology: No treatment-related effects were shown relating to differential white cell counts.
Marrow smears: No treatment-related effects observed.

Table B.6.5-6: Mortality, bodyweight gain and food consumption in mice treated: orally with beflubutamid

Sex	**Male**				**Female**			
Dose (ppm)	0	50	500	5000	0	50	500	5000
No. animals/group	50	50	50	50	50	50	50	50
Mortality								
Incidence	11	15	13#	12	15	17	10	11#
% Mortality	22	30	26	24	30	34	20	22
% Survival	78	70	74	76	70	66	80	78
Bodyweight gain								
Week 0-13 (g/mouse)	14.1	13.1	13.0	10.6**	9.2	9.7	11.8+++	10.1
Week 0-52 (g/mouse)	23.9	22.8	21.8	18.1**	20.4	18.0	23.0	18.0
Week 0-80 (g/mouse)	23.0	22.2	22.0	20.2	23.2	20.9	24.4	17.7**
Food consumption								
Week 1-80 (g/mouse)	3768	3684	3829	3800	3747	3667	3669	3495
% of control	-	98	102	101	-	98	98	93
Food Efficiency								
Week 1-13 (conversion ratio)	43.3	45.8	47.5	55.9	64.6	61.6	50.2	58.5

An additional male of group 3 and one female of group 4 died during the termination period; Statistical significance: **p<0.01 (Williams' test);.+++ p<0.001 (Kruskal-Wallis test)

Organ weights: See also Table B.6.5-7
At 5000 ppm both sexes had statistically significant increased liver and adrenal gland weights (absolute and relative weights).
Macroscopic pathology: See also Table B.6.5-7**.**

At 5000 ppm the incidences of liver enlargement, pale livers and pale area(s) on the liver were increased in male mice compared to control and lower dose groups. The incidence of grossly observed masses in the liver were not increased.

Microscopic pathology: See also Table B.6.5-7.

Neoplastic findings: The incidences of hepatocellular adenomas and hepatocellular carcinomas were slightly increased in male mice at 5000 ppm. No treatment-related effect was seen in the incidence and distribution of other tumours, of mice bearing malignant tumours, mice bearing multiple tumours and in female mice of any dose group.

Non-neoplastic findings: At 500 ppm a dose-dependent increased incidence of centrilobular hepatocyte hypertrophy was mainly noted in male mice. In males, this change was associated with hepatocytes with granular cytoplasm (in mainly centrilobular zones). At 5000 ppm an increased incidence and degree of hepatocyte hypertrophy, either centrilobular or generalised and pigmented sinusoidal cells was observed in both sexes. Additionally, male mice of this dose group showed hepatocytes with granular cytoplasm, parenchymal inflammatory cell foci and centrilobular sinusoidal dilatation/congestion in the liver. These findings were considered to be associated with the higher liver weights, increased incidence of liver enlargement and pallor seen macroscopically.

There were no conclusive histopathological findings in the adrenal glands which may have accounted for increased organ weights.

No treatment-related effect was attributed to other non-neoplastic microscopic findings seen in this study and minor variations in the incidence of these findings were considered to be of no toxicological importance.

Factors contributory to death: No treatment-related effect was seen in any finding considered to be a factor contributory to death.

Table B.6.5-7: Organ weights and pathology:

Sex	Male				Female			
Dose (ppm)	0	50	500	5000	0	50	500	5000
Organ weights								
Liver (absolute means g)	3.07	3.05	3.12	4.56	2.12	2.16	2.27	2.70
Liver (relative means)	5.62	5.67	5.84	8.90**	4.59	5.05	4.88	6.58**
Adrenal glands								
(absolute means, mg)	7.8	7.9	7.7	8.5	12.2	12.3	12.0	13.4
(relative means)	14.5	15.0	14.6	16.8*	27.3	29.4	26.5	33.0*
Macroscopic pathology								
Animals examined:	50	50	50	50	50	50	50	50
Liver:								
- mass(es)	10	12	11	13	5	1	1	1
- enlarged	5	3	6	30	3	5	5	6
- pale	4	6	7	17	9	15	6	3
- pale area(s)	3	3	5	10	2	3	3	1
Microscopic pathology								
Neoplastic findings								
Animals examined:	50	50	50	50	50	50	50	50
Liver:								
-Hepatocellular adenoma	7	10	10	12	4	1	1	0
-Hepatocellular carcinom.	3	3	0	4	0	0	0	0
Non-neoplastic findings								
Animals examined:	50	50	50	50	50	50	50	50
Liver:								
- Centrilobular hepatocyte hypertrophy[#] Total	2	2	8*	32**	0	0	5*	4
Minimal	0	1	3	7**	0	0	3	2
Slight	2	1	5	12**	0	0	2	2
Moderate	0	0	0	5*	0	0	0	0
Marked	0	0	0	8**	0	0	0	0
- Generalised hepatocyte hypertrophy[#] Total	3	3	1	11*	1	1	1	12**
Minimal	1	2	1	1	1	0	1	8*
Slight	1	1	0	3	0	1	0	4
Moderate	1	0	0	6	0	0	0	0
Marked	0	0	0	1	0	0	0	0
- Hepatocytes with granular cytoplasm Total	0	0	3	22**	0	0	0	0
- Parenchymal inflammat. cell foci Total	0	2	3	10**	3	5	5	3
- Pigmented sinusoidal cells Total	0	1	0	9**	1	0	1	6
- Sinusoidal dilatation/ congestion Total	0	0	0	7**	0	0	0	1

[#] Incidence described as total/minimal/slight/moderate/marked; Statistical significance: *p<0.05; **p<0.01; n.d.: not determined

Conclusion:

The no observed adverse effect level, NOAEL, was found to be 50 ppm (6.4 mg/kg bw/d for male and 8.5 mg/kg bw/d for female) based on centrilobular hepatocyte hypertrophy and hepatocytes with granular cytoplasm in the liver of males at the next higher dose of 500 ppm (67 mg/kg bw/d for males and 78 mg/kg bw/d for females).

This NOAEL is not in accordance with the proposal of the notifier who derived a NOAEL of 500 ppm considering the liver findings as an adaptive response solely.

B.6.6 Reproductive toxicity (Annex IIA 5.6)

The reproductive toxicity and teratogenicity studies were conducted during 1997-1998. All studies were performed and reported in accordance with EU testing guidelines with exceptions listed accordingly and were fully compliant with GLP. The pilot study on non-pregnant rabbits and the preliminary study on pregnant female rabbits were evaluated in addition. A summary of these results is presented in Table B.6.6-1.

Beflubutamid had no adverse effects on fertility and no effects on the parturition process or on peri- and post-natal survival of the offspring at dosages up to 3200 ppm (~243 mg/kg bw/d for males, ~338 mg/kg bw/d for females) over two generations in the Sprague Dawley rat. The below mentioned reproductive and developmental effects on the fetuses were seen in presence of parental/maternal toxicity.

In the **2-generation reproductive toxicity study in rats** the main target organs were the kidney and the liver evidenced by increased organ weights at 800 ppm and/or 3200 ppm in the adults which is in line with changes noted in short- and long-term studies. Reductions in body weight gain were noted at 800 ppm and 3200 ppm in parental animals as well as in the offspring. In the F1- and F2-pups body weight gain was decreased mainly during the lactational phase, reflecting impaired pup growth. Additionally, at 800 ppm and 3200 ppm a significant delay in age for vaginal opening occurred among females of the F1-generation. No clear effect of treatment on the mean age of balano-preputial separation could be demonstrated but a marginal delay was suggested. At necropsy of F1- and F2-offspring increased incidences of uni-/bilateral renal cavitation of the kidney and uni-/bilateral hydroureters were noted at 3200 ppm. The findings in the offspring were considered adverse reproductive effects.
The NOAEL for parental and reproductive toxicity was 200 ppm (~ 17 mg/kg bw/d for males; ~19 mg/kg bw/d for females).

Reproduction toxicity studies to investigate **developmental toxicity in the rat** revealed an increased incidence of fetuses with rudimentary/absent renal papilla and with dilated ureters at 300 and 1000 mg/kg bw/d when compared to control and low dose group. One fetus of the 300 mg/kg bw/d group had an absent left kidney and ureter, a duplicated inferior vena cava, and a malpositioned left testis. Left anophthalmia occurred in one fetus of the high dose group versus none in the control and other dose groups. Incomplete ossification of the thoracic vertebral centra occurred at the highest dose tested (1000 mg/kg bw/d). In the dams clinical signs (post-dosing salivation, hair loss), higher water intake as well as a transient reduction in food intake and body weight gain was noted at dose levels of 300 and/or 1000 mg/kg bw/d.
The NOAEL for maternal and developmental toxicity was 100 mg/kg bw/d.

In the **rabbit developmental toxicity study** no treatment-related effect was seen even at the highest dose level tested (100 mg/kg bw/d). Therefore, the pilot study on non-pregnant female rabbits (Report no. UBE 9/951721) and the preliminary study on pregnant rabbits (Report No. UBE 10/952279) were evaluated in addition. In the pilot study each two non-pregnant female rabbits were exposed to doses of either 100, 500 and 1000 mg/kg bw/d. Marked weight loss and mortalities were noted at the two highest dose-levels, suggesting the maximum tolerated

dose level somewhere between 500 and 100 mg/kg bw/d. In the preliminary study groups of 6 pregnant female rabbits received the test material once daily by oral gavage at 0, 100, 200 and 350 mg/kg b/d from Days 6 to 18 of assumed pregnancy. The results from this study support a NO(A)EL for maternal toxicity at 100 mg/kg bw/d, based on emaciation and premature sacrifice of one dam at the next higher dose of 200 mg/kg bw/d. A NOAEL for developmental toxicity can also be suggested at 100 mg/kg bw/d, due to the occurrence of one abortion and preimplantation losses at 200 mg/kg in the presence of maternal toxicity. Therefore, the results from all studies support NOAELs for maternal toxicity and for developmental toxicity at 100 mg/kg bw/d in the rabbit.

Table B.6.6-1: Summary of reproductive toxicity and teratogenicity studies with beflubutamid

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
2-generation study Crl:CD BR rat (Sprague Dawley) 0, 200, 800, 3200 ppm	Parental and reproductive toxicity: ~ 17/~19 m/f (200 ppm)	800 ppm Parental toxicity: Decreased body weight gains, increased kidney weights. Reproductive toxicity: Impairment of body weight development during lactation, delay in age for vaginal opening (F1-females only); At 3200 ppm kidney changes at necropsy.
Developmental toxicity Crl:CD BR rat (VAF/Plus strain) 0, 100, 300, 1000 mg/kg bw/d days 6-15	Maternal toxicity: 100 Developmental toxicity: 100	300 mg/kg bw/d: Maternal toxicity: Increased water consumption, decreased food intake in the period day 6-8 of pregnancy, 1 incidence of post-dose salivation, at 1000 mg/kg bw/d: post-dose salivation, hair loss, bw loss, increased water consumption. Developmental toxicity: Increased incidences of rudimentary and/or absent renal papilla and dilated ureters at 300 and 1000 mg/kg bw/d, at 1000 mg/kg bw/d: Increased incidences of incomplete ossification of thoracic/lumbar vertebral centra.
Developmental toxicity New Zealand White rabbit 0, 10, 30, 100 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	No treatment-related effects
Preliminary study: Developmental toxicity New Zealand White rabbit 0, 100, 200, 350 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	200 mg/kg bw/d: Maternal toxicity: Emaciation, premature sacrifice Developmental toxicity: Abortion and preimplantation losses at maternally toxic doses.
Pilot study: New Zealand White rabbit (non-pregnant) 100, 500, 1000 mg/kg bw/d	100	500 mg/kg bw/d: Marked body weight loss, mortalities

m: males; f: females; bw: bodyweight

B.6.6.1 Multi-generation studies

B.6.6.1.1 Rat two-generation reproduction toxicity

Report: D.P. Myers, A.M. Bottomley (1999); UR-50601: Study of reproductive performance in CD rats treated continuously through two successive generations by dietary administration; UBE Industries, Ltd., unpublished report no. UBE 073/992298, 03.11.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 05.11.1997 to 18.08.1998.

Test Material: Beflubutamid; Batch 507003; Purity: 97.79%.

Test Animals: Crl:CD BR rat (of Sprague Dawley origin); bw (commencement of treatment): males 155-252g, females: 128-198 g; Source: Charles River UK Ltd., Margate, Kent, UK

GLP: Yes

Test Method: 87/302/EEC Part B., OECD 416, adopted 26 May 1983 (JMAFF 59 NohSan No. 4200, EPA FIFRA)

Deviations: Statistical analyses were not performed on foetal necropsy.

Acceptability: The study is considered to be acceptable.

Material and Methods:
In a preliminary study, treatment at 6400 ppm and to a lesser extent at 3200 ppm showed clear effects on bodyweight and retarded growth of offspring. [Report no. UED008/973099 performed at Huntingdon Life Sciences Ltd., UK, 20.11.97]. Based on this 3200 ppm is chosen as highest dose level for the main study. In this study, groups of 32 male and 32 female rats received the test material by dietary administration at 0, 200, 800 and 3200 ppm throughout the three generations. Both the F0 and F1 generation received treatment for a minimum of 10 weeks from selection throughout pairing, gestation and lactation. The F2 generation received treatment until all animals had attained sexual maturity. All F0 and F1 adult animals were subjected to necropsy, organ weights, reproductive capacity and histopathology assessments (reproductive organs and gross changes of controls and highest dose level). F1 and F2 offspring were subjected to a necropsy examination.
Test diets were prepared at weekly intervals throughout the study. The diet was then stored at 4°C in the dark until required. Achieved concentration was measured at all dose levels in diet samples during the study. Homogeneity and stability of beflubutamid in the diet were assessed at 25 ppm and 10000 ppm.

Findings:
Formulation Analysis: The concentration in the mixes analysed over the whole treatment period averaged 100 ± 3.65%, 98.8 ± 1.97% and 99.2 ± 1.46% of the intended concentration for the lowest, intermediate and highest dosage levels, repectively. The achieved concentrations are considered satisfactory. Homogeneity and stability of beflubutamid in the rodent diet formulation was confirmed for a previous study (Report No. UED008/973099).

F0- (parental) generation (see Table B.6.6-2)
Clinical signs: General condition remained similar in all groups and clinical signs were largely restricted to areas of hair loss and coat staining.
Mortality: No treatment-related deaths occurred. Incidental deaths not considered to be related to treatment were observed, one female in the control group and one female in the 800 ppm group.
Bodyweight gain, males: At 3200 ppm body weight gain was lower throughout the study period (weeks 0-16) reaching statistical significance at all occasions. At 800 ppm body weight gain was also lower when compared to control and low dose group although without statistical significance.
Bodyweight gain, females: At 3200 ppm statistically significant lower bodyweight gain prior to pairing and during gestation was noted for females.
During lactation (Days 1 to 21) a significantly greater overall weight gain was noted for females at 800 and 3200 ppm.
Food consumption: Food consumption of males and of females prior to pairing was unaffected by treatment. From Days 13 to 19 of gestation continuing to Day 3 of lactation females at 3200 ppm showed a slightly but significantly higher food intake.
Achieved chemical intake: The chemical intake is considered accordingly, reducing staedily as the animals became older and increasing during lactation in line with the rise in food intake at peak physiological demand.
Oestrus cycles, mating performance, fertility: No treatment-related effects observed.
Gestation length, parturition: No treatment-related effects observed.
Litter size, sex ratio, survival: No treatment-related effects observed.
Sperm evaluation adults: No treatment-related effects observed.
Organ weights adults: Terminal body weight was lower in males at 800 ppm and in both sexes at 3200 ppm, though without statistical significance.
Kidney weights (absolute and relative) were increased at 800 ppm and 3200 ppm in both sexes, although without statistical significance in males at 800 ppm. At 3200 ppm liver weights (absolute and relative) were increased in both sexes.
At 200 ppm males showed a significantly lower relative liver weight. Since this change did not follow a dose-response relationship it was considered to be incidental in nature.
At 3200 ppm relative weights for epididymides and testes were increased but were considered to be of no biological/toxicological significance since changes were minor and there was no effect on fertility or microscopy. The higher relative brain weight was considered to reflect the lower absolute bodyweight.
Necropsy and histopathology adults: No treatment-related effects were observed on reproductive organs of animals of the control and high dose group (3200 ppm). Macroscopically observed changes which were examined in all groups did not reveal any relation to treatment.
Microscopic examination on kidneys and livers were not performed routinely in this study. Therefore and taking into account findings seen in the short- and long-term toxicity studies treatment-related changes of liver and kidney can be assumed.

Table B.6.6-2 Overview of F0-parental generation treated orally with beflubutamid

Sex	Male				Female			
Dose (ppm)	0	200	800	3200	0	200	800	3200
Achieved chemical intake (mg/kg bw/d)								
Before pairing	-	15	60	243	-	16	68	277
During gestation	-	-	-	-	-	15	60	258
During lactation	-	-	-	-	-	25	112	480
Bodyweight gain (g)								
Week 0-16	435	429	415	396*	-	-	-	-
Week 0-10	-	-	-	-	152	152	148	134*
Day 0-20 gestation	-	-	-	-	143	145	144	134*
Day 1-21 lactation	-	-	-	-	27	29	47**	54**
Food consumption (g/rat/d)								
Day 13-19 gestation	-	-	-	-	28	28	28	31**
Day 1-3 lactation	-	-	-	-	40	37	44	47
Terminal bw	642.4	634.9	616.8	606.3	357.4	359.0	360.0	346.6
Organ weights								
Kidney – absolute (g)	4.496	4.367	4.568	4.747	2.899	2.944	3.092*	3.275**
Kidney – relative (%)	0.7029	0.6902	0.7427	0.7865**	0.8115	0.8213	0.8593**	0.946**
Liver – absolute (g)	25.1	23.6	24.2	25.9	21.2	21.0	22.0	25.5**
Liver – relative (%)	3.92	3.71*	3.91	4.28**	5.94	5.85	6.12	7.39**

Statistical significance: *p<0.05; **p<0.01 (Dunnett's test)

F1- (offspring) generation (see Table B.6.6-3)

Offspring bodyweight gain: At 800 ppm and 3200 ppm bodyweight of offspring at Day 1 of age was slightly lower when compared to control and low dose group, although not dose-related and without statistical significance. To weaning day 21 the difference became obvious for both sexes, although significance at 800 ppm was attained for males only. This is considered to reflect impaired pup growth which was apparent prior to standardisation of litter size at Day 4 of age and persisted thereafter.

Offspring development and necropsy: No treatment-related effects observed in offspring development. The onset and completion of pinna detachment, hair growth, tooth eruption and eye opening was similar between all groups.

At 3200 ppm an increased incidence of unilateral renal cavitation of the kidney together with unilateral hydroureter was noted at necropsy after weaning.

Necropsy of offspring before weaning revealed absence of milk in the stomach as a consistent finding, unrelated to treatment.

Table B.6.6-3: F1-generation: Offspring bodyweight gain

Sex	Male				Female			
Dose (ppm)	0	200	800	3200	0	200	800	3200
Bw gain (g) - Offspring:								
Days 1-4	2.5	2.4	1.9	2.2	2.4	2.3	1.9	1.8
Days 1-21	47.4	46.2	43.4*	41.3**	44.4	43.8	41.9	38.8**

Statistical significance: *p<0.05; **p<0.01 (Dunnett's test)

F1- (parental) generation (see Table B.6.6-4)

Clinical signs: General condition remained similar in all groups and clinical signs were largely restricted to areas of hair loss and coat staining.

Mortality: No treatment related deaths occurred.

Incidental deaths, one female in the 200 ppm group (no. 2165) and one male in the 800 ppm

group (no. 2087) were observed and not considered to be related to treatment.
Bodyweight gain, males: At 800 ppm and 3200 ppm body weight gain was noticeable lower throughout the study period (weeks 1-17) reaching statistical significance at almost all occasions.
Bodyweight gain, females: At 3200 ppm statistically significant lower bodyweight gain prior to pairing and during gestation was noted for females. During lactation (Days 1 to 21) a significantly greater overall weight gain was noted for females at 3200 ppm and these females did not show the expected late (Days 14 to 21) lactation weight loss.
Anyhow, absolute bodyweights at the start of the F1 generation in males and females receiving 3200 or 800 ppm were marginally lower than controls. Mean bodyweights at termination (males) or week 10 (females) expressed as a percentage of controls were comparable to the percentage difference at Week 0 (for male, week 0: 92%, week 17: 89%, for female, week 0: 89%, week 10: 89%). This indicates that the overall growth rate of treated groups was comparable to the controls from selection at weaning to termination and differences in weight gain were mainly attributable to persistence of effects established before weaning.
Food consumption: At 3200 ppm there was a tendency to a marginally lower food intake for both sexes, attaining significance during Week 8 for males and during Week 5 for females.
Achieved chemical intake: The chemical intake is considered accordingly, reducing staedily as the animals became older and increasing during lactation in line with the rise in food intake at peak physiological demand.
Sexual maturation: At 800 and 3200 ppm a significant delay in age for vaginal opening among females was observed, but mean bodyweights at opening were comparable to controls.
There was no clear effect of treatment on the mean age of balano-preputial separation of males. A marginal delay can be suggested at 3200 ppm but intergroup diffferences were less than one day and did not attain statistical significance.
Oestrus cycles, mating, fertility: No treatment-related effects observed.
At 800 ppm a higher incidence of irregular or extended cycles among females occurred, but in the absence of a similar finding at 3200 ppm this is considered to be coincidental and unrelated to treatment.
Gestation length, parturition: No treatment-related effects observed.
At 3200 ppm there was a slightly higher incidence of females with a shorter gestation length with the difference attaining statistical significance. The biological significance of this is uncertain but since there were no adverse effects on litter viability indices or pup bodyweights on Day 1 of age it is considered to be of no toxicological concern.
Litter size, sex ratio, survival: No treatment-related effects observed.
Sperm evaluation adults: No treatment-related effects observed.
Organ weights adults (F1): At 800 ppm mean terminal body weights were lower in males and at 3200 ppm in both sexes with the following percentages given. Males: 102%, 93% and 88%; Females: 103%, 100% and 92% of the controls at 200 ppm, 800 ppm and 3200 ppm, respectively.
Slightly increased kidney weights were noted at 800 ppm, reaching statistical significance in males only, and at 3200 ppm in both sexes. Additionally, at 3200 ppm liver weights were increased.
At 3200 ppm spleen weights were decreased in both sexes and relative weights for epididymides, testes and brain (both sexes) were increased. These differences were considered to be of no biological/toxicological significance since there was no effect on fertility or microscopic appearance and it might be a reflection of lower bodyweight.
Necropsy and histopathology adults (F1): No treatment-related effects were observed on reproductive organs of animals of the control and high dose group (3200 ppm).

Macroscopically observed changes which were examined in all groups did not reveal any relation to treatment.
Microscopic examination on kidneys and livers were not performed routinely in this study. Therefore and taking into account findings seen in the short- and long-term toxicity studies treatment-related changes of liver and kidney can be assumed.

Table B.6.6-4: Overview of parental F1-generation treated orally with beflubutamid

Sex	**Male**				**Female**			
Dose (ppm)	0	200	800	3200	0	200	800	3200
Achieved chemical intake (mg/kg bw/d)								
Before pairing	-	19	78	323	-	21	85	360
During gestation	-	-	-	-	-	16	66	288
During lactation	-	-	-	-	-	23	100	482
Bodyweight gain (g)								
Week 0-17	553	566	516	491**	-	-	-	-
Week 0-10	-	-	-	-	222	229	218	196**
Day 0-20 gestation		-	-	-	151	143	146	132**
Day 1-21 lactation	-				13	21	23	49**
Sexual maturation								
mean day of age for:								
- Vaginal opening (VO)	-	-	-	-				
- Balano-preputial					33.0	33.7	34.3 a	36.5 b
separation (BPS)	46.7	47.5	46.9	47.6	-	-	-	-
Bodyweight (g) at VO/BPS	249	252	234 a	229 b	113	115	113	118
Terminal bw	638.8	649.3	596.6	565.2**	341.0	351.9	341.5	314.3*
Organ weights								
Kidney – absolute (g)	4.302	4.309	4.348	4.556	2.766	2.896	2.909	2.871
Kidney – relative (%)	0.6778	0.6665	0.7365*	0.8101**	0.8116	0.8250	0.8532	0.913**
Liver – absolute (g)	23.5	24.0	23.1	24.1	19.2	19.9	19.6	23.1**
Liver – relative (%)	3.69	3.71	3.91	4.28**	5.64	5.67	5.78	7.36**

Statistical significance: *p<0.05; **p<0.01 (Dunnett's test)
Significant when compared with control group: a – p<0.05; b – p<0.01

F2- (offspring) generation (see Table B.6.6-5)
Bodyweight gain: Bodyweight of offspring at Day 1 of age was unaffected. At 3200 ppm statistically significant lower bodyweight gain for both sexes to weaning at 21 days of age, reflecting impaired pup growth which was apparent prior to standardisation of litter size at Day 4 of age and persisted thereafter.
Offspring development, anogenital distance and necropsy: There was no treatment-related effects in offspring development and anogenital distance. At necropsy the incidence of offspring smaller in size and gaseous content in the gastrointestinal tract was increased. An increased incidence of bilateral renal cavitation of the kidney together with bilateral hydroureter was mainly noted at necropsy before weaning (see Table B.6.6-6).
Offspring before weaning revealed absence of milk in the stomach as a consistent finding, unrelated to treatment.

Table B.6.6-5: F2-generation: Offspring bodyweight gain

Sex	**Male**				**Female**			
Dose (ppm)	0	200	800	3200	0	200	800	3200
Bw gain (g) - Offspring:								
Days 1-4	2.1	2.3	2.2	1.9	2.0	2.2	2.2	1.9
Days 1-21	45.0	45.7	43.4	39.3 b	42.2	41.5	41.2	38.2 a

Significant when compared with control group: a – p<0.05; b – p<0.01

Table B.6.6-6: Necropsy findings of offspring F1- and F2-generation

Dose (ppm)	0	200	800	3200
No. of F1- offspring (litter) examined after weaning:	151 (27)	163 (29)	157 (28)	177 (31)
– unilateral renal cavitation – unilateral hydroureter	6 (5) 2 (2)	5 (3) -	6 (5) 1 (1)	16 (9) 4 (2)
No. of F2- offspring (litter) examined before weaning:	36 (14)	40 (11)	18 (10)	50 (14)
– gastrointestinal tract – content gaseous – offspring small in size – bilateral renal cavitation – bilateral hydroureter	- 2 (1) 2 (1) 2 (1)	- 2 (2) 2 (1) 1 (1)	- 3 (3) 2 (2) -	6 (3) 9 (5) 5 (2) 5 (2)

No statistics performed

F2-generation (reared into adulthood, day 63) (see Table B.6.6-7)
Clinical signs: The general condition of the animals was similar in all groups.
Mortality: There were no mortalities.
Bodyweight gain: Absolute bodyweight gain of males receiving 3200 or 800 ppm and females receiving 3200 ppm were noticeable lower than controls. Anyhow, mean bodyweights at termination (Day 63) expressed as a percentage of controls were comparable to the percentage difference at Day 28. This indicates that the overall growth rate of treated groups was comparable to the controls from selection at weaning to termination and differences were mainly attributable to persistence of effects established before weaning.
Sexual maturation: The mean age for attainment of vaginal opening was comparable in all groups, occurring at a significantly lower bodyweight at 3200 ppm, indicating no primary delay in sexual maturation. There was a slight delay in age at attainment of preputial separation among males at 800 ppm and 3200 ppm, although without statistical significance.
Necropsy and histopathology adults: Macroscopically observed changes which were examined histopathologically did not reveal a relation to treatment.

Table B.6.6-7: Overview of F2-Generation rats reared into adulthood

Sex	Male				Female			
Dose (ppm)	0	200	800	3200	0	200	800	3200
Bodyweight gain (g)								
day 28-35	52	52	48 a	44 b	40	41	39	37 b
day 28-63	301	302	283 b	254 b	160	166	159	148 a
Sexual maturation								
mean day of age for:								
- Vaginal opening (VO)	-	-	-	-	34.6	33.8	35.2	35.0
– Balano-preputial separation (BPS)	46.4	46.8	47.6	48.4	-	-	-	-
Bodyweight (g) at VO/BPS	243	248	238	224 b	116	114	116	108 a

Significant when compared with control group: a – p<0.05; b – p<0.01

Discussion:
Under the conditions of this study, beflubutamid had no adverse effects on fertility, on the parturition process or on peri- and postnatal survival of the offspring when rats were continuously orally exposed up to 3200 ppm (~243 mg/kg/day for males, ~338 mg/kg/day for females) through two successive generations.
The main target organs were the liver and the kidneys confirming the results obtained in

short- and long-term studies. In this study increases in organ weights of liver (3200 ppm) and kidney (800 and 3200 ppm) were seen. Macroscopically observed renal cavitation and hydroureters at offspring necropsy were therefore considered treatment-related at the dose level of 3200 ppm. Treatment-related effects on gonads were not observed in this study.
Reductions in body weight gains were noted at 800 ppm and 3200 ppm for parental animals as well as for the offspring. When comparing the body weight development for example in the F1-generation it became obvious that absolute bodyweights of males and females receiving 3200 ppm or 800 ppm were marginally lower than controls at the start of the F1-generation. Nevertheless, mean bodyweights at termination expressed as a percentage of controls were comparable to the percentage difference at Week 0. This indicates that the overall growth rate of treated groups was comparable to the controls from selection at weaning to termination and differences in weight gain were mainly attributable to persistence of effects established before weaning. Therefore it can be concluded that body weight development was impaired in pups mainly during the lactational phase. In the present 2-generation study in rats it remained unclear whether the reduced growth of young has been caused by reduced milk production, by palatability or quality problems, by ingestion of high amounts of beflubutamid secreted into the milk or by poor suckling ability. From the toxicokinetic studies it can be seen that after single and repeated oral doses of radiolabelled beflubutamid in addition to the gastrointestinal tract, liver and kidneys, where the highest radioactivity occurred, the next higher levels were found in abdominal fat, plasma and whole blood. Because of the tendency for mobilization of lipids from adipose tissue and their secretion into the milk, milk may contain lipophilic substances at even higher concentrations than those present in the blood or organs of the dam. In the present study the impaired development of the offspring was considered an adverse reproductive effect.
Additionally, at 800 ppm and 3200 ppm there was a significant delay in age for vaginal opening among females of the F1-generation. Concerning balano-preputial separation in males, no clear effect of treatment on the mean age was seen. In the F1-generation, a marginal delay could be suggested at 3200 ppm but intergroup diffferences were less than one day and did not attain statistical significance. In the F2-generation, a slight delay was observed among males at 800 ppm and 3200 ppm, although without statistical significance. These developmental landmarks are indicators of onset of puberty and depend upon the androgen and estrogen status of males and females, repectively. Exogenous agents may either accelerate or delay these endpoints and both may be considered adverse.
The biological significance of the slightly shorter gestation length noted in females of the F1-generation at 3200 ppm is uncertain. Since no mortalities occurred and body weight of offspring at day 1 post partum was not affected, no biological/toxicological significance was attributed to this finding.

Conclusion:
The NOAEL for parental toxicity as well as for reproductive toxicity was found to be 200 ppm (~ 17 mg/kg bw/d for males; ~19 mg/kg bw/d for females), based on lower body weight gains and increased kidney weights in parental animals, as well as on impairment of body weight development mainly during the lacational phase in pups and on a delay in age for vaginal opening at the next higher dose of 800 ppm.

The notifier did not consider the impaired pup growth during lacation and the delay in age for vaginal opening as an adverse reproductive effect which resulted in the proposal of a NOAEL for reproductive toxicity of 3200 ppm. The notifier did not propose a NOAEL for parental toxicity.

B.6.6.2 Developmental toxicity studies

B.6.6.2.1 Rat teratogenicity (oral)

Report: L.A. Waterson, S.J. Crome, D.M. John, I.S. Dawe (1997a); UR-50601: A study of the effect on pregnancy of the rat (gavage administration); UBE Industries, Ltd.; unpublished report no. UBE 038/971422, 11.11.1997 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 11.02.97 to 27.02.1997.

Test Material: Beflubutamid; Batch 507001; Purity: 97.46%.

Test Animals: Rat (Crl:CD BR VAF/Plus strain), bw (commencement of treatment): 181-238 g; Source: Charles River UK Ltd., Margate, Kent, UK

GLP: Yes

Test Method: 87/302/EEC Part B, OECD No. 414 adopted May 1981 (JMAFF 59 NohSan No. 4200, EPA FIFRA 83-3)

Deviations: (1) Statistical analyses were not performed on foetal necropsy, skeletal and visceral examinations data.
(2) Acclimatisation period for Batch A animals was 4 days not 5 days.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Groups of 25-time-mated female rats received the test material once daily by oral gavage at 0, 100, 300 and 1000 mg/kg/day from Days 6 to 15 of assumed pregnancy. The day of mating, as judged by the appearance of sperm or by the presence of vaginal plug, was considered as Day 0 of pregnancy. On Day 20 of assumed pregnancy, all rats were sacrificed and examined for any gross pathological defects.
Samples of dose formulations taken on day 1 of dosing and towards the end of the dosing phase were analysed.
Findings: (see Table B.6.6-8)
Formulation Analysis: The results of the analyses were between 2% and 13% below nominal concentrations confirming accurate preparation. Although the concentration was –13% of samples taken from group 4 formulation a 3-fold dose increment between group 3 and 4 was maintained.
Mortality: No unscheduled deaths were observed.
Clinical signs: At 1000 mg/kg bw/d post dose salivation was noted for 23/25 animals as well as a higher incidence of hair loss (mainly in the dorsal region). At 300 mg/kg bw/d post dose salivation was noted for a single animal on Day 8.
Bodyweight gain: In the period day 6 to 8 and 6 to 9 of pregnancy significant bodyweight losses were evident for the majority of individual females at 1000 mg/kg bw/d. Thereafter gains were similar compared to controls.
Food and water consumption: In the period Day 1 to 3 of treatment a statistically significant dose-related lower food intake was noted at 300 and 1000 mg/kg bw/d. Significantly higher water intake was noted for animals during both the dosing and the after dosing phase.

Gross pathology: At 1000 mg/kg bw/d the higher incidence of hair loss was confirmed at autopsy .
Litter data: There were no treatment-related findings.

Table B.6.6-8: Findings in the rat teratogenicity study after exposure to beflubutamid (Dams data)

	Dosage (mg/kg bw/d)			
	0	**100**	**300**	**1000**
No. of animals mated	25	25	25	25
No. of animals non-pregnant	1	2	0	1
No. surviving to Day 20 with live litters	24	23	25	24
Number unscheduled death	0	0	0	0
Clinical signs	-	-	Post-dosing salivation in one animal	Post-dosing salivation, hair loss
Bodyweight change (g)				
day post coitum 7-8	6.2	4.8	6.7	- 0.3**
8-9	6.0	7.0	6.8	10.7**
8-15	50.6	50.5	51.3	54.1
8-20	117.5	117.5	119.2	126.3
Food consumption (cumulative g/rat)				
day post coitum 6-8	75	73	71**	66**
9-15	182	177	189	185
16-19	115	110	120	119
Water consumption (cumulative g/rat-% of control)				
day post coitum 8-15	301	308 / 102%	357* / 119%	455** / 151%
16-19	172	171 / 99%	196* / 114%	198** / 115%
Gross pathology				
Hair loss	5/25	9/25	8/25	21/25

Statistical significance: * p <0.05; ** p <0.01 (William's test)

Foetal examination: (see Table B.6.6-9)
At 300 and 1000 mg/kg bw/d there was a higher incidence of fetuses with rudimentary/absent renal papilla and with dilated ureters compared to control and low dose group. The dilated renal pelvis (unilateral) observed in one fetus at 300 mg/kg bw/d (litter no. 64; fetus no. 1) occurred together with a rudimentary renal papilla and dilated ureters. One fetus of the 300 mg/kg bw/d group (litter no. 64; fetus no. 11) had an absent left kidney and ureter, a duplicated inferior vena cava, and a malpositioned left testis. Left anophthalmia (absent eye bulge) occurred in one fetus of the high dose group (litter number 92, fetus no. 13) versus none in the control and other dose groups. These changes are considered as malformations.
At 1000 mg/kg/day a slightly higher number of fetuses and a consequently higher number of litters showing incomplete ossification of thoracic vertebral centra was noted. These changes are considered as variations.

Table B.6.6-9: Necropsy data (Foetal examination)

	Dosage (mg/kg bw/d)			
	0	**100**	**300**	**1000**
Visceral anomalies (no. fetuses affected / no. litter affected)				
No. of fetus examined	146	151	147	155
No. of litters examined	24	23	25	24
- Rudimentary/absent papilla in the kidney	-/-	1/1	4/4	3/3
- Dilated kidney pelvis	-/-	-/-	1/1	-/-
- Dilated ureters	5/4	4/3	11/8	12/6
- Absent kidney and ureter#	-/-	-/-	1/1	-/-
- Duplicated inferior v. cava#	-/-	-/-	1/1	-/-
- Cryptorchid (malpos. testis)#	-/-	-/-	1/1	-/-
- Anophthalmia	-/-	-/-	-/-	1/1
Skeletal anomalies (no. fetuses affected / no. litter affected)				
No. of fetus examined	152	151	148	154
No. of litters examined	24	23	25	24
- Incomplete ossification of thoracic/lumbar vertebral centra	7/6	5/4	6/6	12/10##

No statistics performed
Occurrence in 1 fetus (no. 11, litter no. 64)
outside historical control data for this strain of rat and the performing laboratory (incidence of incomplete ossification of thoracic/lumbar vertebrae from teratogenicity studies conducted during 1997 (number fetuses (litters) examined: 6 (4); 6 (5), 3 (3), 4 (3).

Discussion:

A substance-related effect leading to malformations in the urinary system of fetuses at 300 and 1000 mg/kg bw/d (rudimentary/absent papilla, one incidence of absent kidney and ureter) possibly due to a multifactorial threshold concept cannot be ruled out. With the exception of fetus no. 11 (litter no. 62) from group 3 (300 mg/kg bw/d), the finding of rudimentary/absent papilla in the kidney occurred together with uni- or bilateral dilatation of the ureters, whereas a dilatation of the ureter also occurred as a single finding. The dilated renal pelvis (unilateral) observed in one fetus at 300 mg/kg bw/d (litter no. 64; fetus no. 1) occurred together with a rudimentary renal papilla and dilated ureters. A single occurrence of unilateral anophthalmia was additionally noted in the high dose group versus none in the control and other treated dose groups. The incidence of rudimentary/absent papilla in the kidney are within the historical control data provided by the notifier but “absent kidney and ureter” and “anophthalmia” was not reported in six teratogenicity studies in rats conducted during 1996-1997.

Additionally, an increase in the incidence of incomplete ossification of the thoracic/lumbar vertebral centra was noted in the fetuses of the high dose group (1000 mg/kg bw/d). These changes were considered to be the result of maternal toxicity observed in the high dose dams, mainly decreased body weight gain.

Since the kidney was considered a target organ in rats, an effect on the kidney can also be suggested for the dams, evidenced by a marked increase of water consumption observed on almost all occasions at 300 and 1000 mg/kg bw/d. Additionally, at 300 mg/kg bw/d post-dosing salivation was noted in 1/25 animals and at 1000 mg/kg bw/d post-dosing salivation and hair loss occurred in almost all animals. The causes of hair loss are manifold but it is known that hair loss may occur especially during pregnancy due to disturbances in the nutritional balance, e.g. zinc deficiency.

Conclusion:
The results from this study support a NOAEL for maternal toxicity and for developmental toxicity at 100 mg/kg bw/d.
The NOAEL for maternal toxicicty is based on increased water consumption, a slightly decreased food intake in the period day 6-8 of pregnancy, and a single incidence of post-dose salivation at the next higher dose of 300 mg/kg bw/d.
The NOAEL for developmental toxicity is based on the occurrence of rudimentary and/or absent papilla and dilated ureters at the next two higher dose levels of 300 and 1000 mg/kg bw/d when compared to control and low dose level.

The NOAEL for maternal toxicity is in accordance with the proposal of the notifier. The NOAEL for developmental toxicity is not in accordance with the proposal of the notifier who derived a NOAEL at 1000 mg/kg bw/d, stating that there was no evidence of any adverse effect on embryo-fetal development.

B.6.6.2.2 Rabbit teratogenicity (oral) – Main study

Report: L.A. Waterson, S.J. Crome, D.M. John, I.S. Dawe (1997b); UR-50601: A study of the effect on pregnancy of the rabbit (gavage administration); UBE Industries, Ltd.; unpublished report no. UBE 43/971457, 18.12.1997; dates of experimental work: 10.02.1997 to 19.03.1997.

Test Material: Beflubutamid; Batch 507001; Purity: 97.46%.

Test Animals: New Zealand White rabbit, females, bw (on arrival): 3.0-3.9 kg, Source: Harlan Interfauna Ltd., Huntingdon, Cambridgeshire, UK.

GLP: Yes

Test Method: 87/302/EEC Part B., OECD No. 414 adopted May 1981 (JMAFF 59 NohSan No. 4200, EPA FIFRA 83-3)

Deviations: (1) Due to a death during the pre-dose period an additional animal from Batch 6 was obtained and treated as indicated in the procedure section of the report.
(2) Statistical analyses were not performed on skeletal variant data except on the data relating to the mean % of fetuses per litter with 12/13 or 13/13 ribs at the request of the Sponsor.
(3) The dose selection is not conform to guideline OECD No. 414 because no effects were noted even at the highest dose of 100 mg/kg bw/d.

Acceptability: The study is considered to be acceptable on the basis of the preliminary study (Report No. UBE 10/952279) and on the pilot study (Report no. UBE 9/951721) in rabbits.

Material and Methods:
Groups of 16 pregnant female New Zealand white rabbits received the test material once daily

by oral gavage at 0, 10, 30 and 100 mg/kg b/d from Days 6 to 18 of assumed pregnancy. These doses were based on a pilot study in rabbits [Report no. UBE 9/951721 performed at Huntingdon Life Sciences Ltd., UK, 21.07.98] and a preliminary study in pregnant rabbits [Report no. UBE 10/952279 performed at Huntingdon Life Sciences Ltd., UK, 24.01.96]. In the latter one, conducted at 100, 200, and 350 mg/kg/day, clear signs of maternal toxicity were evident at both 350 and 200 mg/kg/day and consisted of 3 deaths, clear reduction in bodyweight gain and food intake at 350 mg/kg/day and 1 death and slightly reduced bodyweight gain at 200 mg/kg/day. Therefore, 100 mg/kg/day was derived as a suitable high dose level for rabbits. The day of mating was considered as Day 0 of pregnancy. On Day 29 of assumed pregnancy all rabbits were sacrificed and examined for any gross pathological defects.
Prior to commencement of the study the proposed formulation procedure was checked by chemical analysis to confirm that the method was acceptable and that the homogeneity and stability of the formulation was satisfactory under the conditions of the study.

Findings: (see Table B.6.6-10)
Formulation Analysis: The results for test formulations analysed during the study were between 3% and 8% below nominal concentrations confirming accurate formulation. The stability and homogeneity in vehicle was demonstrated at concentrations of 1-200 mg/l.
Mortality: There were 2 unscheduled deaths (control and lowest dose group) neither of them associated with treatment.
Clinical signs: There were no treatment-related findings.
Bodyweight gain: There were no treatment-related findings.
Food consumption: There were no treatment-related findings.
Gross pathology of dams: There were no treatment-related findings.
Litter data: There were no treatment-related findings.
Foetal examination: There were no treatment-related findings.

Table B.6.6-10: Findings in the rabbit teratogenicity study after exposure to beflubutamid

	Dosage (mg/kg bw/d)			
	0	**10**	**30**	**100**
Dams data				
No. of animals	16	17*	16	16
No. surviving to Day 29 with live litters	14	15	15	16
No. unscheduled death	1	1*	0	0
Not pregnant	1	1	1	0
Clinical signs	-	-	-	-
Bodyweight change	-	-	-	-
Food consumption	-	-	-	-
Gross pathology	-	-	-	-
Litter data	No treatment-related findings			
Foetal abnormalities	No treatment-related findings			

* Includes one animal which died during the pre-dose period and was subsequently replaced.

Discussion:
Under the conditions of this study there were no treatment-related findings even at the highest dose level of 100 mg/kg bw/d in this study. Therefore, the preliminary study (Report No. UBE 10/952279) and the pilot study in rabbits (Report no. UBE 9/951721) were additionally evaluated.

In the pilot study each two non-pregnant female rabbits were exposed to doses of either 100, 500 and 1000 mg/kg bw/d. Marked weight loss and mortalities were noted at the two highest dose-levels, suggesting the maximum tolerated dose level somewhere between 500 and 100 mg/kg bw/d.
In the preliminary study groups of 6 pregnant female rabbits received the test material once daily by oral gavage at 0, 100, 200 and 350 mg/kg b/d from Days 6 to 18 of assumed pregnancy. The results from this study support a NO(A)EL for maternal toxicity at 100 mg/kg bw/d, based on emaciation and premature sacrifice of one dam (no. 306) at the next higher dose of 200 mg/kg bw/d. A NOAEL for developmental toxicity can also be suggested at 100 mg/kg bw/d, due to the occurrence of one abortion at 200 mg/kg in the presence of maternal toxicity of dam no. 306.

Conclusion:
The results from all studies support NOAELs for maternal toxicity and for developmental toxicity at 100 mg/kg bw/d.

This NOAEL is in accordance with the proposal of the notifier.

B.6.6.2.3 Rabbit teratogenicity (oral) – Preliminary study

Report: D.P. Myers, S.M. Fulcher, C. Gopinath, D.M. John, I.S. Dawe (1996); UR-50601: A preliminary study of the effect on pregnancy of the rabbit (gavage administration); UBE Industries, Ltd.; unpublished report no. UBE 10/952279, 24.01.1996; dates of experimental work: 24.07.1995 to 17.08.1995.

Test Material: Beflubutamid; Batch 950427; Purity: 97.74%.

Test Animals: New Zealand White rabbit, females, bw (on arrival): 3.2-4.3 kg, Source: Harlan Interfauna Ltd., Huntingdon, Cambridgeshire, UK.

GLP: Yes

Test Method: 87/302/EEC Part B., OECD No. 414 adopted May 1981 (JMAFF 59 NohSan No. 4200, EPA FIFRA 83-3)

Deviations: None which are considered to have impact on the validity or integrity of the study.

Acceptability: The study is considered to be acceptable as a preliminary study.

Material and Methods:
Groups of 6 pregnant female New Zealand white rabbits received the test material once daily by oral gavage at 0, 100, 200 and 350 mg/kg b/d from Days 6 to 18 of assumed pregnancy. All animals that were sacrificed for human reasons were subjected to post mortem examination and pregnancy status was determined. For animals sacrificed on day 29 of pregnancy, litter values were determined and fetuses sexed and examined for gross macroscopic changes.
Statistical analysis was not performed due to low group size.

Prior to commencement of the study the proposed formulation procedure was checked by chemical analysis to confirm that the method was acceptable and that the homogeneity and stability of the formulation was satisfactory under the conditions of the study.

Findings: (see Table B.6.6-11)
Formulation Analysis: The results for test formulations analysed on the first day of treatment of groups 2, 3 and 4 were within 7% of nominal concentration.
Mortality: There were four mortalities on study. Three animals receiving 350 mg/kg bw/d and one animal receiving 200 mg/kg bw/d were sacrificed during Days 16-21 of pregnancy due to their poor physical condition.
Clinical signs: Animals killed had an emaciated appearance and showed reduced or no food intake as well as faecal output. Fur loss occurred in 2 animals at 200 mg/kg bw/d and in one animal at 350 mg/kg bw/d.
Bodyweight gain: Animals killed showed marked weight loss between 519 g and 730 g of bodyweight from day 6 to day of sacrifice. Animal no. 401 of the high dose group gained only 57 g during day 6 to day 29 of pregnancy. Bodyweight gains of the remaining animals were comparable between the dose groups.
Food consumption: There was no obvious effect of treatment on food consumption. During days 6 to 7 of pregnancy high dose animals consumed slightly more food than control and lower dose groups. Only between days 14-18 of pregnancy high dose animals consumed less food. Follwing the withdrawal of treatment (day 19), intake increased.
Gross pathology of dams: In the uterus of dam no. 306 (200 mg/kg bw/d) which was killed on day 21 of study, nine abortion sites and no evidence of foetal remains were noted upon necropsy. Within the high dose group, early embryonic deaths were noted in the dams no. 404 and 405 (killed day 16 of study). In the uterus of dam no. 403 which was killed on day 17 of study 14 fetuses were counted. No abortions or embryonic deaths occurred in the dams of the control and low dose group (100 mg/kg bw/d).
Further post mortem findings observed for the animals killed consisted in minimal contents in the gastro-intestinal tract and changes to the heart and/or thoracic cavity (pale, content fluid). In the dams which survived until treatment end, animal no. 305 had an enlarged and swollen liver (200 mg/kg bw/d) and hair loss was confirmed in 2/6 animals at 200 mg/kg bw/d (no. 301, 303) and in 1/6 at 350 mg/kg bw/d (no. 401).
Litter data: The assement of litter data is based on 5, 5, 5, and 3 dams at day 29 of pregnancy. At 200 mg/kg bw/d, in the dams no. 302 and 305 a higher preimplantation loss was noted (62.5% and 83.3%, respectively), resulting in only one live young in dam no. 305. No similar percentages were noted other dams of either group.
Foetal examination:
Malformations occurred at 100 mg/kg bw/d where two foetues out of one litter were affected (dam no. 201; fetus no. 1: Retro-oesophageal right subclavian artery; fetus no. 3: Umbilical hernia) and in one fetus at 350 mg/kg bw/d (dam no. 406; fetus no. 3: Cebocephaly with single naris and absent naso-labial sulcus, incisors and tongue; hydrocephaly). No obvious signs of maternal toxicity was noted in dam no. 406.

Table B.6.6-11: Findings in the rabbit preliminary teratogenicity study after exposure to beflubutamid

	Dosage (mg/kg bw/d)			
	0	**100**	**200**	**350**
Dams data				
No. of animals	6	6	6	6
No. surviving to Day 29 with live litters	5	5	5	3
Killed prior day 29	-	-	1	3
Not pregnant	1	1	0	0
Clinical signs - Emaciation - Fur loss	 - -	 - -	 1 2	 3 1
Bodyweight change	-	-	Loss	Loss
Food consumption (g/rbt/d) Days of pregnancy 6-7 14-18 19-22	 92 193 193	 104 153 160	 79 174 181	 128 103 173
Necropsy - pregnant dams - Abortion - Early embryonic deaths	 -/5 -/5	 -/5 -/5	 1/6 -/6	 -/6 2/6
Litter data	At 200 mg/kg bw/d: 2/5 dams with higher percentage of preimplantation loss.			
Foetal abnormalities (individual observations)	No. 7: absent intermediate lung lobe	No. 1: retro-oesophageal right subclavian artery No. 3: Umbilical hernia, ateletatic lungs	No. 3, 7,10: Variation in origin of arteries arising from aortic arch	No. 7: Bilateral corneal opacity No. 3: Cebocephaly, hydrocephaly and atelectatic lungs

Conclusion:
The results from this study support a NO(A)EL for maternal toxicity at 100 mg/kg bw/d, based on emaciation and premature sacrifice of one dam (no. 306) at the next higher dose of 200 mg/kg bw/d.
A NOAEL for developmental toxicity can also be suggested at 100 mg/kg bw/d, due to the occurrence of one abortion at 200 mg/kg in the presence of maternal toxicity of dam no. 306.

B.6.6.2.4 Rabbit teratogenicity (oral) – Pilot study

Report: D.P. Myers, S.M. Fulcher, C. Gopinath, A. Anderson (1995); UR-50601: A pilot study of the effect on the female rabbit (gavage administration); UBE Industries, Ltd.; unpublished report no. UBE 9/951721, 21.07.1998; dates of experimental work: 05.06.1995 to 07.07.1995.

Test Material: Beflubutamid; Batch 950427; Purity: 97.74%.

Test Animals: New Zealand White rabbit, females, bw (on arrival): 3.4 -4.0 kg, Source: Harlan Interfauna Ltd., Huntingdon, Cambridgeshire, UK.

GLP: No

Test Method: Pilot study to provide information of the maximum tolerated dose in the non-pregnant female rabbit.

Deviations: None

Acceptability: The study is considered to be acceptable as a pilot study.

Material and Methods:
Groups of 2 non-pregnant female New Zealand white rabbits received the test material oral gavage at 1000 (Group 1), 500 (Group 2) and 100 (Group 3) mg/kg bw/d. The commencement of the treatment staggered as the object of the study was to provide an indication of the maximum tolerated dose. Treatment at 1000 mg/kg bw/d was initially investigated. Treatment at 500 mg/kg bw/d commenced three days following administration of the last 1000 mg/kg bw/d. Treatment at 100 mg/kg bw/d commenced one day following administration of the last 500 mg/kg bw/d. Animals of groups 1 and 2 were dosed for seven consecutive days. Animals of group 3 were dosed for seven consecutive days and the following a wash-out period of five days were dosed again at the same dosage for a further five days (including day of sacrifice). All animals were observed and weighed daily. The one animal found dead was weighed and subjected to post mortem evaluation. At termination, animals were killed and subjected to macroscopic post mortem examination.

Findings:
One animal from group 1 (no. 102) was found dead on day 8 following administration of the seventh consecutive dose. The remaining animal of this dosage and both animals from group 2 were sacrificed in moribund condition on day 8 due to the magnitude of body weight loss. Findings at macroscopic examination of animal no. 102 revealed a moistened fur in the peri-oral region, diffuse pale subcapsular areas in the liver, a few haemorrhagic depressions in the mucosa of the stomach (corpus) and soft contents in the colon. Animal no. 101 of group 1 showed a yellow-brown staining of the fur in the genital region. Animals of group 2 had multiple punctate plaques on the intima of the aorta, minimally pitted kidneys, watery content in the stomach as well as a few haemorrhagic depressions in the mucosa of the stomach (antrum). No changes were were detected for animals of group 3.

Conclusion:
Under the conditions of this study dose-levels of 1000 and 500 mg/kg bw/d clearly exceeded the maximum tolerated dose.

B.6.7 Delayed neurotoxicity (Annex IIA 5.7)

No signs of neurotoxicity were reported in course of the toxicity studies with beflubutamid, a novel herbicide. Moreover, beflubutamid has no structural relationship to organophosphates and/or carbamates. Therefore, studies on delayed neurotoxicity were not necessary and were not performed.

B.6.8 Further toxicological studies (Annex IIA 5.8)

B.6.8.1 Toxic effects of other metabolites (where different from those identified in animal studies)

The only major metabolite of beflubutamid found in soil and groundwater is UR-50604. It was found in the rat metabolism study (see point B.6.1) as a major metabolite representing up to 31% of the administered dose of beflubutamid in urine. Therefore toxicity of UR-50604 can be evaluated based on the results of the toxicity studies with the parent compound beflubutamid. Furthermore, in the crop rotational study (see point B.7.3) metabolite U1 was found, up to 0.101 ppm, which was unsuccessfully identified but characterised extensively. U1 was only a major metabolite in straw and husks, so consumers will not be exposed to U1 directly via food. U1 is a single polar component, which is water soluble and therefore unlikely to accumulate. U1 is therefore considered to be less toxic than the parent compound beflubutamid.
Based on this no further studies need to be performed on these metabolites.

B.6.8.2 Supplementary studies on the active substance

No supplementary studies on the active substance were submitted.

B.6.9 Medical data and information (Annex IIA 5.9)

B.6.9.1 Medical surveillance on manufacturing plant personnel

No reported poisoning incidents or clinical cases, including irritant and allergenic response to workers during the manufacturing of technical beflubutamid or the application of beflubutamid formulation have been made (Reference - Manufacturing Health Report, Anonymous 1999, is confidential and included in Document K II, Volume 10/10).

B.6.9.2 Direct observation, e.g. clinical cases and poisoning incidents

Following a search, no literature relating to clinical cases and poisoning incidents is available.

B.6.9.3 Observations on exposure of the general population and epidemiological studies, if appropriate

No data are available at this time.

B.6.9.4 Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

No specific signs of toxicity or specific clinical test methods are known at this time.

B.6.9.5 Proposed treatment: first aid measures, antidotes, medical treatment

First aid measures:
If substance is swallowed, wash mouth thoroughly with plenty of water and get medical attention immediately.
If contact with eyes, hold eyelids apart, flush eyes promptly with copious flowing water and get medical attention immediately.
If contact with skin, remove contaminated clothing, wash skin thoroughly with mild soap and plenty of water. Wash clothing before re-use.
If inhaled, remove person to fresh air and get medical attention immediately.
No specific antidote is known.
NOTE: Show the Material Safety Data Sheet of beflubutamid to the physician in cases where treatment becomes necessary.

B.6.9.6 Expected effects of poisoning

Any information of the expected effects and the duration of these effects following poisoning are not available. No medical incidents during manufacturing or application of products have been reported.

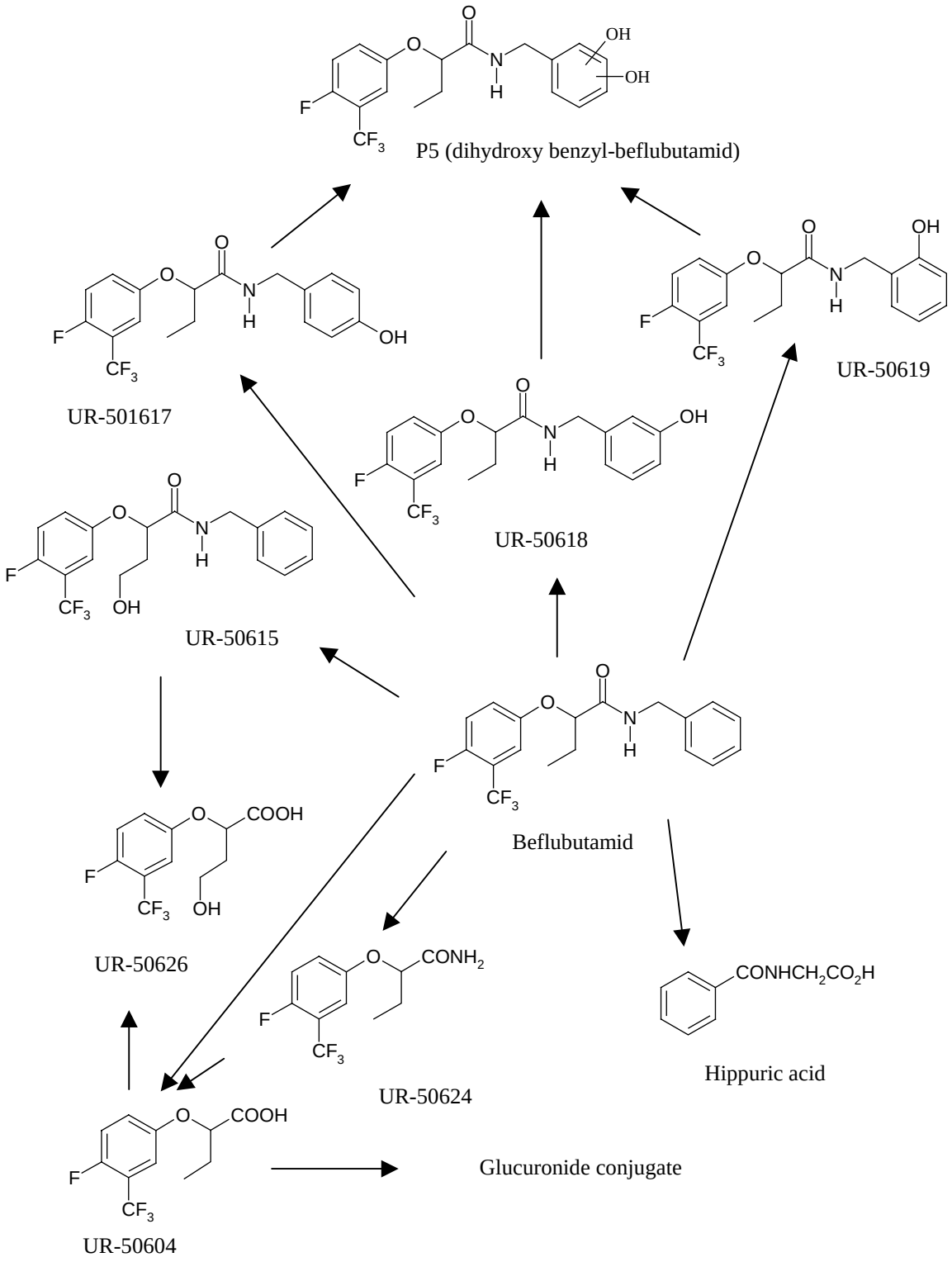
B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and drinking water limit (Annex IIA 5.10)

B.6.10.1 Metabolism / Toxicokinetics

Biodisposition was studied in rats mainly after oral administration of [^{14}C-phenoxy]beflubutamid at nominal dose levels of 35 and 350 mg/kg. [^{14}C-benzylamine]beflubutamid was used for an additional excretion balance study. The extent of absorption was 93% (male) and 83% (female) after a 35 mg/kg dose, and 49% (male) and 56% (female) after a 350 mg/kg dose. Excretion was rapid with >90% of the dose being excreted in 48 hours rather in faeces than urine. Excretion in the bile accounted for 85% (male) and 66% (female) of a 35 mg/kg dose, and 42% (male) and 47% (female) of a 350 mg/kg dose. Whole-blood and plasma analyses indicate that the rate and extent of systemic exposure of rats to radioactivity, (as characterised by C_{max} and AUC_t), increased with increasing dose, however the observed increases in C_{max} and AUC_t were disproportionately lower than predicted from a linear relationship. After repeat dosing there was no indication of accumulation in plasma, however there was some indication of a selective up-take into blood cells.
Whole body autoradiography showed that distribution in tissues was similar for male and female rats, with radioactivity being widely distributed and present in all tissues from rats sacrificed at the time of peak plasma concentration. After a single oral dose of 35 mg/kg the highest concentrations (excluding gastrointestinal tract), occurred in the liver and kidney, the organs of metabolism and excretion. The concentrations in the gastrointestinal tract after 6 and 10 hours were similar suggesting that the administered radioactivity was undergoing entero-hepatic circulation. After a single oral dose of 350 mg/kg tissue concentrations were 2-6 times higher at 6 hours after dosing than seen at the lower level.
Beflubutamid was rapidly and extensively metabolised. The major metabolite found in the plasma and excreted in the urine from rats treated with [^{14}C-phenoxy]beflubutamid was

phenoxybutyric acid (UR-50604) formed by cleavage of the amide bond. Urinary excretion of this metabolite accounted for 23 – 31 % of the administered dose. Therefore, the toxicity from this metabolite can be evaluated based on the toxicity studies with beflubutamid. In faeces the metabolites were hydroxylated derivatives of beflubutamid which were generally eliminated via the bile as glucuronide conjugates. After administration of [^{14}C-benzylamine]beflubutamid the major radiolabelled urine metabolite was hippuric acid. There was no evidence of significant stereoselective metabolism.

Figure B.6.10-1: Proposed biotransformation pathway for beflubutamid in the rat



UR-50617, UR-50618, UR-50619 eliminated in bile as glucuronide conjugates

B.6.10.2 Acute toxicity, local irritation and skin sensitizing properties

Beflubutamid has a low acute toxicity after oral, dermal and inhalation exposure. Slight signs of toxicity (wet fur, hunched posture and pilo-erection) were observed after inhalation of the test material. After application of beflubutamid to the eye of rabbits slight transient ocular irritation was observed. No skin irritation was observed in rabbits after dermal application. In a Maximisation test according to Magnusson and Kligman, no signs of allergic skin reactions in the test animals were recorded. Based on these test results, no classification is required for acute toxicity of beflubutamid according to the criteria in Council Directive 67/548/EEC.

Table B.6.10-1: Summary of acute toxicity studies with beflubutamid

Test	Species	Result
LD_{50} oral (Limit test)	Rat	(m/f) > 5000 mg/kg bw
LD_{50} dermal (Limit test)	Rat	(m/f) > 2000 mg/kg
LC_{50} inhalation (Nose only)	Rat	(m/f) > 5 mg/l air
Skin irritation	Rabbit	Non irritant
Eye irritation	Rabbit	Non irritant
Skin sensitization – Magnusson/Kligman Test	Guinea pig	Non sensitizing

B.6.10.3 Short-term toxicity

In the short-term toxicity studies in rats, mice and dogs, the liver was the target organ identified in all animal species under investigation. In addition, the kidneys, thyroid gland and adrenal glands were affected in rats, mainly evidenced by organ weight changes. All species under investigation revealed decreased body weight gains at the upper dose levels.

Rats: In the 28-day study in rats (0, 50, 400, 3200 ppm) higher kidney weights were recorded in both sexes at 3200 ppm. A reduction in adipose tissue was noted in 1/5 rats at 400 ppm and in 5/5 rats at 3200 ppm. The NOAEL was found to be 400 ppm (39.9 mg/kg bw/d for males; 38.4 mg/kg bw/d for females).
In the 90-day study in rats (0, 100, 400, 3200 ppm) a prolongation of thrombotest clotting time, higher methaemoglobin (males), plasma cholesterol and phospholipid values, increased liver, thyroid, kidney, and adrenal weights were noted at the high dose level of 3200 ppm. Histopathological examination revealed centrilobular hypertrophy of hepatocytes and renal pelves dilatation (females). No histopathological changes were noted in the thyroid gland and adrenal glands which may have accounted for increased organ weights. The NOAEL was found to be 400 ppm (29 mg/kg bw/d in males; 35 mg/kg bw/d in females).

Mice: In the 90-day study in mice (0, 400, 1600, 3200, 6400 ppm) higher liver weights and centrilobular hepatocyte hypertrophy was noted in all treated groups. The severity of this finding was increasing with increasing dose levels in male mice whereas females were affected with lower severity at higher dose levels. In addition, females of the two highest dose groups showed a generalised liver hepatocyte hypertrophy and periportal hepatocytes with cytosplasmic eosinophilia. Since the liver is the target organ in all animal species under investigation, the conclusion of the notifier that the liver findings are considered to have arisen solely as the result of an adaptive effect and are not considered to be indicative of toxicity, is not supported. Therefore, the LOAEL was found to be 400 ppm (61 mg/kg bw/d in males; 87 mg/kg bw/d in females) based on the incidence of centrilobular hepatocyte hypertrophy and liver weight changes at this dose level. A NOAEL of 50 ppm (6.4 mg/kg bw/d

for males and 8.5 mg/kg bw/d for females) can be derived from the carcinogenicity study in mice.

Dogs: In addition to the liver weight increases and hepatocyte hypertrophy, the 90-day study in dogs (0, 100, 300, and 1000 mg/kg bw/d) showed increased activities of hepatic enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase), an activated partial thromboplastin time (APTT), delayed prothrombin time (PT) as well as degenerative changes in the liver and bile ducts (hepatocyte loss, necrosis, inflammation, bile duct proliferation, prominent major bile ducts). In dogs at 300 and 1000 mg/kg bw/d histopathological changes in the prostate (acinar atrophy/fibrosis), epididymides (absent spermatozoa, round spermatids and spermatocytes in ductules) and testes (degenerate/exfoliate round spermatids and spermatocytes) together with lower gonad weights at the high dose group are of equivocal toxicological relevance. The NOAEL was found to be 100 mg/kg bw/d.

The 12-month study in dogs (0, 12, 60, and 300 mg/kg bw/d) confirmed the findings of the 90-day study with respect to changes in haematological and clinical chemistry parameters, i.e. increased clotting times and increased hepatic enzyme activities as well as lower plasma protein concentrations, liver weight increases together with a similar pattern of histopathological changes but additionally early portal to portal bridging and centrilobular collapse with hepatocyte necrosis occurred. Effects on testes and/or epididymides were not observed in this study. The NOAEL was was found to be 60 mg/kg bw/d .

Table B.6.10-2: Summary of short-term toxicity studies with beflubutamid

Study type / species / dose levels	NOAEL mg/kg bw/d	LOAEL / Critical effects
28-day feeding Crl:CD BR rat 0, 50, 400, 3200 ppm	39.9 / 38.4 m/f [400 ppm]	3200 ppm: Higher kidney weight, reduction in adipose tissue.
90-day feeding Crl:CD BR rat 0, 100, 400, 3200 ppm	29 / 35 m/f [400 ppm]	3200 ppm: Prolongation of thrombotest clotting time (m), higher methaemoglobin (m), plasma cholesterol and phospholipid values, higher liver, thyroid, kidney, adrenal weight, centrilobular hypertrophy of hepatocytes (m), renal pelves dilatation (f).
90-day feeding Crl:CD-1 BR mouse 0, 400, 1600, 3200, 6400 ppm	< 61 / 87 m/f [<50/< 50 ppm m/f] (ca. 6.4 / 8.5 m/f [50 ppm], carcinogenicity study)	400 ppm: Centrilobular hepatocyte hypertrophy of the liver
90-day oral (gelatine capsule) Beagle dog 0, 100, 300, 1000 mg/kg bw/d	100 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin time, higher liver weights. At 1000 mg/kg bw/d: increase in prothrombin time, higher activities of liver enzymes, degenerative changes in liver and bile duct.
52-week oral (gelatine capsule) Beagle dog 0, 12, 60, 300 mg/kg bw/d	60 mg/kg bw/d	300 mg/kg bw/d: Increase in activated partial thromboplastin and prothrombin time, increases in alkaline phosphatase and alanine aminotransferase, reductions in plasma total protein, higher liver weight, liver enlargement, severe degenerative changes in the liver.

m: male; f: female; bw: bodyweight, d: day

B.6.10.4 Genotoxicity

The mutagenic potential of beflubutamid was studied in bacteria and mammalian cells *in vitro* by using two gene mutation assays and a chromosome aberration assay and *in vivo* by means of a micronucleus test. All tests performed showed no mutagenic effect of the test compound. In the *in vivo* micronucleus test no bone marrow toxicity was observed, but at the two highest dose levels systemic toxicity was recorded.

Table B.6.10-3: Summary of genotoxicity testing with beflubutamid

Test system	Test object	Concentration	Purity (%)	Results
Gene mutation assays (*in vitro*)				
Reverse mutation test for bacteria	*Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100) *Escherichia coli* WP2 *uvrA*	Main Test -/+ S9 mix: 312.5, 625, 1250, 2500, 5000 µg/plate	97.61	Negative
Gene mutation test (to thioguanine resistance)	Mouse lymphoma L5178Y cells	Test 1 S9 mix: 10, 25, 50, 75, 100, 125, 150, 200 µg/ml + S9 mix: 5, 10, 25, 50, 75, 100, 125, 150 µg/ml Test 2 -/+ S9 mix: 1, 5, 10, 25, 50, 75, 100 µg/ml	97.46	Negative
Chromosome aberration assays (*in vitro*)				
Cytogenetic assay	Cultured human lymphocytes	Test 1 - 21 hr sampling time - S9 mix: 2.5, 5, 10, 20, 30, 40 µg/ml. + S9 mix: 25, 50, 100, 150, 200, 250, 500, 1000 µg/ml 45 hr sampling time – S9 mix: 10, 20, 30, 40, 50, 80, 100 µg/ml + S9 mix: 125, 250, 500, 1000, 5000 µg/ml Test 2 - 21 hr sampling – S9 mix: 10, 20, 30, 40, 50, 60 µg/ml + S9 mix: 150, 200, 250, 500, 750 µg/ml	97.61	Negative
Chromosome aberration assays in somatic cells *(in vivo)*				
Micronucleus test	Male and female CD-1 Swiss mice - bone marrow cells	125, 250, 500 mg/kg bw	97.46	Negative

B.6.10.5 Long term toxicity and carcinogenicity

The liver was found to be the target organ in rats and mice again after prolonged dietary administration of beflubutamid. In rats the thyroid gland and the kidneys were affected as well. The treatment with beflubutamid had no effects on the survival of both animal species and did not reveal a carcinogenic potential relevant to humans.

Rat: In the 24-month combined chronic toxicity/carcinogenicity study in rats (0, 50, 400, 3200 ppm; achieved chemical intakes male/female: 2.2/3.0; 17.7/24.4; 150/207 mg/kg bw/d) lower body weight gains (males, 400 ppm, both sexes 3200 ppm), a prolongation of

thrombotest clotting time (males, 400 ppm and 3200 ppm) as well as higher plasma cholesterol and phospholipid values (both sexes, 3200 ppm) were observed. Additionally, in female rats at the highest dose level (3200 ppm) higher plasma total protein levels, mainly due to a simultaneous increase of albumin and globulins were recorded. Higher amounts of proteins were noted in the urine of female rats at 3200 ppm at almost all occasions being most evident after 78 weeks of treatment onwards and at week 104 investigation also at 400 ppm. Liver and kidney weights were increased in both sexes at 3200 ppm, thyroid weights were increased in male rats (3200 ppm). At week 105, female rats at 400 and 3200 ppm also showed higher thyroid weights although without statistical significance. Both at the interim and terminal sacrifice centrilobular hepatocyte hypertrophy was noted (males, 400 ppm, both sexes 3200 ppm). In females of the high dose level (3200 ppm) progressive glomerulonephrosis in the kidney was observed with slightly higher incidence at terminal sacrifice.
The incidence of thyroid gland follicular tumours was slightly increased in male rats receiving 3200 ppm at terminal sacrifice but without reaching statistical significance and with incidences lying in the upper range of historical control data for males. In female rats, each one thyroid follicular adenoma and one carcinoma was observed in the 400 ppm and 3200 ppm group, respectively, versus none in the control and low dose group. These neoplastic findings are considered to be without relevance to humans
The NOAEL was was found to be 50 ppm (2.2 mg/kg bw/d for male and 3.0 mg/kg bw/d for female).

Mice: In the 18-month carcinogenicity study in mice (0, 50, 500, 5000 ppm; achieved chemical intakes male/female: 6.4/8.5, 67/78; 723/834 mg/kg bw/d) lower body weight gain (both sexes, 5000 ppm), increased liver and adrenal gland weights (both sexes, 5000 ppm), enlarged and pale liver and liver with pale area(s) (males, 5000 ppm) were noted. Liver centrilobular hepatocyte hypertrophy and hepatocytes with granular cytoplasm was noted in males at 500 ppm, centrilobular/generalised hepatocyte hypertrophy, parenchymal inflammatory cell foci, centrilobular sinusoidal dilation/congestion with pigmented sinusoidal cells was observed in both sexes at 5000 ppm. There were no conclusive histopathological findings in the adrenal glands which may have accounted for increased organ weights.
The incidence of liver tumours was slightly increased in male mice of the high dose group (5000 ppm) but the incidences were well within the historical control data for Crl:CD-1(ICR)BR mice submitted from the performing laboratory.
The NOAEL was was found to be 50 ppm (6.4 mg/kg bw/d for male and 8.5 mg/kg bw/d for female).

Table B.6.10-4: Summary of long-term toxicity studies with beflubutamid

Study type **Species** **Dose levels**	**NOAEL** **mg/kg bw/d**	**LOAEL / Critical effects**
104-week feeding (combined chronic toxicity/ carcinogenicity) Crl:CD BR rat 0, 50, 400, 3200 ppm	2.2 / 3.0 m/f [50 ppm]	400 ppm: Prolongation of thrombotest clotting time, centrilobular hypertrophy of hepatocytes (m), proteinuria at wk 104 (f)
80-week feeding Crl:CD-1 (ICR) BR mouse 0, 50, 500, 5000 ppm	6.4 / 8.5 m/f [50 ppm]	500 ppm: Centrilobular hepatocyte hypertrophy, hepatocytes with granular cytoplasm.

m: males; f: females; bw: bodyweight

B.6.10.6 Reproduction and developmental toxicity (teratogenicity)

Beflubutamid had no adverse effects on fertility and no effects on the parturition process or on peri- and post-natal survival of the offspring at dosages up to 3200 ppm (~243 mg/kg bw/d for males, ~338 mg/kg bw/d for females) over two generations in the Sprague Dawley rat. The below mentioned reproductive and developmental effects on the fetuses were seen in presence of parental/maternal toxicity.
In the **2-generation reproductive toxicity study in rats** the main target organs were the kidney and the liver evidenced by increased organ weights at 800 ppm and/or 3200 ppm in the adults which is in line with changes noted in short- and long-term studies. Reductions in body weight gain were noted at 800 ppm and 3200 ppm in parental animals as well as in the offspring. In the F1- and F2-pups body weight gain was decreased mainly during the lactational phase, reflecting impaired pup growth. Additionally, at 800 ppm and 3200 ppm a significant delay in age for vaginal opening occurred among females of the F1-generation. No clear effect of treatment on the mean age of balano-preputial separation could be demonstrated but a marginal delay was suggested. At necropsy of F1- and F2-offspring increased incidences of uni-/bilateral renal cavitation of the kidney and uni-/bilateral hydroureters were noted at 3200 ppm. The findings in the offspring were considered adverse reproductive effects.
The NOAEL for parental and reproductive toxicity was 200 ppm (~ 17 mg/kg bw/d for males; ~19 mg/kg bw/d for females).

Reproduction toxicity studies to investigate **developmental toxicity in the rat** revealed an increased incidence of fetuses with rudimentary/absent renal papilla and with dilated ureters at 300 and 1000 mg/kg bw/d when compared to control and low dose group. One fetus of the 300 mg/kg bw/d group had an absent left kidney and ureter, a duplicated inferior vena cava, and a malpositioned left testis. Left anophthalmia occurred in one fetus of the high dose group versus none in the control and other dose groups. Incomplete ossification of the thoracic vertebral centra occurred at the highest dose tested (1000 mg/kg bw/d). In the dams clinical signs (post-dosing salivation, hair loss), higher water intake as well as a transient reduction in food intake and body weight gain was noted at dose levels of 300 and/or 1000 mg/kg bw/d.
The NOAEL for maternal and developmental toxicity was 100 mg/kg bw/d.

In the **rabbit developmental toxicity study** no treatment-related effect was seen even at the highest dose level tested (100 mg/kg bw/d). Therefore, the pilot study on non-pregnant female rabbits (Report no. UBE 9/951721) and the preliminary study on pregnant rabbits (Report No. UBE 10/952279) were evaluated in addition. In the pilot study each two non-pregnant female rabbits were exposed to doses of either 100, 500 and 1000 mg/kg bw/d. Marked weight loss and mortalities were noted at the two highest dose-levels, suggesting the maximum tolerated dose level somewhere between 500 and 100 mg/kg bw/d. In the preliminary study groups of 6 pregnant female rabbits received the test material once daily by oral gavage at 0, 100, 200 and 350 mg/kg b/d from Days 6 to 18 of assumed pregnancy. The results from this study support a NO(A)EL for maternal toxicity at 100 mg/kg bw/d, based on emaciation and premature sacrifice of one dam at the next higher dose of 200 mg/kg bw/d. A NOAEL for developmental toxicity can also be suggested at 100 mg/kg bw/d, due to the occurrence of one abortion and preimplantation losses at 200 mg/kg in the presence of maternal toxicity. Therefore, the results from all studies support NOAELs for maternal toxicity and for developmental toxicity at 100 mg/kg bw/d in the rabbit.

Table B.6.10-5: Summary of reproductive toxicity and teratogenicity studies with beflubutamid

Study type **Species** **Dose levels**	**NOAEL** **mg/kg bw/d**	**LOAEL / Critical effects**
2-generation study Crl:CD BR rat (Sprague Dawley) 0, 200, 800, 3200 ppm	Parental and reproductive toxicity: ~ 17/~19 m/f (200 ppm)	800 ppm Parental toxicity: Decreased body weight gains, increased kidney weights. Reproductive toxicity: Impairment of body weight development during lactation, delay in age for vaginal opening (F1-females only); At 3200 ppm kidney changes at necropsy.
Developmental toxicity Crl:CD BR rat (VAF/Plus strain) 0, 100, 300, 1000 mg/kg bw/d days 6-15	Maternal toxicity: 100 Developmental toxicity: 100	300 mg/kg bw/d: Maternal toxicity: Increased water consumption, decreased food intake in the period day 6-8 of pregnancy, 1 incidence of post-dose salivation, at 1000 mg/kg bw/d post-dose salivation, hair loss, bw loss, increased water consumption. Developmental toxicity: Increased incidences of rudimentary and/or absent renal papilla and dilated ureters at 300 and 1000 mg/kg, at 1000 mg/kg: Increased incidences of incomplete ossification of thoracic/lumbar vertebral centra.
Developmental toxicity New Zealand White rabbit 0, 10, 30, 100 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	No treatment-related effects
Preliminary study: Developmental toxicity New Zealand White rabbit 0, 100, 200, 350 mg/kg bw/d days 6-18	Maternal toxicity: 100 Developmental toxicity: 100	200 mg/kg bw/d: Maternal toxicity: Emaciation, premature sacrifice Developmental toxicity: Abortion and preimplantation losses at maternally toxic doses.
Pilot study: New Zealand White rabbit (non-pregnant) 100, 500, 1000 mg/kg bw/d	100	500 mg/kg bw/d: Marked body weight loss, mortalities

m: males; f: females; bw: bodyweight

B.6.10.7 Neurotoxicity/Delayed neurotoxicity

No signs of neurotoxicity were reported in course of the toxicity studies with beflubutamid, a novel herbicide. Moreover, beflubutamid has no structural relationship to organophosphates and/or carbamates. Therefore, studies on delayed neurotoxicity were not necessary and were not performed.

B.6.10.8 Dermal absorption

No data are available on the extent of dermal absorption of beflubutamid. Therefore, a 100% dermal absorption is assumed (worst case). On the basis of the German model and the UK-POEM, applying the worst case assumption of 100% an estimation of operator exposures was

carried out. If PPE were worn, in all cases the calculated values were above the proposed systemic AOEL of 0.3 mg/kg bw/d (SF 100). Since the results do not indicate a risk for operators, a study to provide data on dermal absorption is considered not necessary and was not carried out.

B.6.10.9 Further toxicological studies

No specific studies with metabolites have been conducted.

B.6.10.10 Human experience

No reported poisoning incidents or clinical cases, including irritant and allergenic response to workers during the manufacturing of technical beflubutamid or the application of beflubutamid formulation have been made.

B.6.10.11 Acceptable Daily Intake (ADI)

The calculation of the acceptable daily intake for beflubutamid technical is based on the results from the combined chronic toxicity/carcinogenicity study in rats. A NOAEL of 50 ppm, approximately 2.2 mg/kg bw/d, from the 104-week rat study is the most sensitive dose for the estimation of the ADI of beflubutamid technical in humans. In the absence of genotoxicity, reproductive toxicity, teratogenicity or oncogenicity, an uncertainty factor of 100 is applied to the NOAEL of 2.2 mg/kg bw/d, resulting in an **ADI of 0.022 mg/kg bw/d**.

This ADI value is not in agreement with the proposal of the notifier who derived an ADI-value of 0.17 mg/kg bw/d based on a NOAEL of 17 mg/kg bw/d from the long-term study in rats and applying a safety factor of 100. The difference in the NOAEL setting in the 104-week study in rats was based on the prolongation of thrombotest clotting time, an increased incidence of centrilobular hepatocyte hypertrophy in male rats and the occurrence of proteinuria in female rats at this dose level.

B.6.10.12 Acceptable Operator Exposure Level (AOEL)

The plant protection product ASU 95 510 H is a herbicide to be applied by tractor mounted field crop sprayers on cereals. This will lead to exposure of operators, workers and bystanders mainly by the dermal route and to a lesser extent through inhalation. Oral exposure will be negligible. Since no data are available on dermal or inhalation absorption and there is no human data available on which an AOEL could be based, the AOEL is derived on the basis of so-called mid-term toxicity studies, i.e. the subacute/subchronic studies.
For beflubutamid, the lowest relevant oral NOAEL was established in the 90-day feeding study in rats where a NOAEL of approximately 30 mg/kg bw/d was found. Because the extent of absorption after oral administration of a low dose of beflubutamid was almost complete, a correction from the oral AOEL to a systemic AOEL is not needed. Because of the toxicological profile of beflubutamid and in accordance with current EU assessment practice, the standard assessment factor of 100 should be applied resulting in a **systemic AOEL of 0.3 mg/kg bw/d.**

The notifier had proposed a systemic AOEL of 0.29 mg/kg bw/d derived from the NOAEL of 29 mg/kg bw/d for male rats from the 90-day study. The value was rounded up.

B.6.10.13 Acute Reference Dose (ARfD)

On the basis of the toxicological profile, beflubutamid, a herbicide, is considered unlikely to present an acute hazard for consumers by the ingestion of residue containing food. The acute oral toxicity in rats is low and there are no acute toxicological alerts seen in repeated dose toxicity studies. Furthermore, residues are not to be expected in harvested crops because beflubutamid and its metabolites are degraded rapidly in plants. No significant residues were apparent in the human food and consumer intake via animal products is unlikely due to low levels of residue in plant tissue fed to animals. Therefore, an ARfD is not considered necessary and is not allocated.

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 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.

B.6.11 Acute toxicity including irritancy and skin sensitization of preparations (Annex IIIA 7.1)

The plant protection product ASU 95 510 H (product name: Herbaflex) is formulated as a suspension concentrate (SC) containing two active ingredients: 85 g/l UBH 820 (i.e. UR-50601 = beflubutamid) and 500 g/l isoproturon. The results of the acute toxicity studies including irritancy and skin sensitization are summarised in Table B.6.11-1.

Table B.6.11-1: Overview of acute toxicity studies with ASU 95 510 H

Test	Species	Results
Acute oral LD_{50} (Limit test)	Rat	>2000 mg/kg
Acute dermal LD_{50} (Limit test)	Rat	>2000 mg/kg
Acute inhalation (Snout only)	Rat	>3.20 mg/l air (4 h)
Acute skin irritation	Rabbit	Non irritant
Acute eye irritation	Rabbit	Non irritant
Skin sensitisation – Maximisation test	Guinea pig	Non sensitizing

ASU 95 510 H is of low oral, dermal and inhalation toxicity. Only slight signs of toxicity after oral administration occurred (pilo-erection, hunched posture, lethargy, pallid extremities). Also slight signs of toxicity occurred in the inhalation exposure study (matted fur, (crusty) brown staining around snout and/or jaws, on the head/ventral surface and on the tails). After application of ASU 95 510 H to the eye of rabbits very slight transient ocular irritation was observed. Skin application to rabbits did not give any irritation at all. In a Maximisation test according to Magnusson and Kligman, no signs of allergic skin reactions in the test animals were recorded. 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) and with respect to beflubutamid for ASU 95 510 H no classification/labelling is required.
Due to the information available with respect to the second active ingredient contained in the product (isoproturon), ASU 95 510 H should be classified as "harmful; possible risks of irreversible effects" (Xn; R 40) as it is proposed for the product in the submitted Safety Data Sheet but not in the dossier prepared by the notifier.

B.6.11.1 Acute oral toxicity to the rat

Report: S.J. Mason (1999a); ASU 95 510 H: Acute oral toxicity to the rat; Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 009/984079/AC, 22.10.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 20.07.1998 to 05.08.1998.

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: Rat; Hsd: Sprague-Dawley (CD)

GLP: Yes

Test Method: 92/69/EEC B.1, OECD No. 401

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Following a preliminary study, the test material was administered as supplied to a group of 5 male and 5 female fasted Sprague-Dawley rats by oral gavage at a dose level of 2000 mg/kg bodyweight. All surviving animals were killed and examined macroscopically on Day 15.

Findings:
Mortality data: One female died on Day 3 (Table B.6.11-2). A slight bodyweight loss, congestive changes in subcutaneous and brain tissue, a pale appearance for the liver and kidneys and congestion with fluid contents for the gastro-intestinal tract were observed in this animal.

Table B.6.11-2: Acute oral toxicity of ASU 95 510 H (2000 mg/kg) in rats

Sex	Number of deaths in group of 5	Day of death							
		1		2		3		4 to 15	
		a	b	a	b	a	b	a	b
Male	0/5								
Female	1/5						1		

a: First observation; b: Second observation

Clinical signs: See Table B.6.11-3. Recovery of surviving rats was complete in all instances by Day 4.

Table B.6.11-3: Reactions observed in rats dosed orally with ASU 95 510 H

Signs	No. of rats in group of 1* or 5 showing signs			
	Dose (mg/kg)			
	1000*		2000	
	M	F	M	F
Piloerection	1	1	5	5
Hunched posture	1	1	5	5
Lethargy	1	1	5	5
Pallid extremities	1	1	5	5
Increased lacrimation	0	0	0	1
Prostration (collapsed state)	0	0	1	1
Blue/cold extremities	0	0	1	1

M: male; F: female; *: Preliminary study comprised of one male and one female

Bodyweight: All animals showed expected gain in bodyweight during the study.
Necropsy: No abnormalities were noted.

Conclusion: The acute oral median lethal dose (LD_{50}) of ASU 95 510 H in rats was found to be greater than 2000 mg/kg bodyweight. Therefore, classification is not required.

B.6.11.2 Acute dermal toxicity to the rat

Report: S.J. Mason (1999b); ASU 95 510 H: Acute dermal toxicity to the rat; Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 010/984078/AC, 06.05.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 22.07.1998 to 05.08.1998.

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: Rat; Hsd: Sprague-Dawley (CD)

GLP: Yes

Test Method: 92/69/EEC B.3, OECD No. 402

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.

Acceptability: The study is considered to be acceptable.

Material and Methods:
The test material was administered topically as supplied to 5 male and 5 female Sprague-Dawley rats at 2000 mg/kg bodyweight to the shaved skin of each animal. A gauze pad was then placed over the treated area and held in place with a non-irritative, occlusive dressing for 24 hours. After removal of the dressing the treated area was washed. All animals were killed and examined macroscopically on Day 15.

Findings:
Mortality data: No mortalities were observed (Table B.6.11-4).

Table B.6.11-4: Acute dermal toxicity of ASU 95 510 H in rats

Dose (mg/kg)	Mortality males	Mortality females	LD_{50} (mg/kg bw)
2000	0/5	0/5	>2000

Dermal reactions: No dermal reactions were observed during the study.
Clinical signs: No signs were noted during the study.
Bodyweight: Three females on Day 8 and one female on Day 15 showed a slightly lower bodyweight gain. All other animals showed expected gain in bodyweight during the study.
Necropsy: No abnormalities were noted.

Conclusion:
The acute dermal median lethal dose (LD_{50}) of ASU 95 510 H in rats was found to be greater than 2000 mg/kg bodyweight. Therefore, classification is not required.

B.6.11.3 Acute inhalation (4-hour) toxicity to the rat

Report: G.R. Paul (1999); UR-50601/UBH-820 + IPU: Acute inhalation study in rats (4-hour exposure); Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 008/984506, 19.03.1999, Report amendment 26.04.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 16.09.1998 to 08.10.1998.

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: Rat; Sprague-Dawley

GLP: Yes

Test Method: 92/69/EEC, OECD
(JMAFF, EPA FIFRA)

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Groups of 5 male and 5 female Sprague-Dawley rats were exposed to the test material or to clean air in a snout-only exposure system for 4 hours. The test atmosphere contained a droplet aerosol (1:1 test substance:distilled water) at 3.20 mg test material/l in air. The observation period was 14 days post-exposure. At the end of the observation period rats were killed and macroscopically examined.

Table B.6.11-5: The main exposure parameters of the acute inhalation study

Parameter		Value
Chamber concentration (mg/l)	Chemical analysis ± SD: - UBH-820 - Isoproturon Gravimetric ± SD	 (0.25 ± 0.044) (1.57 ± 0.252) 3.20 ± 0.514
	Nominal	108.8
Particle size (µm)	MMAD ± GSD	4.5 ± 1.75
	% respirable (< 7 µm)	79
Chamber air temperature (°C)	Control group ± SD	21.9 ± 0.49
	Test group ± SD	19.9 ± 0.17
Relative humidity (%)	Control group ± SD	21.2 ± 1.86
	Test group ± SD	66.2 ± 4.41

Findings:
Mortality data: No mortalities were observed (Table B.6.11-6)

Table B.6.11-6: Acute inhalation toxicity of ASU 95 510 H in rats

Dose (gravimetric) **mg/l**	**Mortality males**	**Mortality females**	**LC_{50} (4 hours) mg/l**
3.20	0/5	0/5	> 3.20

Clinical signs: During the observation period wet fur was noted in all test rats for at least 1 hour post-exposure. Brown staining around snout and/or jaws was noted in part of test rats at 1 hour post-exposure and in male test rats on Day 1. Brown staining on the head/ventral surface and matted fur were also noted in some of test rats from 2 hours post-exposure persisting for approximately 2 days. Crusty brown staining around snout and/or jaws was noted in part of test rats on Days 1 and 2. The tails of all test rats were stained by a brown substance from Day 6 onwards.
Bodyweight: There was no treatment-related effect on the bodyweight gain of test rats.
Necropsy: Brown staining was noted on the tails of the test rats. No other macroscopic findings at necropsy were observed.
Other Observations: During exposure a white liquid substance was noted on the head of all test rats from 3 hours of exposure. This also occurred during the observation period in all test rats for at least 1 hour post-exposure.

Conclusion:
The acute inhalation median lethal concentration (LC_{50}, 4 hours) of ASU 95 510 H in the rat was greater than 3.20 mg/l of air. This was the highest attainable practicable concentration under the test conditions, the exposure level achieved was far in excess of any exposure levels that could be generated accidentally.
Only clinical signs were observed, and therefore, classification is not required.

B.6.11.4 Skin irritation to the rabbit

Report: B.I. Parcell (1999a); UR-50601/UBH-820 + IPU: Skin irritation to the rabbit; Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 011/984119/SE, 19.01.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 28.07.1998 to 31.07.1998

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: New Zealand White rabbits

GLP: Yes

Test Method: 92/69/EEC B.4, OECD No. 404

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Three female New Zealand White rabbits received 0.5 ml of test material, which was applied to the shaven skin of each animal. A 2.5 x 2.5 cm gauze pad was then placed over the area and secured in place with an adhesive dressing (semi-occlusive) and left for 4 hours before removal and washing of treated site. The observation period was 3 days after exposure.

Findings:
Dermal responses: No dermal response to treatment was observed in any of the animals throughout the study.
Clinical signs: There were no signs of toxicity or affected health in any of the rabbits during the observation period.

Table B.6.11-7: Dermal reactions to ASU 95 510 H in rabbits

Animal no.	Erythema (E)/ Oedema (O)	Days			
		0*	1	2	3
1065	E	0	0	0	0
	O	0	0	0	0
1066	E	0	0	0	0
	O	0	0	0	0
1067	E	0	0	0	0
	O	0	0	0	0
Mean score 24-72 h.	E		0.0		
	O		0.0		

*: Approximately 60 minutes after removal of the dressing

Conclusion:
No dermal irritation was observed (mean skin irritation scores 24-72 hours after removal of the test article are 0.0) following exposure to the test material. Therefore, there is no need for the test compound to classify as a skin irritant.

B.6.11.5 Eye irritation to the rabbit

Report: B.I. Parcell (1999b); ASU 95 510 H: Eye irritation to the rabbit; Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 012/984105/SE, 10.02.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 03.08.1998 to 08.08.1998

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: New Zealand White rabbits

GLP: Yes

Test Method: OECD No. 405 ≅ 92/69/EEC B.5

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.
The higher value for temperature recorded was 26°C. This exceeded the 20 ± 3°C stated in the guideline, but this deviation is not considered to have affected the integrity or validity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Following the initial treatment of 1 female New Zealand White rabbit ahead of the others to gauge the eye irritation potential of ASU 95 510 H, 2 further female rabbits received a single ocular dose of 0.1 ml in the lower everted lid of one eye. All rabbits were observed for three days after installation.

Findings:
Ocular responses : No corneal damage or iridial inflammation was observed. Transient hyperaemia of blood vessels was seen in all three animals. The reactions had resolved by day one after instillation (see Table B.6.11-8).
Clinical signs: There were no signs of toxicity or affected health in any rabbit during the observation period.

Table B.6.11-8: Ocular reactions to ASU 95 510 H

Animal no.	Region of eye	One hour	Days		
			1	2	3
1050	Cornea - Density	0	0	0	0
	- Area	0	0	0	0
	Iris	0	0	0	0
	Conjunctiva - Redness	1	0	0	0
	- Chemosis	0	0	0	0
1051	Cornea - Density	0	0	0	0
	- Area	0	0	0	0
	Iris	0	0	0	0
	Conjunctiva - Redness	1	0	0	0
	- Chemosis	0	0	0	0
1052	Cornea - Density	0	0	0	0
	- Area	0	0	0	0
	Iris	0	0	0	0
	Conjunctiva - Redness	1	0	0	0
	- Chemosis	0	0	0	0
Mean score 24-72 h.	Cornea - Density		0.0		
	- Area		0.0		
	Iris		0.0		
	Conjunctiva - Redness		0.0		
	- Chemosis		0.0		

Conclusion:
Instillation of ASU 95 510 H into the rabbit eye elicited very slight transient conjunctival irritation in all three rabbits.
On the basis of the eye reactions observed (mean eye irritation scores 24-72 hours after installation of the test article are 0.0), there is no need for the test compound to classify as an eye irritant.

B.6.11.6 Skin sensitisation to the guinea-pig

Report: D.G. Coleman (1999); ASU 95 510 H: Skin sensitisation to the guinea-pig (Magnusson & Kligman Method); Stähler Agrochemie GmbH & Co. KG; unpublished report no. STJ 013/984395/SS, 02.03.1999 [Huntingdon Life Sciences Ltd., UK]; dates of experimental work: 04.08.1998 to 11.09.1998.

Test Material: ASU 95 510 H; Batch 9812; Composition: 85 g/l UBH-820, 500 g/l Isoproturon (i.e. UR-50601/UBH-820 + IPU)

Test Animals: Guinea pig, Dunkin/Hartley strain

GLP: Yes

Test Method: OECD No. 406 ≅ 92/69/EEC B.6 ≅ Magnusson, B. and Kligman, A. M. (1970) *Allergic Contact Dermatitis in the Guinea-pig: Identification of contact allergens*, Thomas, C. C., Springfield, Illinois, USA

Deviations: Any data (identity, composition, purity, homogeneity and stability) supplied by the sponsor were not subjected to review.
On occasion the temperature/humidity of the animal room was outside the range given in the guidelines, however this was not considered to have had an adverse effect on the animals.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Thirty female albino guinea-pigs of the Dunkin/Hartley strain were allocated to two groups as follows:
1. Control for group 2; 10 animals
2. ASU 95 510 H; 20 animals

Based on the results of a preliminary study (intradermal injection 0.1-10% v/v, topical application 25-75% v/v), the following dose levels were selected:

Intradermal injection: 10% v/v in water
Topical application: as supplied
First challenge application: as supplied and 50% v/v in distilled water
Second challenge application: as supplied and 50% v/v in distilled water

The control group (1) was treated similarly to the test group. Topical application was conducted 6 days after the intradermal injection. The first challenge application was conducted two weeks after the topical application with a second application one week later. The induction and challenge applications were held in place with occlusive dressing for 48 and 24 hours respectively. After removal of the patches, the challenge sites were evaluated after 24 and 48 hours. Response to a positive control was evaluated.

Findings:
Dermal responses: Dermal reactions were seen following the induction applications in both groups. After challenge the test compound used as supplied did produce slight dermal reactions in 8 of 20 test animals after 24 hours, with 4 animals showing only a localised dermal reaction. Furthermore, only 3 of 20 test animals produced slight dermal reactions after 48 hours, with 2 having only localised reactions. No reactions were seen at the posterior site exposed to the test substance 50% v/v in distilled water. As it was therefore unclear if these reactions represented sensitisation a second challenge was performed. Fifteen test animals gave negative responses. Two animals gave clear positive responses (score 1) at 24 and 48 hours. The remaining three animals gave inconclusive responses (score 1 at 24 hours only). See Table B.6.11-9.
Clinical signs and bodyweight: No signs of affected health or toxicity were recorded and all guinea-pigs showed bodyweight increases over the period of the study.

Table B.6.11-9: Dermal reactions observed after the challenge application with ASU 95 510 H

Guinea pig	Erythema (E)	Score after first challenge				Score after second challenge				Results
	Oedema (O)	24 hours		48 hours		24 hours		48 hours		+ / - / ±
No.		A	P	A	P	A	P	A	P	
3195	E	0	0	0	0	0	0	0	0	-
	O	0	0	0*	0	0	0	0	0	
3196	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3197	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3198	E	1	0	0	0	1	1	0	0	±
	O	0	0	0*	0	0	0	0	0	
3199	E	0	0	0	0	0	0	0	0	-
	O	0	0	0*	0	0	0	0	0	
3200	E	L1	0	0	0	0	0	0	0	-
	O	0*	0	0*	0	0	0	0	0	
3201	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3202	E	0	0	0	0	0	0	0	0	-
	O	0	0	0*	0	0	0	0	0	
3203	E	L1	0	L1	0	0	0	0	0	-
	O	0*	0	0*	0	0	0	0	0	
3204	E	L1	0	0	0	0	0	0	0	-
	O	0	0	0*	0	0	0	0	0	
3205	E	0	0	0	0	1	1	0	0	±
	O	0	0	0	0	0	0	0	0	
3206	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3207	E	1	0	L1	0	1	0	0	0	±
	O	0	0	0*	0	0	0	0	0	
3208	E	0	0	0	0	1	0	1	0	+
	O	0	0	0*	0	1	0	0	0	
3209	E	L1	0	0	0	0	0	0	0	-
	O	0	0	0*	0*	0	0	0	0	
3210	E	1	0	1	0	0	0	0	0	-
	O	1	0	0*	0	0	0	0	0	
3211	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3212	E	0	0	0	0	0	0	0	0	-
	O	0	0	0	0	0	0	0	0	
3213	E	0	0	0	0	0	0	0	0	-
	O	0	0	0*	0	0	0	0	0	
3214	E	1	0	0	0	1	1	1	0	+
	O	0	0	0*	0	0	0	0	0	

+ positive; - negative; ± inconclusive; *: Other effect obtained - dryness and sloughing of epidermis; L: Localised dermal reaction (restricted to a small area of the challenge site); A: Anterior site, exposed to ASU 95 510 H, as supplied; P: Posterior site, exposed to ASU 95 510 H, 50% v/v in distilled water

Conclusion:

After challenge the test compound used as supplied did produce slight dermal reactions in 8 of 20 test animals after 24 hours and only 3 of 20 test animals after 48 hours with some animals showing only a localised dermal reaction. No reactions were seen if the test substance was diluted 50% v/v in distilled water. After a second challenge, ASU 95 510 H did not

produce evidence of skin sensitisation in fifteen of the twenty test animals. Three animals gave inconclusive responses and the remaining two animals gave positive responses. Overall, the test compound showed very weak positive reactions, and therefore, classification is not required.

B.6.11.7 Supplementary studies for combinations of plant protection products

The plant protection product ASU 95 510 H (product name: Herbaflex) is formulated as a suspension concentrate (SC) containing two active ingredients: 85 g/l UBH 820 (i.e. UR-50601 = beflubutamid) and 500 g/l isoproturon. The possibly toxic properties of the combination are covered by the studies with the preparation.
Further studies have not been done.

B.6.12 Dermal absorption (Annex IIIA 7.3)

No data are available on the extent of dermal absorption of beflubutamid. Therefore, a 100% dermal absorption is assumed (worst case). On the basis of the German model and the UK-POEM, using the assumed dermal absorption rate of 100% as well as the usual default value of 10%, an estimation of operator exposures has been done. In all cases the calculated values were below the proposed systemic AOEL of 0.3 mg/kg bw/d (SF 100) if PPE were worn. A special study to provide data on dermal absorption was not considered necessary and was therefore not carried out.

B.6.13 Toxicological data on non active substances (Annex IIIA 7.4 and point 4 of the introduction)

The plant protection product ASU 95 510 H (product name: Herbaflex) is formulated as a suspension concentrate (SC) containing two active ingredients: 85 g/l UBH 820 (i.e. UR-50601 = beflubutamid) and 500 g/l isoproturon.
Beside the active substances, ASU 95 510 H contains various co-formulants partly known for common use in food, pharmaceutical and cosmetic industrie. Material Safety Data Sheets (MSDS) for all the auxiliaries which are contained are submitted and the possibly toxic properties are covered by the studies with the preparation. Nevertheless, ASU 95 510 H contains the preservative Proxel with the compound 1,2-benzisothiazolin (B.I.T.). There is evidence that B.I.T. may cause skin sensitization at levels above 500 ppm (0.05%) and that products containing more than 500 ppm of B.I.T. should be labelled as potential skin sensitizers. On the basis of the available data, this limit is not reached and a respective classification and labelling is not considered necessary.

B.6.14 Exposure data (Annex IIIA 7.2)

The plant protection product ASU 95 510 H (product name: Herbaflex) is a suspension concentrate (SC) containing two active ingredients: 85 g/l UBH 820 (i.e. UR-50601 = beflubutamid) and 500 g/l isoproturon. It is used as a herbicide and applied to cereals using tractor mounted field crop sprayers. Only applications to field crops are intended.
In this monograph the exposure assessment is only carried out for UR-50601 (beflubutamid) and thus the active substance (a.s.) refers to UR-50601. For estimates of the operator exposure

to the active substance isoproturon (IPU), application rate of 1.5 kg/ha, reference is made to the IPU monograph and data submitted for EU review by Rhone-Poulenc/Aventis.

B.6.14.1 Operator exposure

B.6.14.1.1 Estimation of operator exposure

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 Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, n° 277;

– 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

Table B.6.14-1: Scenarios/use conditions in field crops - for the exposure calculation

Technique	Treated area per working day	Max. use rate		max. in-use concentration (mg a.s./ml)	Model used
		kg a.s./ha	product: l /ha		
Vehicle mounted sprayer	20 ha	0.255	(3)	–	German model
	50 ha	(0.255)	3	1.275	UK-POEM

Estimation of operator exposure using the German model
Assumptions used for the calculation:

Formulation type:	Suspension concentrate (SC)
Application technique:	tractor mounted application/field crops
Area treated per day:	20 ha
Application rate:	0.255 kg as/ha
Dermal absorption rate:	100% (worst case) and 10% (usual default value)
Body weight of an operator:	70 kg
Penetration rate:	Gloves: 1%; standard protective garment: 5%

The estimation of operator exposure was completed for two different scenarios with regard to personal protective equipment (PPE):

without PPE:	Disregarding the recommendations of the label, no personal protective equipment used when handling the undiluted product during loading and during application of the diluted product.
with PPE:	Gloves, standard protective garment (plant protection) and sturdy footwear when handling the undiluted product during loading and standard protective garment (plant protection) and sturdy footwear during application of the diluted product.

It should be noted that this selection of protective measures is not intended to be a recommendation for the necessary PPE when handling ASU 95 510 H. It does not take into

account specific requirements which may arise in individual Member States. Additional PPE can be used to further reduce the exposure of the operator.

Table B.6.14-2: German model calculation for tractor mounted application

Without PPE					
Exposure during mixing/loading:					
I_m	= 0.0006	mg/kg a.s. x 5.1 kg a.s. /d**	=	0.00306	mg/person/d
D_m	= 2.4	mg/kg a.s. x 5.1 kg a.s. /d	=	12.24	mg/person/d
Exposure during application:					
I_a	= 0.001	mg/kg a.s. x 5.1 kg a.s. /d	=	0.0051	mg/person/d
$D_{a(c)}$	= 0.06	mg/kg a.s. x 5.1 kg a.s. /d	=	0.306	mg/person/d
$D_{a(h)}$	= 0.38	mg/kg a.s. x 5.1 kg a.s. /d	=	1.938	mg/person/d
$D_{a(b)}$	= 1.6	mg/kg a.s. x 5.1 kg a.s. /d	=	8.16	mg/person/d
With PPE					
Exposure during mixing/loading					
I_m	= 0.006	mg/kg a.s. x 5.1 kg a.s. /d	=	0.00306	mg/person/d
D_m	= 2.4	mg/kg a.s. x 5.1 kg a.s. /d x 0.01*	=	0.1224	mg/person/d
Exposure during application:					
I_a	= 0.001	mg/kg a.s. x 5.1 kg a.s. /d	=	0.0051	mg/person/d
$D_{a(c)}$	= 0.06	mg/kg a s. x 5.1 kg a.s. /d	=	0.306	mg/person/d
$D_{a(h)}$	= 0.38	mg/kg a.s. x 5.1 kg a.s. /d	=	1.938	mg/person/d
$D_{a(b)}$	= 1.6	mg/kg a.s. x 5.1 kg a.s. /d x 0.05*	=	0.408	mg/person/d

Abbreviations: I = estimated inhalation exposure m = during mixing/loading (c) = head
D = estimated dermal exposure a = during application (h) = hands
* reduction coefficient (b) = body
** Amount handled per day = treated area x use rate = 20 ha/d x 0.255 kg a.s./ha = 5.1 kg a.s./d.

Table B.6.14-3: German model: Estimated operator exposure without and with PPE

		Estimated operator exposure (mg/person/d)			
		100% dermal absorption		**10% dermal absorption**	
		without PPE	**with PPE**	**without PPE**	**with PPE**
Derm. exp.	Mixing/loading	12.24	0.1224	1.224	0.01224
	Application	10.404	2.652	1.0404	0.2652
	Total	22.644	2.7744	2.2644	0.27744
Inh. exp.	Mixing/loading	0.00306	0.00306	0.00306	0.00306
	Application	0.0051	0.0051	0.0051	0.0051
	Total	0.00816	0.00816	0.00816	0.00816
Total systemic exposure (dermal + inhal., absorbed)		22.6522	2.78256	2.27256	0.28560

A summary of the estimated operator exposures is provided in Table B.6.14-3. Using the German model, under worst case conditions (100% dermal absorption; without PPE), the operator exposure is calculated to be 22.7 mg/person/d. This value is reduced to 2.8 mg/person/d if the recommended PPE is worn.

Estimation of operator exposure using the UK-POEM
Assumptions used for the calculation:

Formulation type:	Suspension concentrate (SC)
Application technique:	tractor mounted application/field crops
Area treated per day:	50 ha
Application rate:	3 litre/ha (i.e. 0.255 kg a.s./ha)
Application volume:	200 l/ha
Container:	10 litre, wide-neck
Dermal absorption rate:	100% (worst case) and 10% (also calculated with by the notifier)
Body weight of an operator:	60 kg
Penetration rate:	Gloves during mixing/loading: 5%; during application: 10%

The calculation of the estimated operator exposure was made for two different scenarios with respect to personal protective equipment (PPE):

without PPE:	Disregarding the recommendations of the label, no personal protective equipment used when handling the undiluted product during loading and during application of the diluted product.
with PPE:	Gloves when handling the undiluted product during mixing/loading and during application of the diluted product.

Table B.6.14-4: UK POEM calculation for tractor mounted hydraulic boom and nozzles (100% dermal absorption)

A	**PRODUCT DATA**					
1	Product	ASU 95 510 H				
2a	Active substance	UR-50601				
2b	Concentration	85	mg/ml			
3	Formulation type	SC				
4	Main solvent / concentration of solvent					
5	Maximum in-use a.s. concentration	1.275	mg/ml			
B	**EXPOSURE DURING MIXING AND LOADING**					
1a	Container size	10	litres			
1b	Hand contamination/operation	0.1	ml			
2	Application dose	3	litres product/ha			
3	Work rate	50	ha/day			
4	Number of operations	15	per day			
5	Hand contamination	1.5	ml/day			
6	**Protective clothing**	**NONE**		**GLOVES**		
7	Transmission to skin	100	%	5	%	
8	Dermal exposure to formulation	1.5	ml/day	0.075	ml/day	
C	**EXPOSURE DURING SPRAY APPLICATION**					
1	Application technique - tractor mounted field sprayer					
2	Application volume	200	spray/ha			
3	Volume of surface contamination	10	ml/h			
4	Distribution	Hands	Hands	Trunk	Legs	
		65	65	10	25	%
5	Clothing	NONE	GLOVES	permeable	permeable	
6	Penetration	100	10	5	15	%
7	Dermal exposure	6.5	0.65	0.05	0.375	ml/h
8	Duration of exposure	6	h			
	PPE	**NONE**		**GLOVES**		
9	Total dermal exposure to spray	41.55	ml/day	6.45	ml/day	

D	**ABSORBED DOSE**					
	Mix/load with and without PPE	**NONE**		**GLOVES**		
1	Dermal exposure	1.5	ml/day	0.075	ml/day	
2	Concentration of a.s.	85	mg/ml	85	mg/ml	
3	Dermal exposure to a.s.	127.5	mg/day	6.375	mg/day	
4	Percent absorbed	100	%	100	%	
5	Absorbed dose	127.5	mg/day	6.375	mg/day	
	Application with and without PPE	**NONE**		**GLOVES**		
1	Dermal exposure	41.55	ml/day	6.45	ml/day	
2	Concentration of a.s.	1.275	mg/ml	1.275	mg/ml	
3	Dermal exposure to a.s.	52.97625	mg/day	8.22375	mg/day	
4	***Percent absorbed***	***100***	***%***	***100***	***%***	
5	Absorbed dose	52.97625	mg/day	8.22375	mg/day	
E	**INHALATION EXPOSURE DURING SPRAYING**					
1	Inhalation exposure	0.01	ml/h			
2	Duration of exposure	6	h			
3	Concentration of a.s.	1.275	mg/ml			
4	Inhalational exposure to a.s.	0.0765	mg/day			
5	Percent absorbed	100	%			
6	Absorbed dose	0.0765	mg/day			
F	**PREDICTED EXPOSURE**			**For a 60 kg operator**		
1	No Gloves	180.55275	mg/day	3.0092125	mg/kg bw/day	
2	Gloves only when mixing and loading	59.42775	mg/day	0.9904625	mg/kg bw/day	
3	Gloves only during spray application	135.80025	mg/day	2.2633375	mg/kg bw/day	
4	Gloves during mixing/loading & appl.	14.67525	mg/day	0.2445875	mg/kg bw/day	

Table B.6.14-5: UK POEM calculation for tractor mounted hydraulic boom and nozzles (10% dermal absorption)

A	**PRODUCT DATA**					
1	Product	ASU 95 510 H				
2a	Active substance	UR-50601				
2b	Concentration	85	mg/ml			
3	Formulation type	SC				
4	Main solvent / concentration of solvent					
5	Maximum in-use a.s. concentration	1.275	mg/ml			
B	**EXPOSURE DURING MIXING AND LOADING**					
1a	Container size	10	litres			
1b	Hand contamination/operation	0.1	ml			
2	Application dose	3	litres product/ha			
3	Work rate	50	ha/day			
4	Number of operations	15	per day			
5	Hand contamination	1.5	ml/day			
6	**Protective clothing**	**NONE**		**GLOVES**		
7	Transmission to skin	100	%	5	%	
8	Dermal exposure to formulation	1.5	ml/day	0.075	ml/day	
C	**EXPOSURE DURING SPRAY APPLICATION**					
1	Application technique - tractor mounted field sprayer					
2	Application volume	200	spray/ha			
3	Volume of surface contamination	10	ml/h			
4	Distribution	Hands	Hands	Trunk	Legs	
		65	65	10	25	%
5	Clothing	NONE	GLOVES	permeable	permeable	
6	Penetration	100	10	5	15	%
7	Dermal exposure	6.5	0.65	0.05	0.375	ml/h

8	Duration of exposure	6	h			
	PPE	**NONE**		**GLOVES**		
9	Total dermal exposure to spray	41.55	ml/day	6.45	ml/day	
D	**ABSORBED DOSE**					
	Mix/load with and without PPE	**NONE**		**GLOVES**		
1	Dermal exposure	1.5	ml/day	0.075	ml/day	
2	Concentration of a.s.	85	mg/ml	85	mg/ml	
3	Dermal exposure to a.s.	127.5	mg/day	6.375	mg/day	
4	***Percent absorbed***	***10***	***%***	***10***	***%***	
5	Absorbed dose	12.75	mg/day	0.6375	mg/day	
	Application with and without PPE	**NONE**		**GLOVES**		
1	Dermal exposure	41.55	ml/day	6.45	ml/day	
2	Concentration of a.s.	1.275	mg/ml	1.275	mg/ml	
3	Dermal exposure to a.s.	52.97625	mg/day	8.22375	mg/day	
4	Percent absorbed	10	%	10	%	
5	Absorbed dose	5.297625	mg/day	0.822375	mg/day	
E	**INHALATION EXPOSURE DURING SPRAYING**					
1	Inhalation exposure	0.01	ml/h			
2	Duration of exposure	6	h			
3	Concentration of a.s.	1.275	mg/ml			
4	Inhalational exposure to a.s.	0.0765	mg/day			
5	Percent absorbed	100	%			
6	Absorbed dose	0.0765	mg/day			
F	**PREDICTED EXPOSURE**			**For a 60 kg operator**		
1	No Gloves	18.124125	mg/day	0.30206875	mg/kg bw/day	
2	Gloves only when mixing and loading	6.011625	mg/day	0.10019375	mg/kg bw/day	
3	Gloves only during spray application	13.648875	mg/day	0.22748125	mg/kg bw/day	
4	Gloves during mixing/loading & appl.	1.536375	mg/day	0.02560625	mg/kg bw/day	

Table B.6.14-6: UK-POEM: Estimated operator exposure without and with PPE

		Estimated operator exposure (mg/person/d)			
		100% dermal absorption		**10% dermal absorption**	
		without PPE	**with PPE**	**without PPE**	**with PPE**
Derm. exp.	Mixing/loading	127.5	6.375	12.75	0.6375
	Application	52.97625	8.22375	5.297625	0.822375
	Total	180.47625	14.59875	18.047625	1.459875
Inh. exp.	Mixing/loading	-	-	-	-
	Application	0.0765	0.0765	0.0765	0.0765
	Total	0.0765	0.0765	0.0765	0.0765
Total systemic exposure (dermal + inhal., absorbed)		180.55275	14.67525	18.124125	1.536375

A summary of the estimated operator exposures is provided in
Table B.6.14-6. Using the UK-POEM, under worst case conditions (100% dermal absorption; without PPE), the operator exposure is calculated to be 180.6 mg/person/d. This value is reduced to 14.7 mg/person/d if gloves are worn during mixing/loading and application.

Determination of the tolerable operator exposures

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 assess via the absorption rates on the basis of the systemic AOEL derived for the active ingredient.
To derive the oral AOEL for beflubutamid, a NOAEL of 30 mg/kg bw/d established in an oral subchronic toxicity study in rats should be used (see B.6.10). The oral AOEL can be calculated by using a safety factor of 100. Because the extent of absorption was almost complete after oral administration of a low dose of beflubutamid, a correction from the oral AOEL to a systemic AOEL is not needed. Thus, the calculation results in a **systemic AOEL of 0.3 mg/kg bw/d.**

For the exposure assessment according to the German model, the NOAEL of the oral toxicity studies (30 mg/kg bw/d) should be used to derive both the tolerable dermal and inhalation exposure. The "degree of exposure" in the German model (multiplied with 100) is then comparable to the calculation of the total absorbed dose as percentage of the AOEL, oral/systemic, if the same value for body weight is used.
Assuming 100% and 10% for dermal absorption (see B.6.12: worst case = 100%) and 100% for inhalation absorption, a body weight of 70 kg, and an assessment factor of 100, the tolerable dermal (D_{tol} = AOEL, dermal) and inhalation (I_{tol} = AOEL, inhalation) exposures are calculated to be:

D_{tol} =	30 mg/kg bw/d	x 70	/ 100	x 1	= 21 mg/person/d = 0.3 mg/kg bw/d
D_{tol} =	30 mg/kg bw/d	x 70	/ 100	x 0.1	= 210 mg/person/d = 3 mg/kg bw/d
I_{tol} =	30 mg/kg bw/d	x 70	/ 100	x 1	= 21 mg/person/d = 0.3 mg/kg bw/d

Comparison of estimated and tolerable exposure
German model:
Using the following equation, the total degree of exposure (E) can be calculated for the two conditions of operator protection assumed: values of E < 1 indicate that a sufficient margin of safety for the applicator exists.

$$E = \frac{I}{Itol} + \frac{D}{Dtol}$$

a1) without PPE (100% dermal absorption):

$$E = \frac{0.00816}{21} + \frac{22.644}{21} = 0.00039 + 1.07829 = 1.07868$$

a2) without PPE (10% dermal absorption)

$$E = \frac{0.00816}{21} + \frac{22.644}{210} = 0.00039 + 0.10783 = 0.10822$$

b1) with PPE (100% dermal absorption):

$$E = \frac{0.00816}{21} + \frac{2.7744}{21} = 0.00039 + 0.13211 = 0.13250$$

b2) with PPE (10% dermal absorption):

$$E = \frac{0.00816}{21} + \frac{2.7744}{210} = 0.00039 + 0.01321 = 0.01360$$

The results of the calculations for beflubutamid using the German model show, that the inhalation exposure is very low compared to the dermal exposure. When using 100% dermal absorption as a default for the absolute worst case, the value of E ≥ 1 (1.079) shows that gloves are needed to stay below the tolerable exposure.

UK-POEM:

In the UK-POEM, only the total estimated systemic exposures are to be compared with the systemic AOEL.

For a better comparison of the results of the two models, all the calculated systemic exposures are compared with the proposed systemic AOEL of 0.3 mg/kg bw/d. The values are given in Table B.6.14-7.

Table B.6.14-7: Results of the model calculations and a comparison with the proposed systemic AOEL

Model used		**PPE**	**Systemic exposure*** (mg/kg bw/d)		**Percentage of AOEL** (0.3 mg/kg bw/d)	
			100% derm. abs.	10% derm. abs.	100% derm. abs.	10% derm. abs.
German model	20 ha/d	none	0.3236	0.0325	108%	11%
		m/l: gloves; appl.: garment	0.0398	0.0041	13%	1%
UK POEM	50 ha/d	none	3.0092	0.3021	1038%	104%
		m/l: gloves; appl.: gloves	0.2446	0.0256	84%	9%

*See Table B.6.14-3 and Table B.6.14-6; in the calculations a body weight of 70 kg (German model) or 60 kg (UK-POEM) and dermal absorption rates of 100% and 10% are used.

In both models, the German as well as the UK-POEM, the results show that the operator exposure for hydraulic boom and nozzles application is higher than the acceptable operator exposure when no personal protection is used. But also with a 100% default for dermal absorption, PPE could be worn to get an estimated operator exposure which is acceptable (German model: 13% of systemic AOEL; UK-POEM: 84% of systemic AOEL).

Regarding beflubutamid, it can be concluded that ASU 95 510 H can be handled safely under the recommended conditions of use.

Nevertheless for a complete risk assessment of ASU 95 510 H, additional attention has to be payed to the second active substance: isoproturon.

B.6.14.1.2 Measurement of operator exposure

Since the risk assessment carried out indicated that the Acceptable Operator Exposure Level will not be exceeded under practical conditions of use, a study to provide operator exposure data specific to ASU 95 510 H under field conditions was therefore not carried out.

B.6.14.2 Bystander exposure

Given the low vapour pressure of the active substance beflubutamid in ASU 95 510 H and its low inhalation toxicity, problems for bystanders by the inhalation route are not anticipated. Dermal exposure due to drift of spray material, is a potential route of bystander exposure. Exposure to bystanders would be incidental and would not occur repeatedly to the same individuals, but would be without protective clothing. In all cases any bystander exposure is expected to be lower than the exposure to operators involved with application, and therefore, the estimated exposure is lower than the AOEL.

B.6.14.3 Worker exposure

B.6.14.3.1 Estimation of worker exposure

ASU 95 510 H is used as a herbicide and applied to cereals, and it is not necessary, nor is it normal practice, to enter these crops shortly after spraying. It is therefore not necessary to determine a particular re-entry time for workers. It is expected that exposure of workers entering a field after application will be much lower than for spray operations. Even for spray operations, with the worst-case assumption of 100% dermal penetration, operator exposure is acceptable (exposure < systemic AOEL; German model: without PPE; UK-POEM: with gloves). Therefore no particular requirement for protective equipment is necessary for other field workers.

B.6.14.3.2 Measurement of worker exposure

Workers are unlikely re-enter the ASU 95 510 H treated cereal fields, and if they do so, exposure will be minimal and pose no risk. Therefore a study to provide worker exposure data under field conditions is not considered necessary.

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	Dean, G.M.	2000	UR-50601: Metabolism in the rat (main study). UBE 079/984961 GLP, unpublished TOX2000-1538	Y	UBE
AIIA-5.1	McEwen, A.B.	1998	UR-50601: Metabolism in the rat (pilot study). UBE 35/971187 GLP, unpublished TOX2000-1539	Y	UBE

[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-5.2.1	Snell, K.	1995	UR-50601: Acute oral toxicity (Limit Test) in the rat. 512/26 GLP, unpublished TOX2000-1540	Y	UBE
AIIA-5.2.2	Snell, K.	1995	UR-50601: Acute dermal toxicity (Limit Test) in the rat. 512/27 GLP, unpublished TOX2000-1541	Y	UBE
AIIA-5.2.3	Blagden, S.M.	1995	UR-50601: Acute inhalation toxicity (nose only) study in the rat. 512/028 GLP, unpublished TOX2000-1542	Y	UBE
AIIA-5.2.4	Parcell, B.I.	1995	UR-50601: Skin irritation to the rabbit. UBE 1/950843/SE GLP, unpublished TOX2000-1543	Y	UBE
AIIA-5.2.5	Parcell, B.I.	1995	UR-50601: Eye irritation to the rabbit. UBE 2/951189/SE GLP, unpublished TOX2000-1544	Y	UBE
AIIA-5.2.6	Allan, S.A.	1996	UR-50601: Skin sensitisation in the guinea-pig (incorporating a positive control using formalin). UBE 3/951150/SS GLP, unpublished TOX2000-1545	Y	UBE
AIIA-5.3.1	Barker, M.H.	1996	UR-50601: Toxicity to rats by repeated dietary administration for 4 weeks. UBE 11/952715 GLP, unpublished TOX2000-1546	Y	UBE
AIIA-5.3.2	Barker, M.H.	1997	UR-50601: Preliminary toxicity study in dogs by repeated oral administration for 2 weeks. UBE 39/971150 GLP, unpublished TOX2000-1551	Y	UBE
AIIA-5.3.2	Barker, M.H.	1999	UR-50601: Toxicity study by oral capsule administration to beagle dogs for 52 weeks. UBE 072/992120 GLP, unpublished TOX2000-1552	Y	UBE

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	Barker, M.H.	1997	UR-50601: Palatability study in mice by dietary administration for 2 weeks. UBE 33/963913 GLP, unpublished TOX2000-1549	Y	UBE
AIIA-5.3.2	Barker, M.H.	1997	UR-50601: Toxicity to dogs by repeated oral administration for 13 weeks. UBE 40/973046 GLP, unpublished TOX2000-1550	Y	UBE
AIIA-5.3.2	Barker, M.H.	1997	UR-50601: Toxicity to mice by dietary administration for 13 weeks. UBE 34/971905 GLP, unpublished TOX2000-1548	Y	UBE
AIIA-5.3.2	Barker, M.H.	1997	UR-50601: Toxicity to rats by dietary administration for 13 weeks. UBE 31/963207 GLP, unpublished TOX2000-1547	Y	UBE
AIIA-5.4.1	Adams, K.	1998	UR-50601: Mammalian cell mutation assay. UBE 046/971304 GLP, unpublished TOX2000-1555	Y	UBE
AIIA-5.4.1	Johnson, A.L.	1995	UR-50601: An in vitro test for induction of chromosome damage: Cytogenetic study in cultured human peripheral lymphocytes. 95/UED001/0580 GLP, unpublished TOX2000-1554	Y	UBE
AIIA-5.4.1	Jones, E.	1995	UR-50601: Bacterial mutation assay. UBE 4/951063 GLP, unpublished TOX2000-1553	Y	UBE
AIIA-5.4.2	Mason, Ch.E.	1998	UR-50601: Mouse micronucleus test. UBE 084/983640 GLP, unpublished TOX2000-1556	Y	UBE
AIIA-5.5	Barker, M.H.	2000	UR-50601: Carcinogenicity study by dietary administration to CD-1 mice for 80 weeks. UBE 070/993289 GLP, unpublished TOX2000-1558	Y	UBE

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	Barker, M.H.	2000	UR-50601: Potential tumorigenic and toxic effects in prolonged dietary administration to rats. UBE 044/993288 GLP, unpublished TOX2000-1557	Y	UBE
AIIA-5.5	Funaki, E.	2002	UR-50601: Carcinogenicity study by dietary administration to CD-1 mice for 80 weeks (UBE 070/993289). not GLP, unpublished TOX2002-702	Y	TSU
AIIA-5.6.1	Myers, D.P.	1997	UR-50601: Preliminary study of effects on reproductive performance in CD rats treated by dietary administration. UED 008/973099 GLP, unpublished TOX2000-1561	Y	UBE
AIIA-5.6.1	Myers, D.P.	1999	UR-50601: Study of reproductive performance in CD rats treated continuously through two successive generations by dietary administration. UBE 073/992298 GLP, unpublished TOX2000-1559	Y	UBE
AIIA-5.6.2	Myers, D.P.	1996	UR-50601: A preliminary study of the effect on pregnancy of the rabbit (gavage administration). UBE 10/952279 GLP, unpublished TOX2000-1565	Y	UBE
AIIA-5.6.2	Myers, D.P.	1998	UR-50601: A pilot study of the effect on the female rabbit (gavage administration). UBE 9/951721 GLP, unpublished TOX2000-1566	Y	UBE
AIIA-5.6.2	Myers, D.P.	1995	UR-50601: A preliminary study of the effect on pregnancy of the rat (gavage administration). UBE 8/951331 GLP, unpublished TOX2000-1563	Y	UBE
AIIA-5.6.2	Waterson, L.A.	1997	UR-50601: A study of the effects on pregnancy of the rabbit (gavage administration). UBE 43/971457 GLP, unpublished TOX2000-1564	Y	UBE

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-5.6.2	Waterson, L.A.	1997	UR-50601: A study of the effect on pregnancy of the rat (gavage administration). UBE 038/971422 GLP, unpublished TOX2000-1562	Y	UBE
AIIA-5.9	Anonym	1999	Manufacturing health report. not GLP, unpublished TOX2000-1865	Y	UBE
AIIIA-7.1.1	Mason, St.J.	1999	ASU 95 510 H: Acute oral toxicity to the rat. STJ 009/984079/AC GLP, unpublished TOX2000-1567	Y	ASU
AIIIA-7.1.2	Mason, St.J.	1999	ASU 95 510 H: Acute dermal toxicity to the rat. STJ 010/984078/AC GLP, unpublished TOX2000-1568	Y	ASU
AIIIA-7.1.3	Paul, G.R.	1999	UR-50601/UBH-820 + IPU: Acute inhalation study in rats (4-hour exposure). STJ 008/984506 GLP, unpublished TOX2000-1569	Y	ASU
AIIIA-7.1.4	Parcell, B.I.	1999	UR-50601/UBH-820 + IPU: Skin irritation to the rabbit. STJ 011/984119/SE GLP, unpublished TOX2000-1570	Y	ASU
AIIIA-7.1.5	Parcell, B.I.	1999	ASU 95 510 H: Eye irritation to the rabbit. STJ 012/984105/SE GLP, unpublished TOX2000-1571	Y	ASU
AIIIA-7.1.6	Coleman, D.G.	1999	ASU 95 510 H: Skin sensitization to the guinea-pig (Magnusson & Kligman Method). STJ 013/984395/SS GLP, unpublished TOX2000-1572	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

Annex B

Beflubutamid

B-7: Residue data

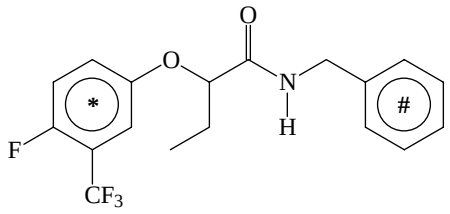
B.7 Residue data

B.7.1 Metabolism, distribution and expression of residues in plants (Annex IIA 6.1; Annex IIIA 8.1)

Following an initial pilot study (McEvers, 1998, RIP2000-1891) the metabolism of beflubutamid in winter wheat was investigated in plants maintained in a netted area outdoors (main study). The results of the pilot study were not considered for evaluation since immature plant parts only were sampled at 2 hours and 28 days after application. There was no investigation on quantity and nature of residues in the mature wheat plant at normal harvest.

Report: Haynes, 2000, RIP2000-1890:
UR-50601 Metabolism in wheat; UBE Industries Ltd., Stähler Agrochemie GmbH & Co. KG, unpublished report no. UBE 66/974473, 15 February 2000 [Huntingdon Life Sciences Ltd., UK].

Test material: Beflubutamid (UR-50601):



*) position of radiolabel in [ring-UL-^{14}C-phenoxy] beflubutamid
#) position of radiolabel in [ring-UL-^{14}C-benzylamine] beflubutamid

Guidelines: 91/414/EEC Directive as amended by 96/68/EC Directive, Annex 1, Section 6.1.

GLP: Yes.

Deviations: None.

Acceptability: The study is considered to be acceptable.

Materials and Methods:

Wheat containers (70 x 50 x 30 cm) sown at an approximate rate of 300 seeds/m^2 were treated with formulated [ring-UL-^{14}C-phenoxy] beflubutamid and [ring-UL-^{14}C-benzylamine] beflubutamid (see below) at a nominal application rate of 255 g as/ha when the plants were at growth stage BBCH 33 (3-nodes).

Samples of the treated wheat plants were taken on the day of application (2 h after) and at suitable intervals (4 weeks - forage, 11 weeks – immature heads and straw and 15 weeks – mature grain, husk, straw) after application by cutting the plants at the soil surface prior to separation where possible into grain, husk and straw. Separated samples were homogenised with frozen CO_2 prior to combustion of aliquots to determine total radioactive residue. Further subsamples were sequentially extracted using solvent, enzyme, acid and alkali hydrolysis. Extracts were quantified by LSC and analysed by chromatography (TLC and HPLC) to assess the proportions and nature of any degradation products. Air dried residues left after extraction of plant material were combusted/radioassayed.

Findings:

Total Radioactive Residues:

As shown in Table B.7.1-1 initial concentrations of total radioactive residues in forage samples accounted for 5.40 and 5.36 mg/kg in wheat treated with [ring-UL-^{14}C-phenoxy] beflubutamid and [ring-UL-^{14}C-benzylamine] beflubutamid, respectively. The concentrations in the first intermediate samples (DAT 28) had declined to 1.08 mg/kg and 1.37 mg/kg, respectively. Concentrations in the second intermediate sample taken four weeks before harvest (DAT 77) were 0.05 - 0.02 mg/kg in the immature heads and 1.50 - 1.29 mg/kg in the intermediate straw. At harvest (DAT 105) concentrations were 0.04 - 0.01 mg/kg in the grain, 0.10 - 0.05 mg/kg in the husk and 1.37 - 1.09 in the straw.

Table B.7.1-1: Mean[1] concentrations of TRR (µg equiv. as/g) in forage and harvest samples

Sampling time	Sample	Phenoxy labelled	Benzylamine labelled
DAT 0 / 2 hours	Forage	5.40	5.36
DAT 28 / 4 weeks	Forage	1.08	1.37
DAT 77 / 11 weeks	Grain/husk[2]	0.05	0.02
	Straw	1.50	1.29
DAT 105 / 15 weeks	Grain	0.04	0.01
	Husk	0.10	0.05
	Straw	1.37	1.09

[1]) n = 2
[2]) immature heads

Extractability:

As noted in Table B. 7.1-2 extraction efficiency of residues in mature matrices ranged at about 80 % TRR from the [ring-UL-^{14}C-phenoxy] labelled beflubutamid treatment and at about 60 % TRR from the [ring-UL-^{14}C-benzylamine] labelled beflubutamid treatment.

Characterisation and identification:

A summary is given in Table B. 7.1-2.

In *straw* at harvest 22.9 - 25.5 % TRR corresponding 0.250 - 0.349 mg/kg was found to be associated with unchanged beflubutamid. The major identified metabolite in straw treated with [ring-UL-^{14}C-phenoxy] beflubutamid was UR-50604 accounting for 12.8 % TRR (0.175 mg/kg). Other identified metabolites were UR-50624, UR-50617, UR-50618 and UR-50619 at concentrations of 2.4 - 7.9 % TRR (0.033 - 0.108 mg/kg). An unidentified component U1 (2.8 % TRR, 0.038 mg/kg) was observed in the phenoxy label treated wheat extracts. U1 was not present in extracts from [ring-UL-^{14}C-benzylamine] beflubutamid treated straw.

Radioactive components in [ring-UL-^{14}C-phenoxy] beflubutamid treated *grain* extracts (TRR = 0.04 %) were similar to straw, with UR-50604 accounting for 27.6 % TRR (0.011 mg/kg) and the unknown component U1 accounting for 17 % TRR (0.007 mg/kg). The TRR that was observed in grain at harvest after application of [ring-UL-^{14}C-benzylamine] beflubutamid was only 0.01 mg/kg. Therefore, no chromatographic analyses of these grain extracts were performed.

Radioactive components observed in *husk* treated with [ring-UL-^{14}C-phenoxy] beflubutamid were similar to straw with UR-50604 and U1 accounting for 26.2 % TRR (0.026 mg/kg) and 14 % TRR (0.014 mg/kg) respectively. In [ring-U-^{14}C-benzylamine] beflubutamid treated husk, UR-50619 accounted for 7.6 % TRR (0.004 mg/kg). Bound residues did not represent >25 % TRR after the various hydrolysis procedures were undertaken.

No evidence of significant selective stereometabolism of beflubutamid or UR-50604 was found. A proposed metabolic pathway is given in Figure B.7.1-1. Beflubutamid was metabolised via C-N cleavage, generating UR-50604 and UR-50624 and hydroxylation of the benzylamine ring at the 2, 3 and 4 positions. Unknown component U1, a phenoxy metabolite, is thought to be related to UR-50604, and was determined to be polar and water soluble.

Samples were frozen from sampling through to analysis. Quantitative data from analysis before and after freezer storage indicated that there was no appreciable concern over storage stability.

Table B. 7.1-2: Total ^{14}C-beflubutamid radioactive residues (TRR) expressed as % TRR and µg equivalents as/g fresh weight in straw, husk and grain at *harvest*

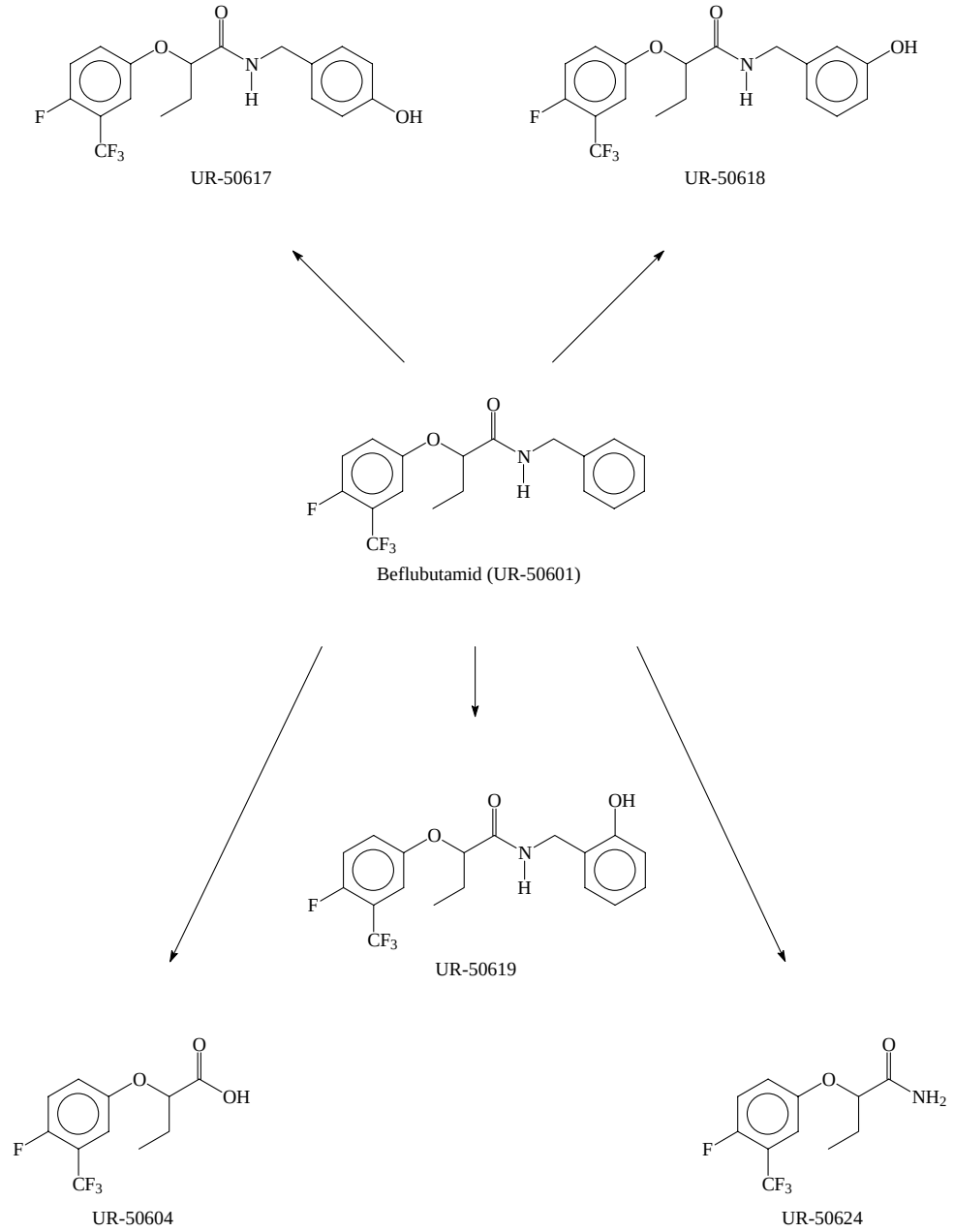
Component	[^{14}C-phenoxy] beflubutamid						[^{14}C-benzylamine] beflubutamid					
	Straw		Husk		Grain		Straw		Husk		Grain[1]	
	[%]	[µg/g]	[%]	[µg/g]	[%]	[µg/g]	[%]	[µg/g]	[%]	[µg/g]	[%]	[µg/g]
TRR	100	1.37	100	0.10	100	0.04	100	1.09	100	0.05	100	0.01
Polars[2]	15.4	0.211	15.8	0.016	17.5	0.007	18.9	0.206	18.7	0.009	-	
U1[3]	2.8	0.038	14.0	0.014	17.0	0.007	-	-	-	-	-	
Benzoic acid	-		-		-		1.9	0.021	-		-	
UR-50604	12.8	0.175	26.2	0.026	27.6	0.011	-		-		-	
UR-50624	4.3	0.059	<2.6	<0.003	<1.6	<0.001	-		-		-	
UR-50617	5.8	0.079	<2.6	<0.003	<1.6	<0.001	4.4	0.048	<2.7	<0.001	-	
UR-50618	7.9	0.108	<2.6	<0.003	<1.6	<0.001	6.7	0.073	5.5	0.003	-	
UR-50619	2.4	0.033	<2.6	<0.003	<1.6	<0.001	3.0	0.033	7.6	0.004	-	
Beflubutamid	25.5	0.349	4.3	0.004	<1.6	<0.001	22.9	0.250	2.8	0.001	-	
Unidentified; each ≤;	≤2.5	≤0.034	≤2.6	≤0.003	≤2.1	≤0.001	≤2.1	≤0.023	≤5.1	≤0.003	-	
Characterised extracts:												
Not chromatographed	1.9	0.026	-		4.6	0.002	2.1	0.023	15.2	0.008	57.4	0.006
5M NaOH	2.1	0.029	3.6	0.004	-		2.3	0.025	3.6	0.002	-	
1M HCl	0.5	0.007	-		-		1.8	0.020	-		-	
Total extracted residues	84	1.148	79	0.079	83	0.033	66	0.722	62	0.031	60	0.006
Unextractable residues	5.3	0.073	15.8	0.016	19.8	0.008	23.9	0.261	20.5	0.010	42.6	0.004

[1]) not analysed as total radioactive residue in acetone : water extracts was 0.002 mg/kg (20.4% TRR)
[2]) determined in straw at harvest to be a mixture of components: phenoxy label ≤4.9 % TRR (≤0.067 mg/kg), benzylamine label ≤7.4 % TRR (≤0.081 mg/kg); benzoic acid was determined to be present in straw only
[3]) U1 present in the acetone : water extract only

Conclusion:

In wheat beflubutamid is metabolised via C-N cleavage, generating UR-50604 and UR-50624 and hydroxylation of the benzylamine ring at the 2, 3 and 4 positions. The unknown component U1, a phenoxy metabolite, is thought to be related to UR-50604, and is determined to be polar and water soluble.
UR-50604 is of no toxicological significance as it is present in the rat plasma and urine as observed in the metabolism study with beflubutamid (up to 31 % excreted in urine). The other identified metabolites UR-50624 found in rat bile, UR-50617 and UR-50618 both found in rat excreta (see table B.6.1-8 and figure B.6.10-1) are not considered to be of toxicological concern. Furthermore, U1 from the crop rotational study, is considered to be a derivative or conjugate of UR-50604 and therefore not considered to be of toxicological concern.

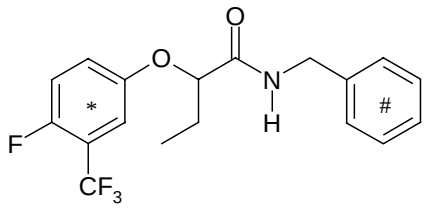
Figure B.7.1-1: Proposed metabolic pathway of beflubutamid in wheat



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 UR-50601 (beflubutamid) was investigated using [ring-U-^{14}C-phenoxy] beflubutamid and [ring-U-^{14}C-benzylamine] beflubutamid in lactating goats.

Figure B.7.2-1: Radiolabelled beflubutamid used in livestock metabolism study



* Position of radiolabel in [ring-U-^{14}C-phenoxy] beflubutamid
# Position of radiolabel in [ring-U-^{14}C-benzylamine] beflubutamid

B.7.2.1 Lactating goats

Report: L.F. Elsom (1998); ^{14}C-UR-50601: Metabolism in the lactating goat; UBE Industries, Ltd., unpublished report no. UBE 55/973900, 26 Oktober1998 [Huntingdon Life Sciences Ltd., UK];

Test Material: [Ring-U-^{14}C-phenoxy] beflubutamid: Batch number: CFQ 9257, Radiochemical purity: >98%, Specific activity: 1.63 GBq/mmol.
[Ring-U-^{14}C-benzylamine] beflubutamid: Batch number: CFQ 9258, Radiochemical purity: >98%, Specific activity: 1.63 GBq/mmol.

Test Animals: Lactating goat.

GLP: Yes.

Test Method: 91/414/EEC Directive as amended by 96/68/EC Directive
US EPA Pesticide Assessment Guidelines, Subdivision O, Residue Chemistry, Section 171-4(b)
US EPA Residue Chemistry Test Guidelines OPPTS 860.1300.

Deviations: None.

Acceptability: The study is considered to be acceptable.

Objectives of the study:

This study was designed to investigate the excretion and distribution of the test compound, to quantify the total radioactive residues and major metabolites in milk and edible tissue, and furthermore to obtain a biotransformation pathway in goats orally dosed with ^{14}C-beflubutamid.

Material and Methods:
The absorption and deposition of radioactivity was studied in two lactating goats (British Saanen, age 3-5 years) dosed for 5 consecutive days with ^{14}C-beflubutamid at a nominal dose level of 20 mg a.i./ animal/ day by capsule dosing after the morning milking. This was equivalent to a level of 10 mg/ kg in the diet (dry matter). One goat was dosed with the phenoxy labelled ^{14}C-beflubutamid and the other with benzylamine labelled ^{14}C-beflubutamid.

Sampling and sample storage:
Urine and faeces were collected during 24 hour intervals after each dose. At the end of each 24-hour collection period and after sacrifice the cages were rinsed. Milk was collected twice daily, in the morning and in the afternoon. Blood samples were taken at one hour pre-dose and at 2 hours after each daily dose, additionally after the last dose at 1, 2, 3, 4, 6, 8, 12 hours and immediately prior to sacrifice. The animals were sacrificed 23 hours after the final dose. Liver, kidneys, gastro-intestinal tract contents, muscle (foreleg and rump), peritoneal and subcutaneous fat were sampled. All samples were stored frozen at <-15°C prior to analysis.

Radioactivity measurements:
Liquid samples were radioassayed by LSC, solid samples by combustion or solubilisation and LSC.

Analysis:
Samples of faeces, milk, fat, liver and kidneys were extracted several times with acetonitrile and acetonitrile water mixtures. Fat and milk samples were additionally extracted with hexane. The resultant hexane and acetonitrile extracts were combined for shaking and partitioned again, and two fractions were separated. Urine and extracts of liver and kidney were hydrolysed by β-glucuronidase ("Enzyme treated"). The residues in liver after solvent extraction ("Untreated") were subjected to protease digestion and fractionation with methanol and sodium hydroxide. Extracts were concentrated by evaporation prior to chromatographic analysis. The remaining solids were radioassayed by combustion.
HPLC and TLC were used for quantification. Fractions of HPLC column eluate were collected and radioassayed by LSC. The images of the TLC plates were obtained and quantified with a laser beam scanner and an associated computer workstation.

Findings:

Animal Health:
The goats were deemed to be in good health prior to dose administration. No adverse reactions observed following application. There were no detectable changes in food consumption and milk production from the treatment. Body weights slightly decreased during the dosing period.

Recovery:
Overall recovery was for the phenoxy label 91.64% and for the benzylamine label 86.71% of the total applied radioactivity.
The test material was eliminated primarily via urine and faeces. 46.4% and 35.1 % of the total administered dose was excreted by the phenoxy labelled goat via urine and faeces respectively. The results for the benzylamine labelled goat were accounted for 41.6% and 34.8 % of the total dose in urine and faeces respectively.
Transfer of radioactivity into milk was low and accounted for 0.17% and 0.26% of the total dose for the phenyl and benzylamine label respectively. The excreted radioactivity including the residues in the milk and cage wash ranged from 77.1 % of the total administered dose for the benzylamine label to 82.1 % for the phenoxy label.
Radioactive residues in the tissue samples accounted for 0.58% and 1.34%, and in the gastrointestinal contents 9.0% and 8.2% of the total dose for the phenoxy and the benzylamine label respectively.
A survey of the recovered radioactivity is given in Table B.7.2-1

Table B.7.2-1: Recovery of radioactivity in tissues and excreta of lactating goats sacrificed at 23 hours after the last of 5 daily oral doses of ^{14}C-beflubutamid at a nominal rate of 20 mg/ animal/ day

Sample		Results are expressed as % total administered dose	
		[ring-U-^{14}C-phenoxy] beflubutamid	**[ring-U-^{14}C-benzylamine] beflubutamid**
		Goat 1	**Goat 11**
Urine		46.40	41.57
Faeces		35.14	34.82
Cage washings		0.35	0.49
Milk		0.17	0.26
Total excreted		**82.06**	**77.14**
Intestines		4.07	5.34
Omasum/abomasum		2.09	0.42
Rumen/reticulum		2.85	2.47
Total retained in the gastro-intestinal tract		9.01	8.23
Tissues	Liver	0.20	0.24
	Kidney	0.02	0.02
	Fat	0.24	0.90
	Muscle	0.12	0.18
Total in tissues		0.58	1.34
Total recovery		**91.64**	**86.71**

Concentrations of radioactivity:

Milk: Total radioactive residues in milk reached a peak of 0.049 mg/ kg in the benzylamine labelled milk in the Day 5 pm sample and 0.028 mg/ kg in the phenoxy labelled milk in the day 4 pm sample. The milk samples taken immediately before dosing (i.e. am samples) were significantly lower than the pm samples. (Table B.7.2-2)

Tissues: Concentrations of radiolabel in liver, kidney and muscle were very similar for both goats. Concentrations averaged in the liver 0.170 mg/ kg, in the kidney 0.104 mg/ kg, and in the muscle 0.007 mg/ kg. Concentrations of radioactivity in the fat were approximately 3times greater for the goat dosed with [ring-U-^{14}C-benzylamine] beflubutamid. (Table B.7.2-2)

Plasma and Blood:
Concentrations of radiolabel in the whole blood were proportionally the same as those obtained for plasma and indicated no significant uptake of radioactivity into the blood cells. The level of radioactivity in the blood declined with an apparent half-life of 19 hours between 6 and 23 hours after the final dose by first-order kinetics in the case of the goat dosed with benzylamine labelled beflubutamid.

Table B.7.2-2: Concentrations of radioactivity in tissues and milk

Sample	Results are expressed as equivalent mg/ kg of ^{14}C-beflubutamid	
	[ring-U-^{14}C-phenoxy] beflubutamid	[ring-U-^{14}C-benzylamine] beflubutamid
	Goat 1	Goat 11
Tissues		
Liver	0.170	0.171
Kidney	0.107	0.102
Foreleg muscle	0.006	0.007
Rump muscle	0.007	0.008
Peritoneal fat	0.061	0.154
Subcutaneous fat	0.042	0.132
Milk		
Day 1 pm	0.019	0.019
Day 2 am	0.007	0.015
Day 2 pm	0.022	0.032
Day 3 am	0.008	0.019
Day 3 pm	0.027	0.020
Day 4 am	0.008	0.009
Day 4 pm	0.028	0.030
Day 5 am	0.008	0.023
Day 5 pm	0.011	0.049
Day 6 am	0.009	0.021

Proportions of radioactive components in urine and faeces:

Urine: (Day 2 sample) Most of the radioactivity of the "untreated" urine sample from the phenyl labelled goat was associated with polar components (65.6%). The main metabolite was UR-50604 accounted for 28.9% of the urine radioactivity. In the "enzyme treated" urine sample the metabolites UR-50604, UR-50617 and UR-50618 were detected in significant amounts accounted for 28.1%, 32.3% and 8.3% of the urine radioactivity respectively, whereas the polar components decreased to 3.1%.
Hippuric acid (70.6%) and polar material (27.2%) were the main components of the urine radioactivity of the benzylamine labelled goat. Due to the enzyme treatment the polar material decreased to 3.0%, whereas the component corresponding to UR-50618 increased to 10.7 %, and hippuric acid was nearly constant at 73.5% of the urine radioactivity.
Radioactivity corresponding to unchanged beflubutamid was not detected for both labels.
Faeces: (Day 5 sample) The major radioactive components corresponded to UR-50617 and UR-50618 (combined accounted 47.3% and 49.9%), unchanged beflubutamid (8.8% and 10.5%) and unextracted radioactivity (21.1% and 21.6%) of the faeces radioactivity for the phenoxy and benzylamine label respectively.

Proportions of radioactive components in milk and tissue:

Milk: Milk samples from the pm milking of both goats plus the Day 2 am and Day 6 am sample of the benzylamine labelled goat were used for characterisation of radioactivity. Components were resolved by HPLC.
The Day 3 pm sample of the phenyl labelled goat and the Day 5 pm sample of the benzylamine labelled goat were the most representative samples of each label. The

proportions of the radioactive components in the selected samples are given in Table B.7.2-3. The ranges of results from all analysed milk samples were additionally presented below.

Table B.7.2-3: Proportions of radioactive components in milk of Goat 1 and Goat 11 sacrificed at 23 hours after the last of 5 daily oral doses of [ring-U-^{14}C-phenylamine] and [ring-U-^{14}C-benzylamine] beflubutamid respectively at a nominal rate of 20 mg/ animal/ day

Milk Results expressed as equivalent mg/ kg of ^{14}C-beflubutamid Proportion (%) of the tissue radioactivity is given in parenthesis				
	[ring-U-^{14}C-phenoxy] beflubutamid		**[ring-U-^{14}C-benzylamine] beflubutamid**	
	Goat 1		**Goat 11**	
	Day 3 pm	**Range** (n=5) **Day 1-5**	**Day 5 pm**	**Range** (n=7) **Day 1-5**
TRR mg/ kg	0.027	0.011-0.028	0.049	0.015-0.049
Identified:				
Hippuric acid	-	-	0.0197 (40.6)	0.0036-0.0197 (19.4-72.3)
UR-50604	0.0013 (4.9)	0.0002-0.0016 (2.0-5.5)	-	-
UR-50617	0.0004 (1.3)	0.0001-0.0004 (0.9-1.3)	0.0003 (0.5)	0.0001-0.0005 (0.5-1.5)
UR-50818	*	0.0001-0.0004 (0.5-1.9)	0.0002 (0.4)	0.0002-0.0003 (0.4-1.5)
Beflubutamid	0.0172 (62.9)	0.0074-0.0172 (34.8-70.4)	0.0228 (46.9)	0.0033-0.0228 (16.3-70.8)
Total identified	0.0189 (69.1)	0.0077-0.0189 (42.4-74.2)	0.0430 (88.4)	0.0112-0.0430 (70.6-90.2)
Characterised:				
Resolved peaks	0.0071 (25.9)	0.0023-0.0141 (15.6-49.9)	0.0022 (4.6)	0-0.0022 (0-13.7)
Others [1]	0.0004 (1.4)	0.0006-0.0016 (1.4-7.9)	0.0011 (2.3)	0.0001-0.0027 (0.3-9.0)
Hexane phase	0.0008 (3.1)	0.0003-0.0008 (1.1-3.1)	<0.0001 (<0.1)	<0.0001-0.0006 (<0.1-2.0)
Unextracted residue	0.0001 (0.5)	0.0001-0.0006 (0.5-3.1)	0.0031 (6.5)	0.0004-0.0031 (2.4-12.2)
Recovery	100.0%	99.8-100%	101.8%	99.8-101.8%

* According to the notifier included in others
[1] Others refers to radioactivity not associated with specific components

Tissue: Components were resolved by TLC except for UR-50617 and UR-50618, which were resolved by HPLC. Component UTiP10 from the phenyl labelled samples and UTiB5 from the benzylamine label was the difference between the proportion of radioactivity associated with UR-50617 and UR-50618 by TLC and the sum of these two components quantified by HPLC for each label respectively.
Muscle: Due to the low total radioactive residue in the muscle samples no further investigation was performed.
Fat: The only significant component in subcutaneous and peritoneal fat samples of both labels was unchanged parent beflubutamid.
Liver: The pooled acetonitrile and acetonitrile / water liver extracts were resolved into at least six and seven components and polar radioactivity for the phenoxy and the benzylamine label respectively. The major resolved metabolite from the phenoxy label was UR-50604 accounted

13.8 % and from the benzylamine label UR-50617 accounted 9.1% of the liver radioactivity. Most of the radioactivity was associated with polar components and accounted for 36.2 % and 33.6% of the liver radioactivity respectively. Incubation of the pooled extracts with ß-glucuronidase ("Enzyme treated") increased the number of radioactive components. (Table B.7.2-4 and Table B.7.2-5)
Kidney: Radioactivity in the kidney extracts was mainly associated with UR-50604 (26% of the kidney radioactivity) for the phenoxy label and with hippuric acid (27.6% of the kidney radioactivity) for the benzylamine label and polar material (43.5% and 28.3% respectively). Radioactivity corresponding to unchanged beflubutamid accounted for 2.2-2.5% for both labels. After incubation of the extracts with ß-glucuronidase the proportion of polar material was reduced. This indicated the presence of conjugates.

Metabolites and metabolic pathway:

The major metabolites detected were UR-50604 (urine, milk, liver and kidney), hippuric acid (urine, milk, liver and kidney), UR-50617 and its conjugate (urine, faeces, milk, liver and kidney) and UR-50618 and its conjugate (urine, faeces, liver and kidney, see Table B.7.2-4 and Table B.7.2-5). The only significant radioactive component in fat was parent beflubutamid and this was also the major component in milk.
Beflubutamid is metabolised via C-N cleavage generating UR-50604 and hydroxylation of the benzylamine ring at the 3 and 4 positions generating UR-50618 and UR-50617. Hippuric acid is naturally generated in the kidneys of herbivores due to metabolism of benzoic acid and its derivatives.
The proposed metabolic pathway for beflubutamid is shown in Figure B.7.2-2.

Figure B.7.2-2: Proposed biotransformation pathway in the goat

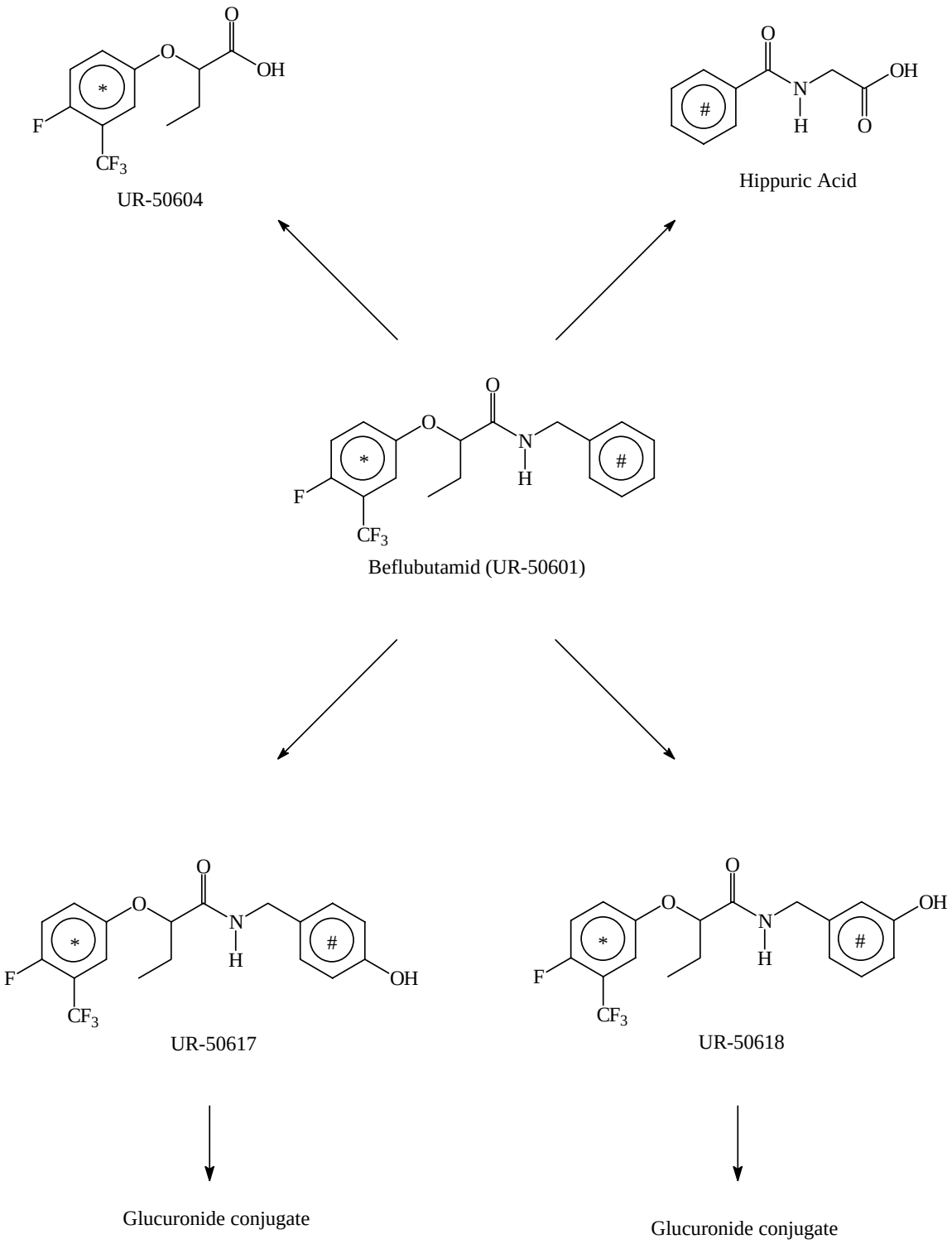


Table B.7.2-4: Proportions of radioactive components in tissues of Goat 1 sacrificed at 23 hours after the last of 5 daily oral doses of [ring-U-^{14}C-phenoxy] beflubutamid at a nominal rate of 20 mg/animal/ day

	Tissue Results expressed as equivalent mg/ kg of ^{14}C-beflubutamid Proportion (%) of the tissue radioactivity is given in parenthesis					
	Fat		**Liver**		**Kidney**	
	Subcutaneous	**Peritoneal**	**Untreated**	**Enzyme treated**	**Untreated**	**Enzyme treated**
Identified:						
UR-50604	0.0013 (3.0)	0.0010 (1.7)	0.0234 (13.8)	0.0108 (6.3)	0.0277 (26.0)	0.0224 (21.0)
UR-50617	0.0007 (1.8)	0.0008 (1.3)	0.0048 (2.9)	0.0135 (8.0)	0.0040 (3.8)	0.0099 (9.3)
UR-50618	*	*	0.0045 (2.7)	0.0087 (5.1)	*	0.0042 (3.9)
Beflubutamid	0.0311 (74.4)	0.0501 (82.0)	0.0111 (6.5)	0.0105 (6.2)	0.0026 (2.5)	0.0038 (3.6)
Total identified	0.0331 (79.2)	0.0519 (85.0)	0.0438 (25.9)	0.0435 (25.6)	0.0343 (32.3)	0.0403 (37.8)
Characterised:						
Polar	0.0025 (6.0)	0.0014 (2.3)	0.0617 (36.2)	0.0267 (15.7)	0.0464 (43.5)	0.0107 (10.1)
UTiP1	*	*	*	0.0209 (12.3)	*	0.0015 (1.4)
Σ UTiP2 -UTiP4	*	*	*	0.0070 (4.1)	*	*
UTiP5	*	*	*	0.0023 (1.4)	*	0.0049 (4.6)
UTiP6	0.0002 (0.4)	0.0002 (0.4)	0.0056 (3.3)	0.0045 (2.6)	0.0012 (1.1)	0.0020 (1.9)
UTiP7 + UTiP8	*	*	*	0.0045 (2.6)	*	*
UTiP 9	*	0.0018 (2.9)	*	0.0019 (1.1)	*	*
UTiP10	0.0012 (2.9)	0.0016 (2.6)	0.0065 (3.8)	0.0027 (1.6)	0.0041 (3.8)	0.0220 (20.6)
Unresolved	0.0039 (9.2)	0.0039 (6.4)	0.0099 (6.5)	0.0111 (6.5)	0.0121 (11.3)	0.0152 (13.7)
Protease digestion:						
Aqueous extract	n/a	n/a	0.0015 (0.9)	n/a	n/a	n/a
Methanol extract	n/a	n/a	0.0122 (7.2)	n/a	n/a	n/a
Sodium hydroxide analysis:						
Aqueous phase	n/a	n/a	0.0137 (8.0)	n/a	n/a	n/a
Methanol phase	n/a	n/a	0.0121 (7.1)	n/a	n/a	n/a
Remaining from extraction:						
Hexane phase	0.0006 (1.4)	0.0002 (0.4)	n/a	n/a	n/a	n/a
Solid residue	0.0005 (2.0)	0.0006 (0.8)	0.0058 (3.4)	n/a	0.0100 (9.4)	n/a
Recovery	0.0420 (100.0)	0.0616 (101.0)	0.1728 (101.6)	0.1251 (73.6)	0.1081 (101.0)	0.0966 (90.3)

* According to the notifier not found, unresolved radioactivity on this positions is included in "Unresolved".
No information about the number of unresolved areas is given. The biggest value of a single unresolved area is reported to be less than 5 ng equivalents/g.
n/a not applicable

Table B.7.2-5: Proportions of radioactive components in tissues of Goat 11 sacrificed at 23 hours after the last of 5 daily oral doses of [ring-U-^{14}C-benzylamine] beflubutamid at a nominal rate of 20 mg/animal/ day

	Tissue Results expressed as equivalent mg/ kg of ^{14}C-beflubutamid Proportion (%) of the tissue radioactivity is given in parenthesis					
	Fat		**Liver**		**Kidney**	
	Subcutaneous	**Peritoneal**	**Untreated**	**Enzyme-treated**	**Untreated**	**Enzyme-treated**
Identified:						
Hippuric acid	*	*	0.0115 (6.7)	0.0072 (4.2)	0.0281 (27.6)	0.0384 (37.7)
UR 50617	0.0009 (0.7)	0.0004 (0.2)	0.0156 (9.1)	0.0186 (10.9)	0.0030 (3.0)	0.0118 (11.6)
UR 50618	0.0010 (0.7)	0.0004 (0.3)	0.0107 (6.3)	0.0126 (7.4)	0.0022 (2.2)	0.0055 (5.4)
Beflubutamid	0.1176 (89.1)	0.1380 (89.5)	0.0055 (3.2)	0.0128 (7.5)	0.0022 (2.2)	0.0054 (5.3)
Total identified	0.1195 (90.5)	0.1388 (90.0)	0.0433 (25.3)	0.0512 (30.0)	0.0355 (35.0)	0.0611 (60.0)
Characterised:						
Polar	*	*	0.0575 (33.6)	0.0562 (32.8)	0.0288 (28.3)	0.0199 (19.5)
UTiB1 (0.07)	*	*	0.0043 (2.5)	*	*	0.0004 (0.4)
UTiB2 (0.21)	*	*	0.0040 (2.4)	0.0010 (0.6)	*	*
UTiB3 (0.40)	*	*	0.0061 (3.6)	0.0005 (0.3)	0.0061 (6.0)	*
UTiB4 (0.66)	0.0013 (1.0)	*	*	0.0081 (4.7)	0.0015 (1.5)	*
UTiB5	-	-	-	0.0150 (8.7)	0.0033 (3.2)	0.0077 (7.5)
Unresolved	0.0098 (7.4)	0.0143 (9.3)	0.0185 (10.8)	0.0018 (1.1)	0.0206 (20.2)	0.0068 (6.7)
Protease digestion:						
Aqueous extract	n/a	n/a	0.0007 (0.4)	n/a	n/a	n/a
Methanol extract	n/a	n/a	0.0189 (11.0)	n/a	n/a	n/a
Sodium hydroxide hydrolysis:						
Aqueous phase	n/a	n/a	0.0047 (2.7)	n/a	n/a	n/a
Methanol phase	n/a	n/a	0.0063 (3.7)	n/a	n/a	n/a
Remaining from extraction:						
Hexane phase	0.0014 (1.1)	0.0006 (0.4)	n/a	n/a	n/a	n/a
Solid residue	0.0007 (0.5)	0.0009 (0.6)	0.0068 (4.0)	n/a	0.0058 (5.8)	n/a

	Tissue Results expressed as equivalent mg/ kg of ^{14}C-beflubutamid Proportion (%) of the tissue radioactivity is given in parenthesis					
	Fat		**Liver**		**Kidney**	
	Subcutaneous	**Peritoneal**	**Untreated**	**Enzyme-treated**	**Untreated**	**Enzyme-treated**
Recovery	0.1327 (100.5)	0.1546 (100.4)	0.1691 (98.9)	0.1338 (78.2)	0.1371 (99.6)	0.0955 (93.6)

* According to the notifier not found, unresolved radioactivity on this positions is included in "Unresolved".
No information about the number of unresolved areas is given. The biggest value of a single unresolved area is reported to be less than 9 ng equivalents/g.
n/a not applicable

Storage stability:
There are no data available from the report. Experimental work was completed within 15 month from sampling. (21 March 1997 -23 June 1998)

Conclusion:

The metabolism of beflubutamid in the lactating goat has been investigated using either [ring-U-^{14}C-phenoxy] or [ring-U-^{14}C-benzylamine] labelled material. The proposed biotransformation pathway is shown in Figure B.7.2-2. The administered dose was equivalent to an intake of diet containing residues of approximately 10 mg/ kg feed.
The majority of the radioactivity was rapidly excreted, primarily with the urine and faeces.
Minimal residues were found in milk and meat. The total daily residue in milk reached a peak in the benzylamine labelled milk in the Day 5 pm milk sample. The major residues were found in the liver and kidneys and the benzylamine labelled fat sample. The difference in radioactive concentration between the phenoxy and benzylamine labelled fat samples was not due to different metabolite residues as almost all the radioactivity was present as beflubutamid.
The metabolic profile was very similar in urine, faeces, milk, liver and kidney.
The major metabolites detected were UR-50604 (urine, milk, liver and kidney); hippuric acid (urine, milk, liver and kidney); UR-50617 and its conjugate (urine, faeces, milk, liver and kidney) and UR-50618 and its conjugate (urine, faeces, liver and kidney). The only significant radioactive component in fat was parent beflubutamid and this was also the major component in milk.
The metabolic pathway of the goat seems comparable to the rat, although the rat shows more extensive degradation.

B.7.2.2 Laying hens

The residue levels of beflubutamid and metabolite UR-50604 in the grain at harvest are less than 0.05 mg/kg, and are therefore not seen as being at significant levels in livestock feed. Thus, a metabolism study in laying hens is not considered necessary.

B.7.2.3 Pigs

The metabolic pathway of beflubutamid and UR-50604 in the rat compared to the goat does not differ significantly. Furthermore, the residue levels of beflubutamid and UR-50604 in the

grain at harvest are both less than 0.05 mg/kg and are therefore not at significant levels in livestock feed. Thus, a metabolism study in the pig is not considered necessary.

B.7.2.4 Proposed residue definition

The metabolism of beflubutamid was investigated in lactating goats. Parent compound was found as the major residue in milk and fat. Hippuric acid was a main metabolite in the benzylamine labelled milk and kidney samples beside UR-50604 as the main metabolite in phenyl labelled kidney. UR-50604 and hippuric acid are of no toxicological significance as they are present in the rat metabolism study.
Therefore it can be concluded that the parent compound beflubutamid is the residue of concern.

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

B.7.3.1 Plants

Metabolism studies on wheat plants show very low total radioactive residues in grain after treatment of nominal rates of 255 g ^{14}C-labelled beflubutamid/ha. Unchanged parent compound was not identified in grain but only in straw at levels of up to 0.35 mg/kg. The only identified component reaching the level of 0.01 mg/kg in grain was the metabolite UR-50604 which however, based on the rat metabolism study was considered as being of no toxicological concern.

Therefore, the residue definition for plant materials is proposed as **beflubutamid**.

B.7.3.2 Animals

The metabolism of beflubutamid was investigated in lactating goats. Parent compound was found as the major residue in milk and fat. Hippuric acid was a main metabolite in the benzylamine labelled milk and kidney samples beside UR-50604 as the main metabolite in phenyl labelled kidney. UR-50604 and hippuric acid are of no toxicological significance as they are present in the rat metabolism study.

Therefore, the parent compound **beflubutamid** is defined as the residue of concern.

B.7.4 Use pattern

Uses of beflubutamid containing products are applied for in cereals in the northern and southern region of Europe. Product type is a SC formulation containing 85 g beflubutamid/L and 500 g isoproturon/L which will be used at rates of 2.0 or 3.0 L/ha. Details of its uses are summarised in chapter B.3.3.

B.7.5 Identification of critical GAPs

Referring to chapter B.3.3 the critical GAP for the use of beflubutamid is based on the highest application rate of a total of 255 g as/ha at the latest possible developing stage in spring of BBCH 29 of cereals crops.

B.7.6 Residues resulting from supervised trials (Annex IIA 6.3; Annex IIIA 8.2)

B.7.6.1 Analytical methods used in the residue trials

In the supervised residue trials samples of green cereal plants, mature grain and straw have been analysed using extraction and detection methods described in chapter B.5. Matrices obtained in the 1997 trials were analysed according to the method reported in AB 95510-GM-002A which was validated to levels of 0.01 mg/kg grain and straw (EC-detector). This method was changed in some parts of the extraction and the detection steps (PND) which was validated and confirmed by independent laboratories to the level of 0.05 mg/kg. The latter method was applied in the trials conducted in the years 1998 and 1999 and will be used for enforcement of MRLs.

Timings of field and analysis phases of all trials are well documented. Storage stability of residues of beflubutamid and its metabolite UR-50604 in deep frozen samples (<-18°C) prior to analysis was proven in several trials by simultaneous tests during the same period of time (see B.7.6.4).

B.7.6.2 Residue trials on winter barley and winter wheat - field information

Table B.7.6-1 contains details of all residue trials conducted to obtain residue values for beflubutamid and its metabolite UR-50604. The product has been applied in winter wheat or spring wheat and barley once during spring time between late March and mid of Mai. The rates were approximately between 250 and 290 g as/ha which corresponds to the intended maximum rate of 255 g as/ha. Three different experimental SC formulations with slightly differing concentrations of the active substance have been used:

- SC 90.4 contained 82 g beflubutamid and 454 g isoproturon / L,
- SC 88.5 contained 88.5 g beflubutamid and 518 g isoproturon / L,
- SC 83.6 contained 83.6 g beflubutamid and 494.5 g isoproturon / L.

As shown in Table B.7.6-2 most of the 18 trials in total have been conducted to generate decline curves. Six of them were run to determine residue levels in grain and straw at normal harvest. Sampling in the decline trials included young green plants just after application and up to 4 weeks as well as grain and straw of the mature cereals plants between DAT 63 and 116.

The locations of the trials were distributed over a few Member States throughout northern and southern EU. Eight trials were run in DE, two in N-FR, two in IT and six in ES.

Table B.7.6-1: GAP information of the residue trials

Crop	Country	Formulation (g as / L)	Application		Sampling period until harvest DAT	Reference
			Actual rate of product L / ha	Actual rate of as g / ha		
1997						
Winter wheat	Germany	SC 90.4	3.09	253	90	RIP 2000-1893
Winter wheat	Germany	SC 90.4	2.97	244	107	
1998						
Spring barley	N. France	SC 88.5	2.87	249	77	RIP 2000-1894
Spring barley	Germany	SC 88.5	3.09	274	85	
Winter wheat	N. France	SC 88.5	2.81	249	97	
Winter wheat	Germany	SC 88.5	3.06	271	116	
Spring wheat	Spain	SC 88.5	2.89	256	70	
Spring wheat	Italy	SC 88.5	2.89	256	66	
Winter wheat	Spain	SC 88.5	2.83	250	108	
Winter wheat	Italy	SC 88.5	2.94	260	105	
1999						
Spring wheat	Germany	SC 83.6	2.9	242	71	RIP 2000-1895
Durum wheat	Germany	SC 83.6	3.2	268	85	
Spring barley	Germany	SC 83.6	3.44	288	76	
Spring barley	Germany	SC 83.6	3.18	266	82	
Spring barley	Spain	SC 83.6	2.95	247	69	
Spring barley	Spain	SC 83.6	2.99	250	63	
Spring barley	Spain	SC 83.6	2.99	250	62	
Spring barley	Spain	SC 83.6	2.99	250	69	

B.7.6.3 Results of the residue trials

Initial residue levels of beflubutamid on the freshly treated young cereals plants differ between 1.46 and 4.63 mg/kg. Rapid decline of these residues in the green plants was observed within about four weeks to values of mostly <0.1 mg/kg. In three samples residues of 0.16, 0.17 and 0.29 mg/kg still exceeded this level but, at harvest at DAT 63 – 116 residues in grain and straw were below the LOQ of 0.05 mg/kg. Residues of the metabolite UR 50604 were never found in any sample.

No difference of the residue levels in green cereals plants, grain, or straw could be observed in the N-EU or S-EU residue trials. Quality and amount of residue data are sufficient to propose an MRL for beflubutamid in cereals.

Concerning the residue situation of isoproturon (IPU) in cereals reference is made to the IPU monograph. No new residue data on IPU have been generated using the present formulations containing beflubutamid.

Table B.7.6-2: Results of supervised residue trials on barley and wheat

Country/ Year	Formulation (g as/ L or kg)	Application: Rate per treatment (kg as/ha)	Application: Growth stage	Application: No.	Portion analysed	Residues (mg/kg): Beflubutamid	Residues (mg/kg): UR-50604	DAT (d)	References
Winter Wheat									
DE / 1996-1997	SC 85	0.253	BBCH 29	1	Straw	<0.01	--	90	RIP2000-1893
					Grain	<0.01	--	90	
DE / 1996-1997	SC 85	0.244	BBCH 30	1	Straw	<0.01	--	107	RIP2000-1893
					Grain	<0.01	--	107	
DE / 1997-1998	SC 85	0.249	BBCH 29	1	Whole plant	2.36	<0.05	0	RIP2000-1894
						0.46	<0.05	8	
						0.1	<0.05	14	
						<0.05	<0.05	28	
					Straw	<0.05	<0.05	97	
					Grain	<0.05	<0.05	97	
DE / 1997-1998	SC 85	0.271	BBCH 29	1	Whole plant	1.87	<0.05	0	RIP2000-1894
						0.36	<0.05	7	
						0.11	<0.05	14	
						0.06	<0.05	27	
					Straw	<0.05	<0.05	116	
					Grain	<0.05	<0.05	116	
ES / 1997-1998	SC 85	0.250	BBCH 27-29	1	Whole plant	2.81	<0.05	0	RIP2000-1894
						1.05	<0.05	8	
						0.36	<0.05	14	
						0.17	<0.05	30	
					Straw	<0.05	<0.05	108	
					Grain	<0.05	<0.05	108	
IT / 1997-1998	SC 85	0.260	BBCH 29	1	Whole plant	1.83	<0.05	0	RIP2000-1894
						0.74	<0.05	7	
						0.12	<0.05	14	
						0.08	<0.05	28	
					Straw	<0.05	<0.05	105	
					Grain	<0.05	<0.05	105	
Spring Wheat									
ES / 1998	SC 85	0.256	BBCH 30	1	Whole plant	1.46	<0.05	0	RIP2000-1894
						0.68	<0.05	7	
						0.22	<0.05	13	
						0.16	<0.05	28	
					Straw	<0.05	<0.05	70	
					Grain	<0.05	<0.05	70	
IT / 1998	SC 85	0.256	BBCH 29	1	Whole plant	1.89	<0.05	0	RIP2000-1894
						0.89	<0.05	7	
						0.12	<0.05	14	
						0.06	<0.05	28	
					Straw	<0.05	<0.05	66	
					Grain	<0.05	<0.05	66	
DE / 1999	SC 85	0.242	BBCH 29	1	Whole plant	4.63	<0.05	0	RIP2000-1895
						2.16	<0.05	7	
						0.46	<0.05	14	
						0.08	<0.05	27	
					Straw	<0.05	<0.05	71	
					Grain	<0.05	<0.05	71	

Country/ Year	Formulation (g as/ L or kg)	Application			Portion analysed	Residues (mg/kg)		DAT (d)	References
		Rate per treatment (kg as/ha)	Growth stage	No.		Beflubutamid	UR-50604		
Durum Wheat									
DE / 1999	SC 85	0.268	BBCH 23	1	Grain	<0.05	<0.05	85	RIP2000-1895
					Straw	<0.05	<0.05	85	
Spring Barley									
DE /1998	SC 85	0.249	BBCH 29	1	Whole plant	1.98	<0.05	0	RIP2000-1894
						0.3	<0.05	7	
						0.19	<0.05	14	
						<0.05	<0.05	28	
					Straw	<0.05	<0.05	77	
					Grain	<0.05	<0.05	77	
DE /1998	SC 85	0.274	BBCH 29	1	Whole plant	2.76	<0.05	0	RIP2000-1894
						1.06	<0.05	7	
						0.27	<0.05	15	
						0.07	<0.05	28	
					Straw	<0.05	<0.05	85	
					Grain	<0.05	<0.05	85	
DE / 1999	SC 85	0.288	BBCH 26	1	Whole plant	3.05	<0.05	0	RIP2000-1895
						0.96	<0.05	8	
						0.13	<0.05	14	
						<0.05	<0.05	27	
					Straw	<0.05	<0.05	76	
					Grain	<0.05	<0.05	76	
DE / 1999	SC 85	0.266	BBCH 21	1	Grain	<0.05	<0.05	82	RIP2000-1895
					Straw	<0.05	<0.05	82	
ES / 1998-1999	SC 85	0.247	BBCH 29	1	Whole plant	3.51	<0.05	0	RIP2000-1895
						0.37	<0.05	7	
						0.11	<0.05	14	
						0.07	<0.05	27	
					Straw	<0.05	<0.05	69	
					Grain	<0.05	<0.05	69	
ES / 1998-1999	SC 85	0.250	BBCH 29	1	Whole plant	2.33	<0.05	0	RIP2000-1895
						0.76	<0.05	7	
						0.5	<0.05	14	
						0.29	<0.05	27	
					Straw	<0.05	<0.05	63	
					Grain	<0.05	<0.05	63	
ES / 1998-1999	SC 85	0.250	BBCH 29	1	Grain	<0.05	<0.05	62	RIP2000-1895
					Straw	<0.05	<0.05	62	
ES / 1999	SC 85	0.250	BBCH 29	1	Grain	<0.05	<0.05	69	RIP2000-1895
					Straw	<0.05	<0.05	69	

B.7.6.4 Storage stability of beflubutamid and UR 50604 residues in grain and straw

The freezer storage stability of beflubutamid and its metabolite UR-50604 in spiked cereals matrices was tested besides the analyses of the treated samples. Essential data of these trials are summarised in Table B.7.6-3 which also contain the results. From these five results on green plants, grain and straw one can assume that residues in corresponding treated field samples should be stable during the same storage period under the same conditions.

Table B.7.6-3: Conditions and results of the storage stability tests

Matrix	Beflubutamid				UR 50604				Reference
	Storage period [d]		Fortification level [mg/kg]	Recovery [%]	Storage period [d]		Fortification level [mg/kg]	Recovery [%]	
	Treated sample	Spiked sample			Treated sample	Spiked sample			
Winter wheat grain	189	202	1.04	101.0	-	-	-	-	RIP2000-1893
Winter wheat straw	189	202	1.04	96.3	-	-	-	-	RIP2000-1893
Winter wheat green plant	237	241	0.55	102.4	237	238	0.20	100.1	RIP2000-1894
Spring barley green plant	200	200	0.55	103.8	200	197	0.20	100.9	RIP2000-1894
Spring barley green plant	165	173	2.01	101.6	165	173	0.52	99.9	RIP2000-1895

B.7.7 Effects of industrial processing and/or household preparation (Annex IIA 6.5; Annex IIIA 8.4)

Metabolism studies and residue trials results indicate that under practical conditions no residues of beflubutamid and its metabolite UR-50604 are expected to exceed the LOQ of 0.05 mg/kg in cereals grain. Therefore, no studies on the level and nature of residues in food of processed grain have been conducted and they are not required.

B.7.8 Livestock feeding studies (Annex IIA 6.4; Annex IIIA 8.3)

No feeding studies on domestic animals have been conducted. The supervised residue trials including treatment with beflubutamid latest at developing stage of BBCH 29 reveal a low residue situation in ***cereals grain and straw***. Therefore, under practical conditions no residues of parent substance and its metabolite UR-50604 above the LOQ of the analysis method are expected in cereals products being potential feeding stuffs for ***ruminants, swine and poultry***.

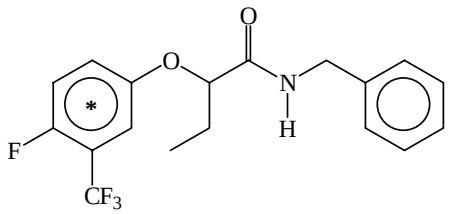
Therefore, this residue situation does not require feeding studies on any type of domestic animals.

B.7.9 Residues in succeeding or rotational crops (Annex IIA 6.6; Annex IIIA 8.5)

Concerning level and nature of residues of beflubutamid in rotational crops one study was conducted on *carrots* and *wheat*. The used active substance was uniform labelled only in the phenoxy ring position as shown below.

Report: Mellor, 2000, RIP2000-1897:
UR-50601 Confined accumulation in rotational crops; UBE Industries Ltd., unpublished report no. UBE 083/992872, 14 January 2000 [Huntingdon Life Sciences Ltd., UK].

Test material: Beflubutamid (UR-50601):



*) position of radiolabel in [ring-UL-^{14}C-phenoxy] beflubutamid

Guidelines: 91/414/EEC Directive as amended by 96/68/EC Directive, and working document 7524/VI/95 rev. 2, Appendix C.

GLP: Yes.

Deviations: None.

Acceptability: The study is considered to be acceptable.

B.7.9.1 Materials and Methods

Loamy sand soil (Speyer 2.2) in pots was treated with formulated [ring-UL-^{14}C-phenoxy] beflubutamid at a nominal application rate of 255 g as/ha and left to age for a period of 30 days after which wheat and carrots at ± 15°C were sown and grown to maturity. The total radioactive residue concentrations (TRR's) were determined in soil and plants.

Timing of sampling

Soil: Application, sowing, immature sampling, earliest possible harvest and normal harvest.
Plants: Immature, earliest possible harvest and normal harvest.

Analysis

Chromatography: HPLC and TLC for quantification and identification. Radioactivity was measured by LSC.

Characterisation of polar component (U1)

Enzyme treatment
Normal harvest straw and husk extracts were hydrolysed by β-glucosidase before TLC analysis.

Acid/base treatment
Normal harvest straw and husk extracts were treated with a range of mild and strong acids and bases, neutralised prior to TLC analysis.

Acetylation
An aliquot of the concentrated aqueous pool produced for chromatographic analysis was acetylated, evaporated and re-suspended in water prior to analysis by TLC.

Methylation
An aliquot of the concentrated aqueous pool produced for chromatographic analysis was methylated, evaporated and re-suspended in water prior to analysis by TLC.

Partitioning behaviour of residues
An aliquot of the concentrated aqueous pool produced for chromatographic analysis was partitioned with dichloromethane and the organic phase removed. The aqueous phase was acidified and partitioned with dichloromethane. After basification, a final partition with dichloromethane was performed

Analysis
MS/MS spectrometry using Finnigan Mass spectrometer and ICIS mass spectrometry software.

B.7.9.2 Findings

Total radioactive residues (TRR) in soil used for growing carrots was 0.218 mg/kg at application, declining to 0.071 mg/kg at normal harvest.
In soil used for growing wheat, the TRR concentration after application was 0.237 mg/kg, and declined to 0.057 mg/kg at normal harvest.
TRR concentrations in untreated soils were less than twice the background at all sampling intervals. Individual results are shown in Table B.7.9-1.

At normal harvest, the TRR concentrations in carrots were 0.033 mg/kg in the foliage and 0.009 mg/kg in the root. The results are summarised in Table B.7.9-2.

At normal harvest, the TRR concentrations in wheat grain, husk and straw were 0.018 mg/kg, 0.105 mg/kg, and 0.131 mg/kg respectively. The results are summarised in Table B.7.9-3.

The transition factors for carrot at normal harvest were 0.46 for foliage and 0.13 for roots. Transition factors for wheat grain, husks and straw were 0.32, 1.8 and 2.3 respectively. These values are summarised in Table B.7.9-4.

The route of degradation in soil was the same as observed in the laboratory aerobic soil metabolism studies. This is outlined in Figure B.7.9-1. The major degradation products were confirmed to be UR-50604 (phenoxybutanoic acid) and UR-50624 (phenoxybutanamide) (see Table B.7.9-5). The unknown minor product U1 was present at the sowing of the rotational crops.

In carrots at harvest only the unknown minor product detected in soil, U1, was present in foliage and root extracts (see Table B.7.9-6). In wheat at harvest a minor degradate was shown to be UR-50604 and U1 was the major degradate in grain, husks and straw (see Table B.7.9-6). U1 was shown to be a single polar, water soluble component.

Table B.7.9-1: TRR in Speyer 2.2 soil in µg equiv.-as/g soil dry weight (% TRR)

DAT	TRR	Extractable residue		Non-extractable residue	
Soil samples (planted with **carrot**)					
0	0.218	0.201	(92.1)	0.017	(7.9)
30	0.158	0.116	(73.6)	0.042	(26.4)
105	0.089	0.014	(16.2)	0.075	(83.8)
161	0.071	0.009	(12.1)	0.062	(87.9)
Soil samples (planted with **wheat**)					
0	0.237	0.224	(94.4)	0.013	(5.6)
30	0.121	0.085	(70.2)	0.036	(29.8)
82	0.106	0.015	(13.8)	0.091	(86.2)
193	0.057	0.006	(10.8)	0.051	(89.2)

Table B.7.9-2: Concentrations of radioactivity in immature carrot and harvest samples in µg equiv.-as/g fresh weight (% TRR)

DAT	Sample	TRR	Extractable residue		Non-extractable residue	
105	Foliage	0.022	0.020	(89.1)	0.002	(10.9)
	Root	0.008	No sample		No sample	
137	Foliage	0.031	0.029	(92.2)	0.002	(7.8)
	Root	0.012	0.010	(84.2)	0.002	(15.8)
161	Foliage	0.033	0.029	(87.3)	0.004	(12.7)
	Root	0.009	0.008	(92.6)	0.001	(7.4)

Table B.7.9-3: Concentrations of radioactivity in immature and harvest wheat samples in µg equiv.-as/g fresh weight (% TRR)

DAT	Sample	TRR	Extractable residue		Non-extractable residue	
82	Forage	0.033	0.031	(95.2)	0.002	(4.8)
180	Grain	0.016	0.009	(53.7)	0.007	(46.3)
	Husks	0.094	0.082	(87.0)	0.012	(13.0)
	Straw	0.096	0.076	(79.6)	0.020	(20.4)
193	Grain	0.018	0.010	(53.4)	0.008	(46.6)
	Husks	0.105	0.102	(97.5)	0.003	(2.6)
	Straw	0.131	0.126	(96.2)	0.005	(3.8)

Table B.7.9-4: Transition factors

Substrate	DAT	Sample	Transition factor
Carrot	105	Foliage	0.25
		Root	0.09
	161	Foliage	0.46
		Root	0.13
Wheat	82	Forage	0.31
	193	Grain	0.32
		Husks	1.8
		Straw	2.3

Table B.7.9-5: Quantities of radioactive components in <u>soil</u> in µg equiv.-as/g soil dry weight (% TRR)

Radioactive component	Approximate retention time (minutes)	DAT			
		0		30	
Soil samples planted with carrot					
U1	4.5	<0.001	(<0.1)	0.002	(1.0)
UR-50604	10.0	0.001	(0.6)	0.024	(15.0)
UR-50624	24.0	<0.001	(<0.1)	0.002	(1.0)
UR-50601	42.0	0.197	(90.2)	0.083	(52.5)
Others[a]	-	0.003	(1.3)	<0.001	(<0.4)
Soil samples planted with wheat					
U1	4.5	0.001	(0.4)	0.002	(1.3)
UR-50604	10.0	<0.001	(<0.1)	0.019	(15.6)
UR-50624	24.0	<0.001	(<0.1)	0.002	(1.6)
UR-50601	42.0	0.220	(92.8)	0.056	(46.5)
Others[a]	-	0.002	(1.0)	0.006	(5.1)

[a]) Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks

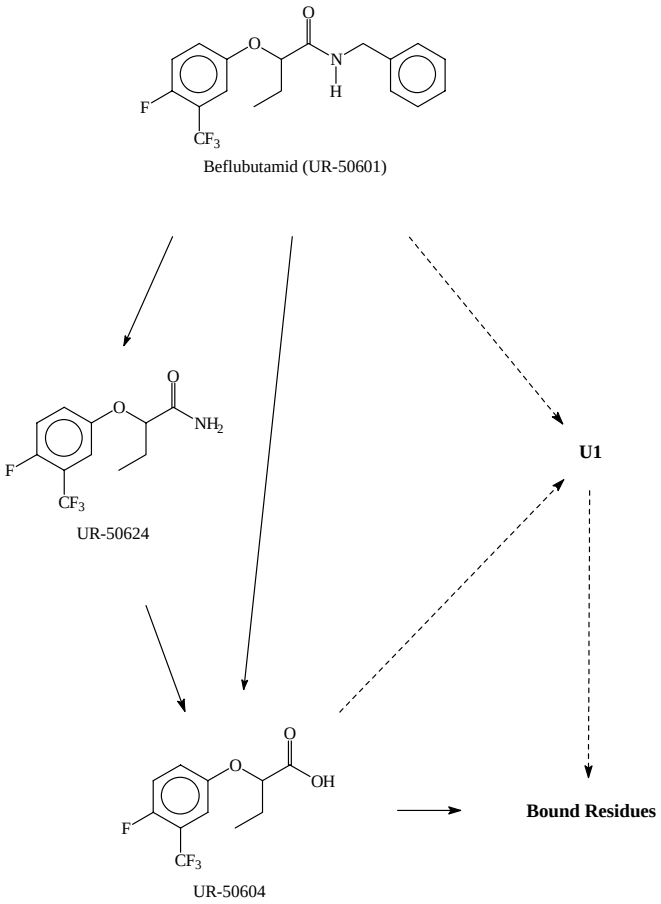
Table B.7.9-6: Quantities of radioactive components in crop immature and harvest carrot and wheat samples in µg equiv.-as/g fresh weight (% TRR)

Immature and harvest **carrot** samples										
DAT	**105**		**137**				**161**			
Matrix	**Foliage**		**Foliage**		**Root**		**Foliage**		**Root**	
U1	0.018	(78.9)	0.027	(87.4)	0.010	(81.6)	0.027	(80.9)	0.008	89.8
UR-50604	<0.001	(<0.5)	<0.001	(<1.0)	<0.001	(<1.2)	<0.001	(<0.5)	<0.001	<2.4
UR-50601	0.001	(3.2)	<0.001	(1.2)	<0.001	(1.2)	<0.001	(<0.5)	<0.001	<2.4
Others[a]	0.001	(6.2)	0.001	(3.0)	<0.001	(<1.2)	0.002	(4.5)	<0.001	<2.4

Immature and harvest **wheat** samples													
DAT	**82**		**180**						**193**				
Matrix	**Forage**		**Grain**		**Husks**		**Straw**		**Grain**		**Husks**		**Straw**	
U1	0.022	(67.1)	0.008	(47.2)	0.077	(82.0)	0.065	(68.2)	0.010	(51.9)	0.088	(83.4)	0.101	(77.1)
UR-50604	0.005	(15.4)	0.001	(6.0)	0.002	(2.1)	0.003	(3.6)	<0.001	(<1.6)	0.002	(2.0)	0.003	(2.0)
UR-50601	0.002	(5.7)	<0.001	(<2.3)	<0.001	(<0.6)	<0.001	(<0.3)	<0.001	(<1.6)	0.001	(0.5)	<0.001	(<0.3)
Others[a]	0.002	(6.9)	<0.001	(<2.3)	<0.001	(<0.6)	0.007	(7.6)	<0.001	(<1.6)	<0.001	<0.5)	0.004	(3.4)

[a]) Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks

Figure B.7.9-1: Proposed degradation pathway in soil



B.7.9.3 Conclusions

The transition factors for carrot determined for foliage and root at normal harvest indicate very little uptake of soil residues of beflubutamid. Also, the normal harvest transition factors for wheat determined for husks, straw and grain indicate that there is very little uptake of residues into grain from the soil and some uptake of residues of beflubutamid from the soil into husks and straw.
The major residues in soil at the time of sowing rotational crops were beflubutamid, UR-50604 and UR-50624. Analysis of plants at early and normal harvest showed that soil residues taken up by the plant had been transformed almost completely to a single polar, water soluble metabolite U1. This was present at levels of less than 0.05 mg/kg in carrot foliage and carrot root. In wheat, levels of U1 were in the range of 0.05 - 0.101 mg/kg in husks and straw and $\underline{\leq}$0.01 mg/kg in grain. U1 was not readily hydrolysed by enzymes, and not further degraded by strong acid and base treatments or derivatised to a more mobile residue. U1 does not contain the benzylamine moiety and although there is no direct evidence, U1 is possibly a stable conjugate or derivative of UR-50604.

B.7.9.4 Field trials on representative crops

From the result of the confined accumulation metabolism study in rotational crops, transition factors of rotational crops were very low [carrot root (0.13), carrot foliage (0.46) and wheat grain (0.32)] and there was no residue of beflubutamid with only one unidentified metabolite U1 at very low residue level (0.008 μg/g for carrot root, 0.027 μg/g for carrot foliage and 0.010 μg/g for wheat grain).
In spite of intensive studies U1 was not identified with only information of a polar and water soluble substance assuming to be a conjugate of UR-50604.
But U1 is considered not to accumulate in animal as it is a polar substance. Due to its water solubility it will be excreted by urine very quickly. Since U1 is not readily hydrolysed by enzymes, and not further degraded by strong acid and base treatments or derivatised to a more mobile residue it is assumed, that it is also not metabolised or break down by enzymes in the gastro-intestinal system.
U1 is assumed to be of no toxicological concern as it is probably a conjugate of the not-relevant metabolite UR-50604. Consumer risk will be at low on uptaking residues of beflubutamid and U1 metabolite through rotational crops as indicated above. Thus it can be safely concluded that and the field residue study of rotational crops is considered not necessary.

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)

Beflubutamid containing products are intended to be used post emergence on spring and winter cereals at the latest timing of the developing stage BBCH 29 in spring. The supervised residue trials on wheat and barley cover this use pattern. With a few exceptions, residues in forage were found to decline to levels at the LOQ within about one month after application and no residues were determined in grain and straw at normal harvest. Therefore, due to the sufficient time left until harvest there is no necessity to set a pre-harvest interval (PHI) in days. *The PHI is covered by the normal vegetation period between last application and harvest*.

B.7.11 Community MRLs and MRLs in EU Member States (Annex IIIA 12.2)

Beflubutamid 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

Based on the intended use pattern beflubutamid will be applied to cereals only. A total of 18 supervised residue trials on barley and wheat were conducted in northern and southern Europe covering the intended use pattern. The results of these trials reveal a "non-residue situation" in grain. No residues have been determined above the LOQ of 0.05 mg/kg. The MRL proposal is therefore

0.05 mg/kg cereals grain and other food of plant origin.

B.7.12.2 MRL proposal for animal products

Because no feeding studies on domestic animals are available MRLs for food of animal origin based on such studies cannot be proposed. Metabolism studies on lactating goats which had received the radiolabelled active substance indicated that beflubutamid is rapidly excreted via urine and feaces.

No residues in cereals *grain and straw* were quantified (LOQ = 0.05 mg/kg) from which a "non-residue situation" for poultry, swine and ruminants can be derived.

It can be concluded that residues in products of animal origin will be below the LOQ of the residue analytical method. A parent only method for enforcement in animal matrices would be sufficient but, to date, there is no such method available (see chapter B.5).

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)

The dietary risk assessment is based on the proposed **ADI value of 0.022 mg/kg bw/d** and the Theoretical Maximum Daily Intake (TMDI) calculation using the total diet of food of plant origin based on both the German and the WHO diet. Since after treatment of small grain cereals no quantifiable residues of beflubutamid are to be expected in edible plant parts the MRL for all food of plant origin is proposed at the LOQ of 0.05 mg/kg. In case of the calculation according to the WHO diet no MRL concerning food of animal origin is included (see Table B.7.15-1and Table B.7.15-2):

Table B.7.15-1: TMDI calculation of beflubutamid - German model

Mean food consumption (g/d) of a 4 to 6 years old girl					
Food	**raw[1]**	**processed[2]**	**whole**	**MRL (mg/kg)**	**Intake (mg/kg bw)**
Food of plant origin	105.8	386.2	492.0	0.05	0.001822
Intake whole (mg/kg bw):	**0.00182**				
Percent of ADI (%):	**8.28**				
Explanations: [1]) raw = without any preparation/processing [2]) processed = e.g. washed, peeled, cooked, baked, preserves					
Mean food consumption (g/d) of a 36 to 50 years old woman					
Food	**raw[1]**	**processed[2]**	**whole**	**MRL (mg/kg)**	**Intake (mg/kg bw)**
Wine grapes (wine)		97.6	97.6	0.05	0.00008133
Tea		1.1	1.1	0.05	0.00000092
Hops		4.9	4.9	0.05	0.00000408
Coffee beans (raw)		26.5	26.5	0.05	0.00002208
Intake whole (mg/kg bw):	**0.00011**				
Percent of ADI (%):	**0.49**				

Table B.7.15-2: TMDI calculation of beflubutamid - WHO model

Mean food consumption in g/d [WHO European diet (1994)]			
Food	**Consumption (g/day)**	**MRL (mg/kg)**	**Intake (mg/kg bw)**
Food of plant origin	1252.1	0.05	0.00104342
Intake whole (mg/kg bw):	**0.001**		
Percent of ADI (%):	**4.74**		

Both calculations lead to very low TMDI values and the contribution to the proposed ADI of 0.022 mg/kg bw/d is 8.3 % and 4.7 % according to the German and the WHO calculation model, respectively.

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 degradation of beflubutamid in winter **wheat** was investigated using two different radiolabels, namely [ring-UL-^{14}C-phenoxy] beflubutamid and [ring-UL-^{14}C-benzylamine] beflubutamid, at an application rate of 255 g as/ha when the plants were at growth stage 33.

The TRR of each identified and not identified components in grain at normal harvest were ≤0.001 mg/kg except of UR-50604 quantified at 0.011 mg/kg (phenoxy-label). Maximum residues in straw were found at up to 0.35 mg beflubutamid/kg representing the highest level of all identified and not identified analytes.

Beflubutamid was shown to be metabolised via C-N cleavage, generating the breakdown products UR-50604 and UR-50624 and via hydroxylation of the benzylamine ring at the 2, 3 and 4 positions. The unknown component U1, a phenoxy metabolite, is thought to be related to UR-50604, and was determined to be polar and water soluble.

UR-50604 is of no toxicological significance as it is present in the rat metabolism study with beflubutamid (up to 31 % excreted in urine). The other identified metabolites UR-50624, UR-50617 and UR-50618, both hydroxylated at the benzylamine ring of beflubutamid, were all found in the rat and are not considered to be of toxicological concern. Furthermore, U1 from the rotational crop study, is considered to be a derivative or conjugate of UR-50604 and therefore not considered to be of toxicological concern. Thus, beflubutamid is considered to be the residue of concern and included in the residue definition as the only analyte.

B.7.16.2 Metabolism in livestock

The metabolism of beflubutamid in the **lactating goat** has been investigated using either [ring-UL-^{14}C-phenoxy] or [ring-UL-^{14}C-benzylamine] labelled material. The administered dose was equivalent to an intake of diet containing residues of approximately 10 mg/kg feed (dry matter).

The majority of the radioactivity was rapidly excreted, primarily with the urine and faeces.

Minimal residues were found in milk and meat. The total daily residue in milk reached a peak in the benzylamine labelled milk in the Day 5 pm milk sample. The major residues were found in the liver and kidneys and the benzylamine labelled fat sample. The difference in radioactive concentration between the phenoxy and benzylamine labelled fat samples was not due to different metabolite residues as almost all the radioactivity was present as beflubutamid.

The metabolic profile was very similar in urine, faeces, milk, liver and kidney.

The major metabolites detected were UR-50604 (urine, milk, liver and kidney); hippuric acid (urine, milk, liver and kidney); UR-50617 and its conjugate (urine, faeces, milk, liver and

kidney) and UR-50618 and its conjugate (urine, faeces, liver and kidney). The only significant radioactive component in fat was parent beflubutamid and this was also the major component in milk.

The metabolic pathway in the goat seems comparable to the rat, although the rat shows more extensive degradation. Therefore, beflubutamid again is considered to be the residue of concern.

B.7.16.3 Toxicological significance of non-mammalian metabolites

Of the metabolites found in the plant metabolism and succeeding crop rotation studies, only U1 is a non-mammalian metabolite. U1 is polar, water soluble and probably a stable conjugate or derivative of UR-50604. It was found at very low levels (0.007 mg/kg) in the grain in the plant metabolism study and as such is considered to be of no toxicological significance.

B.7.16.4 Residues in cereals

A program of a total of 18 residue trials (decline studies and residue data at harvest) was conducted over a 3 year period (1997-1999) on cereals (spring barley, spring wheat, durum wheat, and winter wheat). The locations of the trials covered both the northern (DE) and the southern part (ES, IT) of Europe.

The formulations used in all of the trials were ASU 95 510 H SC formulations, nominally containing 85 g/l UBH-820 and 500 g/l isoproturon. The trials were carried out to cover the maximum use rate of the product, which is one application of 3 l/ha at the latest timing of the growth stage of BBCH 29.

In all cases the residues of beflubutamid and its metabolite UR-50604 in grain and straw were <LOQ of 0.05 mg/kg at harvest. These residue results from wheat and barley are considered equally applicable to the other cereal crops recommended on the label, since application is only made at early growth stages up to BBCH 29 at the latest.

B.7.16.5 Storage stability

Studies were conducted to assess the stability of beflubutamid and UR-50604 in green plant material, grain and straw during freezer storage at the analytical facility prior to analysis.
These studies showed that there was insignificant degradation of both the parent and metabolite residues over the freezer storage period. Also, the length of the storage time for all of the residue samples did not exceed the length of time of proven stability under those conditions.

B.7.16.6 Residues in succeeding crops

In a confined rotational crop study wheat and carrots were treated with phenoxy-labelled beflubutamid at an application rate of 255 g as/ha. In the soil major residues at the time of sowing of the rotational crops were beflubutamid, UR-50604 and UR-50624. The transition factors for carrot determined for foliage and root at normal harvest indicate very little uptake of soil residues of beflubutamid. Also, at normal harvest transition factors for wheat

determined for husks, straw and grain indicate that there is very little uptake of residues into grain from the soil and some uptake of residues of beflubutamid from the soil into husks and straw. Analysis of plants at early and normal harvest showed that soil residues taken up by the plant had been transformed almost completely to a single polar, water soluble metabolite U1. This was present at levels of less than 0.05 mg/kg in carrot foliage and carrot root. In wheat, levels of U1 were in the range of 0.05 - 0.101 mg/kg in husks and straw and <0.01 mg/kg in grain. U1 was not readily hydrolysed by enzymes, and not further degraded by mild acid and base treatments or derivatised to a more mobile residue. U1 does not contain the benzylamine moiety and although there is no direct evidence, U1 is possibly a stable conjugate or derivative of UR-50604.

B.7.16.7 Maximum residue levels, pre-harvest interval and health risk assessment

The MRL for beflubutamid is proposed at the LOQ of the analysis method of 0.05 mg/kg.

The pre-harvest interval is dependent on growing conditions between application and harvest. The latest time of application is BBCH 29. From the trials conducted it would appear that this period is unlikely to be less than 66 days before harvest of cereals.

Consumer intake levels were estimated using the proposed MRL values derived from supervised residue trials conducted in accordance to the critical identified GAP. Using the German and European diet there appears to be no concern with regard to dietary intake of beflubutamid, with the TMDI being 8.3 % or 4.7 % of the ADI, respectively.

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-6.1; AIIIA-8.1	Haynes, L.M., Knight, L.J.L., Mayo, B.C.	2000	UR-50601 Metabolism in wheat (main study). UBE 66/974473 GLP, unpublished RIP2000-1890	Y	UBE
AIIA-6.1; AIIIA-8.1	McEwen, A.B., Mellor, S.J., Knight, L.J.L., Mayo, B.C.	1998	UR-50601 Metabolism in wheat (pilot study). UBE 037/973537 GLP, unpublished RIP2000-1891	Y	UBE
AIIA-6.2; AIIIA-8.1	Elsom, L.F.	1998	C14-UR-50601 Metabolism in the lactating goat. UBE 55/973900 GLP, unpublished RIP2000-1892	Y	UBE

[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-6.3; AIIIA-8.2	Brielbeck, B., Marx, D.	2000	Final Report AB 95510-RU-010D Residue Analysis for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Spring cereals (Green plants, Grain and Straw) after Treatment with 3 l/ha ASU 95510 (85 g/l UBH-820 (UR-50601) + 500 g/l Isoproturon) at Spring 1999 Protocol No.: 95510-RU-010D Study No.: RU0798. AB 95510-RU-010D GLP, unpublished RIP2000-1895	Y	ASU
AIIA-6.3; AIIIA-8.2	Brielbeck, B., Marx, D.	1999	Final Report AB 95510-RU-010C Residue Analysis for the Determination of UBH-820 (UR-50601) and its Metabolite UR-50604 in Summer cereal (Green plant, Grain and Straw) and Winter cereal (Green plant, Grain and Straw) after Treatment with 3 l/ha ASU 95510 H (85 g/l UBH-820 (UR-50601) + 500 g/l Isoproturon) at Spring 1998 Protocol No.: 95510-RU-010C Study No.: RU0789. AB 95510-RU-010C GLP, unpublished RIP2000-1894	Y	ASU
AIIA-6.3; AIIIA-8.2	Brielbeck, B., Marx, D.	1998	Final Report AB 95510-RU-010 Residue Analysis of UBH-820 in Cereals (Harvest Values) Protocol No.: 95510-RU-010 Study No.: RU0497. AB 95510-RU-010 GLP, unpublished RIP2000-1893	Y	ASU
AIIA-6.6; AIIIA-8.5	Mellor, S.J., Mayo, B.C.	2000	UR-50601 Confined accumulation in rotational crops. UBE 083/992872 GLP, unpublished RIP2000-1897	Y	UBE

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
UBE: UBE Industries

Annex B

Beflubutamid

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

G.M. Dean (1997): UR-50601: Aerobic soil metabolism (pilot study), report no. UBE 036/97729, BOD2000-1131

Data requirement: Not designed to fulfil any regulatory requirements
GLP: Yes

The study was designed to obtain **preliminary** information on the degradation of UR-50601 in soil. The test soil was a sandy loam (pH 5.8, organic matter content 2.8%). Soils were treated separately with [ring-U-14C-phenoxy] and [ring-U-14C-benzylamine]UR-50601 at an application rate of 0.255 ppm; equivalent to a rate of use of approximately 255 g ai/ha. Soils were incubated under aerobic conditions at 20°C and 40% maximum water holding capacity for up to 31 days after test substance application.

UR-50601 was degraded in soil with an estimated DT50 of 5 days and DT90 of 15 days. Mineralisation to 14C-carbon dioxide was a major route of degradation. Up to 22% and 46% applied radioactivity (%AR) was attributable to carbon dioxide after 31 days from both radiolabelled compounds. An organic volatile component representing up to 5.6 % and 01 % AR was traped by ethyl digol from soils treated with [ring-U-14C-phenoxy]UR-50601 and [ring-U-14C-benzylamin]UR-50601 respectively.

Extractability of radioactivity from soil treated with both radiolabels declined from being quantitative at zero time to ca 14% AR after 31 days. The non-extactable or bound residue increased to ca 50% Ar over the same period. The bound radioactivity was shown to be associated with the three soil fractions; humin, humic acid and fulvic acid in very similar proportions.

In soils treated with [ring-U-14C-phenoxy]UR-50601 one major product was extracted and identified as a phenoxy butyric acid, (UR-50604). This component increased to a maximum 26% AR at 7 days before declining to 7% AR after 31 days. A second minor product, representing a maximum of 6% AR was also identified as the phenoxy butanamide (UR-50624). IN soil treated with [ring-U-14C-benzylamine]UR-50601 no major degradation products were detected in extracts of soil. A small amount of polar radioactivity (<2% AR) was detected.

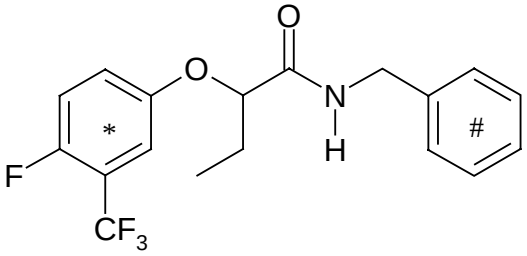
Comment: The study is not acceptable to fulfil data requirements because it is only a prestudy. The corresponding main study see below (G.M.Dean, E. Goslan and B.C. Mayo (1999)(BOD2000-1132).

G.M. Dean, E. Goslan, B.C. Mayo (1999): UR-50601: Aerobic soil metabolism (main study); report no. UBE 67/983000, BOD2000-1132

Guidelines: SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 1.1; US EPA, 1982, Pesticide Assessment Guidelines, Subdivision N, 162-1.

Deviations – none
GLP: Yes

Test system
The rate of degradation of UR-50601 was studied in Arrow sandy loam soil. See Table B.8.1-1 for test soil characteristics. Separate samples of test soil were allowed to acclimatise in darkness under test conditions for at least 7 days prior to test substance application. Soils were treated separately with [ring-U-^{14}C-phenoxy]UR-50601 and [ring-U-^{14}C-benzylamine]UR-50601 (see below) at an application rate of 0.255 ppm; equivalent to a use rate of approximately 255 g ai/ha.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601
# Position of radiolabel in [ring-U-^{14}C-benzylamine]UR-50601
[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >97%, Specific activity: 1.63GBq/mmole.
[Ring-U-^{14}C-benzylamine]UR-50601: Batch number: CFQ9258, Radiochemical purity: >97%, Specific activity: 1.63GBq/mmole

Treated soils were incubated under aerobic conditions in darkness at *ca* 20°C and 40% maximum water holding capacity for up to 152 days after application. Samples were taken for analysis at 0, 1, 3, 7, 14, 31, 60, 90, 119 and 152 days for each radiolabelled test substance. Soil extracts were analysed by chromatography (HPLC and TLC) to assess the proportions and nature of any degradation products. Radiolabelled volatile degradation products were trapped and quantified. Additional soil samples were set up to determine microbial biomass at the beginning and after 119 and 180 days and for treatment at exaggerated rate to enable metabolite identification.

Table B.8.1-1: Characteristics of the test soil

Parameter	Arrow (7/597A)
Particle size distribution (%)[a]:	
International standard	
Clay (<2 μm)	11.94
Silt (2-63 μm)	22.44
Sand (63 μm – 2mm)	65.62
Textural class	Sandy loam
USDA standard	
Clay (<2 μm)	11.58
Silt (2-53 μm)	21.19
Sand (53 μm – 2mm)	67.23
Textural class	Sandy loam
Organic carbon (%)[a]	2.2
Soil pH (1:5 v/v in water)[a]	7.1
Soil pH (0.01 M $CaCl_2$)[a]	6.3
Zero time biomass (μg C/g soil dry weight)[b]	363
Day 119 biomass (μg C/g soil dry weight)[b]	260
Terminal biomass (μg C/g soil dry weight)[b]	nr
Aerobic bacteria (cfu/gram)[c]	6.20×10^7
Aerobic spore forming bacteria (cfu/gram)[c]	4.60×10^5
Actinomyctes (cfu/gram)[c]	3.90×10^6
Fungi (cfu/gram)[c]	1.00×10^4

[a]: Determined by Soil Survey and Land Research Centre; [b]: Determined by Chemex International plc; [c]: Determined by Department of Microbiology at HLS; cfu: Colony forming units; nr: No valid result obtained.

Findings

Recovery of radioactivity from all samples in both treatment groups was in the range 93.2 – 109% applied radioactivity (except day 119 [ring-U-^{14}C-benzylamine]UR-50601 which was 88.4% applied radioactivity). See Table B.8.1-2.

Mineralisation to ^{14}C- carbon dioxide was a major route of degradation. Up to 24.7% and 55.1% applied radioactivity was attributable to carbon dioxide from [ring-U-^{14}C-phenoxy]UR-50601 and [ring-U-^{14}C-benzylamine]UR-50601 treated soils respectively. Neutral organic volatile radioactivity representing up to 3.2% applied radioactivity was trapped from soils treated with [ring-U-^{14}C-phenoxy]UR-50601. Extractability from soil with both labels declined from being quantitative at zero time to 12 – 15.9% applied radioactivity after 152 days. The bound residue increased to a maximum of 50.5% and 40.8% in soil treated with [ring-U-^{14}C-phenoxy]UR-50601 and [ring-U-^{14}C-benzylamine]UR-50601 respectively. This bound activity was shown to be associated with humin, humic acid and fulvic acid fractions in the ratio 1.1-1.3:1:1.5-1.9.

The dissipation of UR-50601 in all soils showed a bi-phasic decline. The data were fitted to a two compartment model described by a bi-exponential equation of the form:

$$R = A \cdot e^{-a \cdot t} + B \cdot e^{-b \cdot t}$$

Where R is % UR-50601, t is time in days and A,B, a and b are constants describing the decay curve. The model was fitted to the data using a weighted least squares algorithm with the weighting factor equal to $1/R^2$.

UR-50601 was degraded with an estimated DT_{50} of 5 days and DT_{90} of 179 days (mean quantities extracted from soil). Correlation coefficient: 0.99.

In soils treated with [ring-U-^{14}C-phenoxy]UR-50601 one major degradation product was identified as phenoxybutyric acid (UR-50604) (see Table B.8.1-3). This increased to a maximum of 26.1% applied radioactivity after 7 days, it remained at about this level up to 90 days before declining to 1.8% after 152 days.

Pseudo-first order reaction kinetics were assumed for the decline of the major metabolite UR-50604 in soil over the time period of the calculation:

$R=A \cdot e^{-a \cdot t}$

with a: rate constant, R: % UR-50604, A AA e : maximum % UR-50604, t time. The DT50 and DT90 for UR-50604 were calculated from the following equations:
DT50= ln 2 / a ; DT90=ln10/a.

The DT_{50} and DT_{90} values for UR-50604 were determined to be 17 and 55 days respectively taking into account values from the 90 – 152 day data. Correlation coefficient: 0.99. -Both S and R isomers of UR-50604 were shown to be present in soil extracts in a ratio of approximately 3 : 7 from day 31 onwards.

A second minor product, representing a maximum of 6.1% applied radioactivity after 14 days was identified as phenoxybutanamide (UR-50624). A transient degradation product, U1 was present in soils treated with both labels. U1 was only detected in significant quantities (10.7% applied radioactivity) 7 days after application before rapidly declining to ≤1.0% after 31 days in [ring-U-^{14}C-phenoxy]UR-50601. In soil treated with [ring-U-^{14}C-benzylamine]UR-50601, unchanged UR-50601 was the only major extractable component. U1 reached a maximum of 11.3% applied radioactivity after 7 days and was not detected 60 days after application.

A proposed degradation pathway for UR-50601 is shown in Figure B.8.1-1.

Table B.8.1-2: Extraction and recovery of radioactivity from Arrow soil after application of UR-50601

Time after application (days)	Results expressed as % applied radioactivity								
	Ring-U-^{14}C-phenoxy					Ring-U-^{14}C-benzylamine			
	Extracts	Not extracted	Volatiles		Total recovery	Extracts	Not extracted	Volatiles CO_2	Total recovery
			Organic[a]	CO_2					
0	98.6	1.4	ns	ns	100	102	0.9	ns	103
1	101	3.4	nd	0.3	105	99.6	4.9	2.3	107
3	96.4	6.9	0.1	1.1	105	82.0	9.4	9.7	101
7	93.6	9.6	0.6	3.7	108	61.1	22.6	25.5	109
14	60.0	32.9	1.9	7.5	102	26.3	40.8	37.3	104
31	51.1	39.9	2.6	10.4	104	24.3	39.5	43.1	107
60	45.2	39.9	3.0	12.5	101	26.7	22.6	47.0	96.3
90	57.8	29.0	3.2	14.2	104	22.7	26.3	49.4	98.4
119	26.1	47.2	3.0	22.4	98.7	11.6	23.5	53.3	88.4
152	15.9	50.5	3.0	24.7	94.1	12.3	25.8	55.1	93.2

ns: No sample; nd: Not detected (gross counts less than twice background); [a]: Organic volatiles measured in extracts of ethyl digol.

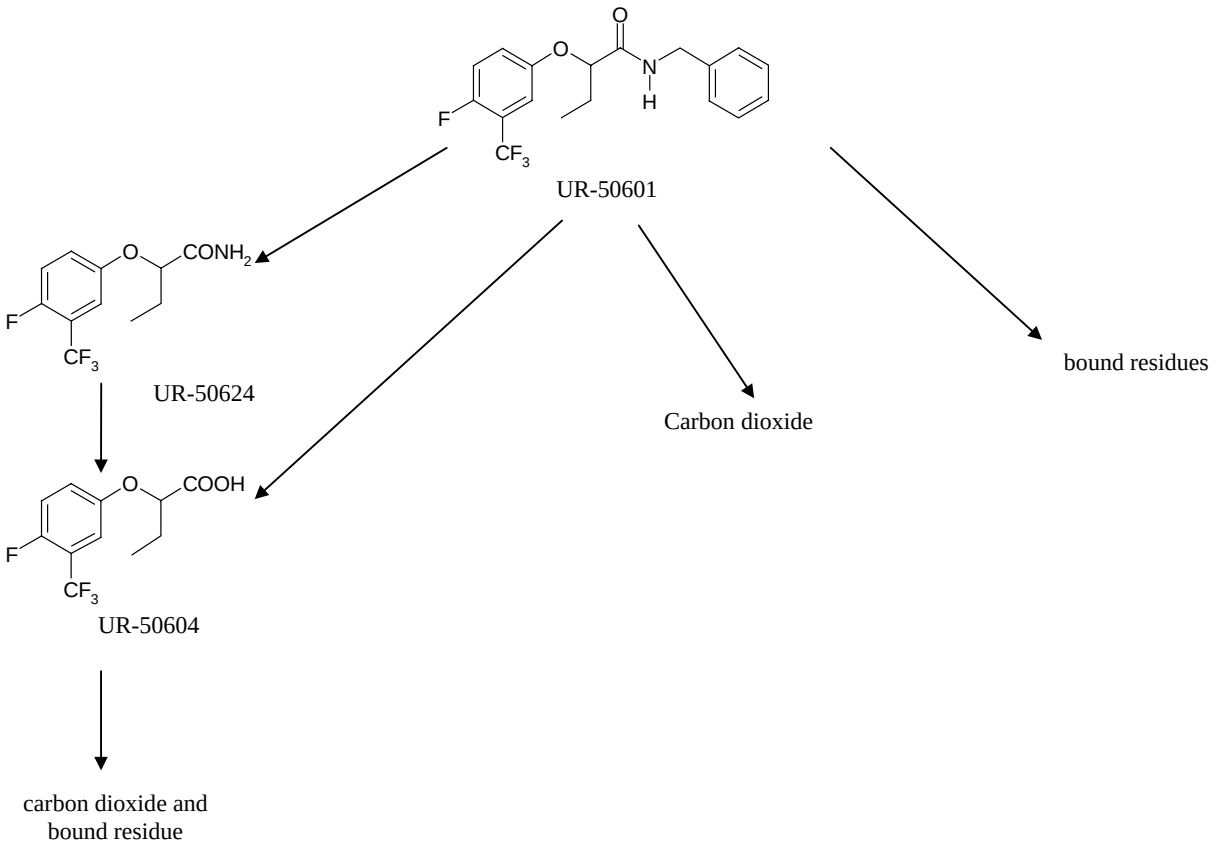
Table B.8.1-3: Proportions of radioactive components in extracts of Arrow soil after application of UR-50601

Radioactive component	Results expressed as % applied radioactivity									
	Time (days after application)									
	0	1	3	7	14	31	60	90	119	152
[Ring-U-^{14}C-phenoxy]										
U1	0.3	<0.2	<0.4	10.1	1.2	1.0	0.8	0.5	1.0	<0.5
UR-50604	0.3	2.3	12.7	26.1	19.8	23.6	18.9	24.3	7.0	1.8
UR-50624	<0.2	0.5	1.4	5.4	6.1	3.0	2.5	3.8	1.3	<0.5
U2	<0.2	<0.2	<0.4	<0.4	<0.4	<0.4	0.5	2.0	<0.3	<0.5
UR-50601	96.9	97.1	79.1	49.5	30.4	21.3	19.9	24.9	14.3	12.9
Others	1.0	<0.2	<0.4	<0.4	<0.4	<0.4	<0.3	<0.4	<0.3	<0.5
[Ring-U-^{14}C-benzylamine]										
U1	0.3	<0.2	<0.3	11.3	1.1	0.7	<0.3	<0.3	<0.4	<0.4
U2	<0.2	<0.2	<0.3	<0.4	<0.4	<0.4	<0.3	2.0	<0.4	<0.4
UR-50601	100	97.4	79.8	46.7	24.4	21.7	24.3	18.6	10.0	10.9
Others	1.4	1.9	<0.3	<0.4	<0.4	<0.4	<0.3	<0.3	<0.4	<0.4

Others: Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks.

Comment: The study is acceptable.
The metabolite UR-50604 was formed and degraded during the study period. The calculation of DT_{50} values ist not well documented. The calculation presented for the metabolite takes into account the last three measurements, but it is not clear if the starting maximum point is an outlier or not. Therefore, the corresponding DT_{50} value is not considered for evaluation.

Figure B.8.1-1: Proposed degradation pathway of UR-50601 in aerobic soil



G.M. Dean, B.C. Mayo (1999): UR-50601: Rate of degradation in three soils, report no. UBE 071/982852, BOD2000-1135

Remark: Although this study was conducted to determine the rate of degradation in soil there are also information regarding route of degradation (mineralisation, non-extrable residues, occurence of metabolites) in soil. Therefore, this study is reported here for both route and rate of degradation.

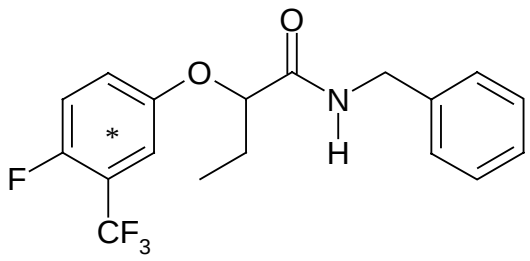
Guidelines: SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 1.1

Deviations – none

GLP: Yes

Test system

The rate of degradation of UR-50601 was studied in three different soils at 20°C and one soil at 10°C. See Table B.8.1-4 for test soil characteristics. Separate samples of test soil were allowed to acclimatise in darkness under test conditions for at least 7 days prior to test substance application. Soils were treated separately with [ring-U-^{14}C-phenoxy]UR-50601 (see below) at an application rate of 0.255 ppm; equivalent to a use rate of approximately 255 g ai/ha.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >97%, Specific activity: 1.63GBq/mmole.

Only UR-50601 uniformly labelled with carbon-14 in the phenoxy ring was used, because studies using UR-50601 uniformly labelled with carbon-14 in the benzylamine ring showed that this portion of the molecule was degraded to a non-extractable fraction and carbon dioxide.

Treated soils were incubated under aerobic conditions in darkness at 40% maximum water holding capacity for up to 120 days after application. Samples were taken for analysis at 0, 1, 3, 7, 14, 30, 59 and 120 days for each soil. Soil extracts were analysed by chromatography (HPLC and TLC) to assess the proportions and nature of any degradation products. Radiolabelled volatile degradation products were trapped and quantified. Additional soil samples were set up to determine microbial biomass at the start and at the end.

Table B.8.1-4: Characteristics of the test soil

Soil	**Wick (28/897A)**	**Speyer 2.2 (18/797B)**	**Evesham 3 (8/997A)**		**Speyer 2.2 (20/598A)**
Particle size distribution (%): International standard					
Clay (<2 µm)	11.95	7.35	31.92		8.09
Silt (2-63 µm)	19.45	15.45	33.27		14.64
Sand (63 µm – 2 mm)	68.59	77.20	34.81		77.26
Textural class	Sandy loam	Loamy sand	Clay loam sand		Loamy sand
Organic carbon (%)[a]	1.0	1.8	2.4		2.8
Organic matter (%)[b]	1.7	3.1	4.1		4.8
Soil pH (1:5 v/v in water)[a]	5.4	6.3	7.8		6.1
Soil pH (0.01M $CaCl_2$)[a]	4.6	5.7	6.8		5.9
	20°C	20°C	20°C	10°C	20°C
Initial biomass	302[c]	251[c]	892[c]	836[c]	933[a]
Terminal biomass[a]	83	195	485	571	150

[a]: Determined by Soil Survey and Land Research Institute; [b]: Organic matter calculated as organic carbon x 1.72;
[c]: Determined by Chemex International plc.

Findings

Recovery of radioactivity from all soils was in the range 92.5 – 108% applied radioactivity. See Table B.8.1-6.

Mineralisation to ^{14}C- carbon dioxide was a major route of degradation. Up to 46.8% applied radioactivity was attributable to carbon dioxide in the Wick soil. Organic volatile radioactivity representing up to 6.9% applied radioactivity was trapped from the different soils. Extractability from all soils declined from being quantitative at zero time to 5.2 –

53.5% applied radioactivity after 120 days. The bound residue increased to a maximum of 32.7% - 49.8% after 120 days.

UR-50601 was degraded at 20°C with an estimated DT_{50} between 5 and 118 days and a DT_{90} between 16 days and >1 year. The first experiment with Speyer 2.2 soil showed a quite slow rate of degradation (DT50 118 days). Therefore the second experiment was carried out with Speyer 2.2 soil where an increased rate of degradation was observed. This increased degradation may be attributed to the higher initial soil microbial biomass compared to that in the first experiment. Nevertheless, the results of the first experiment are also taken into account because this study also fully comply with the requirements for conductance in Annex II and Annex III and the corresponding guidelines.
UR-50601 was degraded more slowly at 10°C with an estimated DT_{50} of 20 days and DT_{90} of 182 days (calculated using a bi-exponential equation) (see Table B.8.1-5). There was no correlation between degradation values and any soil properties. All data were described by an equation of the form $R = A \cdot e^{-a \cdot t} + B \cdot e^{-b \cdot t}$ (second order kinetics, see study above). Correlation coefficients: 0.9951, 0.9941, 0.9940, 0.9961 and 0.9993.

In all soils one major degradation product was identified as phenoxybutyric acid (UR-50604) (see Table B.8.1-7). This increased to a maximum of 22.1% applied radioactivity after 7 days in the Evesham 3 soil, it declined rapidly to 1% after 30 days. In order to determine DT_{50} and DT_{90} values for this degradate simple pseudo first-order kinetics were assumed for the decline phase (7-30 days for the Wick and Evesham 3 soil at 20°C and 30-120 days for the Evesham 3 at 10°C). It should be stressed that this model does not account for any formation of UR-50604 over this period and therefore probably gives an overestimate of the actual DT_{50} and DT_{90} values. The DT_{50} values for UR-50604 were determined to be 5.7 and 5.0 days at 20°C and 80 days at 10°C. The DT_{90} values were 17 and 19 days at 20°C and 265 days at 10°C.

A second minor product, representing a maximum of 6.7% applied radioactivity after 14 days in the Evesham 3 soil was identified as phenoxybutanamide (UR-50624). A transient degradation product, P1 was present in all soils, with a maximum of 3.2% after 30 days in Wick soil. A proposed degradation pathway for UR-50601 under aerobic conditions is shown in Figure B.8.1-1.

Table B.8.1-5: DT_{50} and DT_{90} of UR-50601 and UR-50604

Group	Soil	Temperature (°C)	UR-50601		UR-50604		Period of calculation (days)
			DT_{50}	DT_{90}	DT_{50}	DT_{90}	
A	Wick	20	5	16	6	19	7-30
B[1]	Speyer 2.2	20	118	>1 year	nc	nc	
E[2]	Speyer 2.2	20	12	>1 year	nc	nc	
C	Evesham 3	20	8	62	5	17	7-30
D	Evesham 3	10	20	182	80	265	30-120

nc: not calculated; [1]: The 1st experiment with Speyer 2.2 soil showed a quite slow rate of degradation, different from those of Wick and Evesham 3 soil. Therefore, the 2nd experiment was carried out; [2]: The 2nd experiment with Speyer 2.2 showed an increased rate of degradation. This increase may be attributed to the higher initial soil microbial biomass (ca 930 µg C/g) compared to that in the 1st experiment (ca 250 µg C/g). This difference is most noticeable in the initial phase of the bi-phasic degradation in all soils.

Table B.8.1-6: Extraction and recovery of radioactivity from different soils after application of UR-50601

Radioactive fraction		Results expressed as % applied radioactivity							
		Days after application							
		0[b]	1[b]	3	7	14	30	59	120
Wick soil (group A) at 20°C									
Extracts		98.9	96.0	86.7	58.6	18.3	8.7	6.8	5.2
Not extracted		1.6	3.9	10.0	35.6	43.3	47.0	40.6	49.8
Volatiles	Organic[a]	ns	<0.1	0.6	2.6	4.2	5.1	5.2	5.2
	CO_2	ns	0.4	2.5	11.4	26.7	36.4	41.3	46.8
Total recovery		101	100	99.8	108	92.5	97.2	93.9	107
Speyer 2.2 soil (group B) at 20°C									
Extracts		98.3	95.4	95.7	86.9	73.9	61.6	63.4	53.5
Not extracted		1.3	2.1	2.7	11.7	23.3	32.7	30.7	31.8
Volatiles	Organic[a]	ns	nd	nd	0.1	0.3	0.4	0.4	0.4
	CO_2	ns	0.1	0.3	1.5	4.7	7.6	9.8	12.2
Total recovery		99.6	97.6	98.7	100	102	102	104	97.9
Evesham 3 soil (group C) at 20°C									
Extracts		95.3	81.8	78.2	73.0	51.4	19.6	13.1	9.5
Not extracted		2.5	12.0	24.0	20.1	32.1	59.7	52.7	44.9
Volatiles	Organic[a]	ns	0.1	0.5	1.4	4.7	6.3	6.9	6.9
	CO_2	ns	0.5	2.1	6.4	12.1	20.6	27.1	31.9
Total recovery		97.8	94.4	105	101	100	106	99.8	93.2
Evesham 3 soil (group D) at 10°C									
Extracts		98.2	94.7	92.3	81.8	78.0	67.1	52.0	33.3
Not extracted		3.0	5.6	7.3	15.5	16.2	25.5	37.6	43.5
Volatiles	Organic[a]	ns	nd	<0.1	0.3	0.6	2.0	3.8	4.3
	CO_2	ns	0.1	0.4	1.1	2.6	4.0	7.8	15.6
Total recovery		101	100	100	98.7	97.4	98.6	101	96.7
Speyer 2.2 soil (group E) at 20°C									
Extracts		99.4	97.6	96.0	86.7	59.7	39.1	36.4	33.3
Not extracted		2.9	3.8	4.6	14.5	35.7	41.1	48.7	40.1
Volatiles	Organic[a]	ns	nd	0.1	0.4	1.1	1.8	1.9	1.9
	CO_2	ns	0.2	0.5	1.6	6.0	12.4	16.2	20.1
Total recovery		102	102	101	103	103	94.4	103	95.3

nd: Not detected; ns: No sample; [a]: Organic volatiles measured in ethyl digol; b: These samples were only extracted three times with acetonitrile:water (9:1 v/v).

Table B.8.1-7: Proportions of radioactive components in extracts of different soils after application of UR-50601

Radioactive component	Results expressed as % applied radioactivity							
	Days after application							
	0	1	3	7	14	30	59	120
Wick soil (group A) at 20°C								
P1	0.3	<0.3	<0.4	1.4	2.5	3.2	2.7	1.6
UR-50604	<0.2	3.1	8.3	13.7	4.8	0.8	<0.6	<0.4
UR-50624	<0.2	<0.3	3.3	1.8	1.3	<0.4	<0.6	<0.4
UR-50601	97.5	92.5	71.2	39.2	9.4	3.9	3.0	2.0
Others	<0.2	<0.3	<0.4	<0.4	<0.5	<0.4	<0.6	<0.4
Speyer 2.2 soil (group B) at 20°C								
P1	<0.3	<0.2	<0.4	<0.4	<0.4	1.0	<0.4	0.7
UR-50604	<0.3	0.4	3.6	9.0	7.0	3.7	3.7	3.5
UR-50624	<0.3	<0.2	<0.4	1.0	1.0	0.6	<0.4	0.4
UR-50601	96.1	94.7	90.0	76.0	63.2	54.6	57.4	48.0
Others	<0.3	<0.2	<0.4	<0.4	<0.4	<0.4	<0.4	<0.4
Evesham 3 soil (group C) at 20°C								
P1	<0.3	<0.2	<0.4	<0.5	<0.5	1.9	1.9	2.1
UR-50604	<0.3	2.2	9.1	22.1	12.9	1.0	<0.5	<0.4
UR-50624	<0.3	1.0	1.1	2.3	6.7	3.4	<0.5	0.7
UR-50601	94.9	77.1	64.4	46.9	30.4	12.7	9.8	5.2
Others	<0.3	1.4	<0.4	<0.5	<0.5	<0.5	1.0	<0.4
Evesham 3 soil (group D) at 10°C								
P1	0.4	<0.2	<0.4	<0.5	<0.7	<0.4	1.0	1.8
UR-50604	<0.3	1.2	2.9	7.4	18.6	21.9	19.3	10.3
UR-50624	<0.3	0.5	1.2	1.9	2.5	3.8	2.5	2.7
UR-50601	94.5	92.6	86.9	71.7	56.9	39.0	27.4	16.0
Others	2.7	<0.2	<0.4	<0.5	<0.7	<0.4	<0.5	<0.4
Speyer 2.2 soil (group E) at 20°C								
P1	0.5	<0.3	<0.4	<0.4	1.1	1.4	1.3	0.9
UR-50604	<0.2	0.9	6.3	14.9	12.0	3.5	3.1	2.6
UR-50624	<0.2	<0.3	<0.4	1.2	2.0	<0.4	<0.4	<0.4
UR-50601	99.0	95.9	87.2	69.4	42.1	31.8	31.2	25.7
Others	<0.2	<0.3	<0.4	<0.4	2.4	<0.4	<0.4	<0.4

Others: Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks.

Comment: The study is acceptable.

In all laboratory studies the metabolite UR-50604 was formed and degraded during the study periods. The calculations of DT_{50} values is not well documented. Both, the calculations for the Speyer 2.2 soils are based on first order kinetics but the concentrations after 30 days stay at a level of about 4 %. Consequently, the use of first order kinetic is not adequate and these DT_{50} values are also not considered for evaluation. Only the calculated DT_{50} values of teh Wick and Evesham3 soils are considered as valid although they may not represent worst case values.

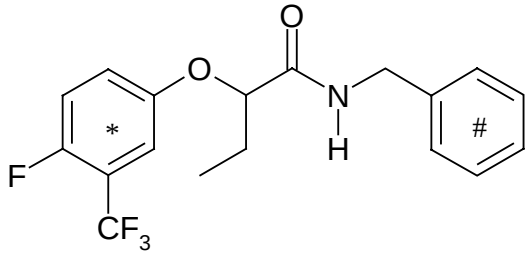
B.8.1.1.2 Supplemental studies

Anaerobic degradation

G.M. Dean, K.V. Batt, B.C. Mayo (1998); UR-50601: Anaerobic soil metabolism; report no. UBE 076/982926, BOD2000-1133

Guidelines: SETAC Procedure for assessing the environmental fate and ecotoxicity of pesticides, Section 1.2.
Deviations – none.
GLP: Yes

Test system
The rate of degradation of UR-50601 was studied in Arrow sandy loam soil (see Table B.8.1-8 for soil characteristics). Separate samples of the flooded test soil was allowed to acclimatise in darkness at *ca* 20°C under a flow of nitrogen for 28 days prior to test substance application, to establish anaerobic conditions in the soil and water. Soils were treated separately with [ring-U-^{14}C-phenoxy]UR-50601 and [ring-U-^{14}C-benzylamine]UR-50601 (see below) at an application rate of 0.25 ppm; equivalent to a use rate of approximately 255 g ai/ha.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601
# Position of radiolabel in [ring-U-^{14}C-benzylamine]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.
[Ring-U-^{14}C-benzylamine]UR-50601: Batch number: CFQ9258, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

Treated soils were incubated under anaerobic conditions in darkness at *ca* 20°C for up to 120 days after application. Samples were taken for analysis at 0, 3, 7, 14, 30, 62, 90 and 120 days for each radiolabelled test substance. Water and soil extracts were analysed separately by chromatography (HPLC and TLC) to assess the proportions and nature of any degradation products. Radiolabelled volatile degradation products were trapped and quantified. Additional soil samples were set up to determine microbial biomass at the beginning and end of the study and for the measurement of soil redox potential.

Table B.8.1-8: Characteristics of the test soil

Parameter	Arrow
Particle size distribution (%)[a]:	
ISO standard	
Clay (<2 μm)	11.18
Silt (2-63 μm)	22.54
Sand (63 μm – 2mm)	66.28
Textural class	Sandy loam
USDA standard[a]	
Clay (<2 μm)	11.22
Silt (2-53 μm)	21.17
Sand (53 μm – 2mm)	67.61
Textural class	Sandy loam
Organic carbon (%)[a]	1.8
Soil pH (1:5 v/v in water)[a]	5.8
Soil pH (1:5 v/v in 0.01 M $CaCl_2$)[a]	5.4
Initial biomass (μg C/g soil dry weight)[b]	148
Terminal biomass (μg C/g soil dry weight)[a]	142

[a]: Determined by Soil Survey and Land Research Centre; [b]: Determined by Chemex International plc.

Findings

Recovery of radioactivity from all samples in both treatment groups was in the range 90.3 – 98.3% applied radioactivity (see Table B.8.1-9).

Radioactivity in the water overlaying the test soil in both treatment groups initially declined rapidly, with less than 10% of the applied radioactivity remaining after 14 days. In the [ring-U-^{14}C-benzylamine]UR-50601 treatment, the level continued to decrease reaching 2.2% applied radioactivity after 120 days. In the [ring-U-^{14}C-phenoxy]UR-50601 treatment, due to the degradation of UR-50601 to the more water soluble degradate UR-50604 there was a slight increase in radioactivity.

In the total system UR-50601 was degraded slowly from a mean of 90.9% applied radioactivity at zero time to 64.4% after 120 days. Pseudo-first order reaction kinetics were assumed for the decline of the UR-50601 in water and water/soil test system. The DT_{50} value for the degradation of UR-50601 in anaerobic soil was estimated as approximately 260 days.

The DT_{50} and DT_{90} values for the decline of UR-50601 in the water phase were determined as 3.7 and 12 days respectively. Correlation coefficient 0.9927 and 0.9600 respectively.

HPLC and TLC analysis of the water and soil extracts showed the presence of one major degradate UR-50604, formed by the cleavage of UR-50601 and only found in samples treated with [ring-U-^{14}C-phenoxy]UR-50601. UR-50604 had increased to a maximum of 23.1% applied radioactivity after 120 days (see Table B.8.1-10). No significant extractable metabolites were found in the water or soil extracts from the [ring-U-^{14}C-benzylamine]UR-50601 treatment. Degradation products derived from this label appeared to be adsorbed to the soil and then mineralised to carbon dioxide (6.1% applied radioactivity after 120 days). No mineralisation was observed in the [ring-U-^{14}C-phenoxy]UR-50601 treatment.

A proposed degradation pathway for UR-50601 is shown in Figure B.8.1-2. Analysis of soil extracts showed that degradation maybe stereoselective with a larger proportion of the S-

isomer remaining after 62 days (S:R = 56.3:43.7). Non-extractable or bound residue increased to a maximum of 4.7% applied radioactivity (day 62) in [ring-U-^{14}C-phenoxy]UR-50601 treated samples whilst in samples treated with [ring-U-^{14}C-benzylamine]UR-50601 it increased with time to 11.2% (day 62) reaching 19.4% after 120 days. This non-extractable residue was distributed throughout the humin, humic acid and fulvic acid fractions in the ratio (at days 60 and 120) 5.8-5.9:1:2.0:2.1.

Table B.8.1-9: Extraction and recovery of radioactivity from Arrow soil after application of UR-50601

Radioactive component		Results expressed as % applied radioactivity							
		Days after application							
		0	3	7	14	30	62	90	120
[Ring-U-^{14}C-phenoxy]									
Water		78.9	22.3	13.9	7.3	7.8	6.1	8.9	10.0
Extracts		15.1	70.1	77.9	84.7	83.7	87.5	83.0	81.6
Not extracted		nd	0.6	1.6	2.2	2.9	4.7	3.1	4.1
Vola-tiles	Organic[a]	ns	nd	nd	nd	Nd	nd	<0.1	<0.1
	CO_2	ns	nd	nd	nd	Nd	nd	nd	nd
Total recovery		94.0	93.0	93.4	94.2	94.4	98.3	95.0	95.7
[Ring-U-^{14}C-benzylamine]									
Water		79.0	22.3	12.8	6.0	4.5	4.2	2.6	2.2
Extracts		13.6	69.3	76.1	83.0	82.5	78.4	72.8	64.4
Not extracted		nd	1.0	1.4	4.3	6.9	11.2	15.4	19.4
Vola-tiles	Organic[a]	ns	nd	nd	nd	nd	nd	nd	nd
	CO_2	ns	nd	nd	nd	nd	0.2	1.8	6.1
Total recovery		92.6	92.6	90.3	93.3	93.9	94.0	92.6	92.1

nd: Not detected; ns: No sample; [a]: Organic volatiles measured in extracts of polyurethane foam bungs and ethyl digol.

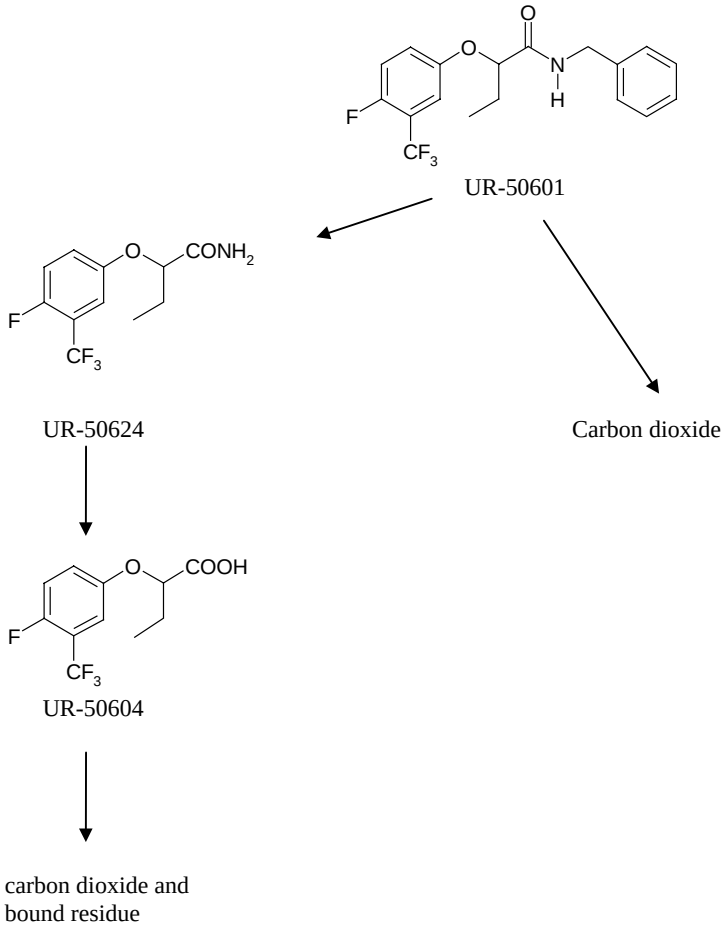
Table B.8.1-10: Proportions of radioactive components in anaerobic Arrow soil and overlying water after application of UR-50601: total soil extracts and water

Radioactive component	Results expressed as % applied radioactivity							
	Days after application							
	0	3	7	14	30	62	90	120
[Ring-U-^{14}C-phenoxy]								
P1		<0.4	<0.4	0.5	<0.3	<0.3	<0.5	<0.4
P2	-	0.4	1.0	0.4	1.0	1.1	<0.5	<0.4
UR-50604	0.4	0.5	2.3	4.0	8.1	12.2	18.3	23.1
UR-50624	<0.3	<0.4	<0.4	<0.4	0.5	<0.3	<0.5	<0.4
UR-50601	91.9	87.1	86.9	85.6	79.1	78.3	70.7	66.0
Others	<0.3	<0.4	<0.4	<0.4	<0.3	<0.3	<0.5	<0.4
[Ring-U-^{14}C-benzylamine]								
B1	<0.2	<0.4	0.6	1.1	0.8	1.5	1.2	0.7
B2	0.6	0.4	0.8	1.1	2.3	2.9	1.3	1.0
B3	0.2	0.4	0.5	0.4	0.7	1.0	1.5	0.6
UR-50601	89.8	88.1	83.7	85.9	82.4	74.3	66.9	62.8
Others	1.4	0.6	<0.3	<0.4	<0.4	2.7	4.4	<0.3

Others: Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks.

Comment: The study is acceptable.

Figure B.8.1-2: Proposed degradation pathway for UR-50601 in anaerobic soil

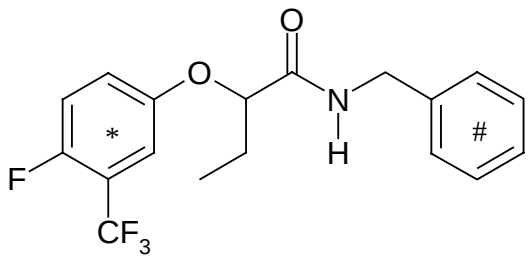


Soil photolysis

S.J. Mellor, K.V. Batt, G.M. Dean, B.C. Mayo (1998): UR-50601: Soil photolysis; report no. UBE 077/983818, BOD2000-1134.

Guidelines: SETAC, Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 2.
Deviations – none.
GLP: Yes

Test system
The photodegradation of UR-50601 was studied on thin layers (*ca* 2mm) of Arrow sandy loam soil (see Table B.8.1-11 for soil characteristics). Two different radiolabelled forms of the test material was used:



*Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601
Position of radiolabel in [ring-U-^{14}C-benzylamine]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

[Ring-U-^{14}C-benzylamine]UR-50601: Batch number: CFQ9258, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole

The test material was applied to the soil thin layers at a concentration of 2.5 µg/cm^2. This equates to a field rate of 255 g a.i./ha. The thin layers of soil were continuously irradiated, using a xenon arc light source for up to 10 days at *ca* 20°C. Control soil thin layers were incubated in darkness. Humidified air was passed over irradiated/incubated soil thin-layers and passed into a series of trapping solutions and polyurethane foam bungs to trap any volatiles evolved. For each radiolabelled form of UR-50601, duplicate irradiated and non-irradiated soil plates were taken for analysis at 1, 2, 3, 5, 7, and 10 days after test substance application. Duplicate plates were taken for analysis immediately after test substance application and provided a zero-time sample for both irradiated and non-irradiated experiments. HPLC and TLC investigated the proportions and identities of degradation products in soil extracts.

Table B.8.1-11: Characteristics of the test soil

Parameter	**Arrow (batch 16/1297A)**	
Particle size distribution (%)[a]:		
International standard		
Clay (<2 µm)	11.4	
Silt (2-63 µm)	22.8	
Sand (63 µm – 2mm)	65.9	
Textural class	Sandy loam	
Organic carbon (%)[a]	2.3	
Organic matter (%)[b]	4.0	
Soil pH (1:5 v/v in water)[a]	6.2	
Soil pH (1:5 v/v in 0.01 M $CaCl_2$)[a]	5.7	
	^{14}C-phenoxy	^{14}C-benzylamine
Bacteria (cfu/gram)[c]	6.15 x 10^6	9.75 x 10^6
Bacterial spores (cfu/gram)[c]	8.40 x 10^5	6.55 x 10^5
Actinomycetes (cfu/gram)[c]	1.08 x 10^6	3.00 x 10^6
Fungi (cfu/gram)[c]	3.95 x 10^4	2.90 x 10^4

[a]: Determined by Soil Survey and Land Research Centre; [b]: Organic matter calculated as organic carbon (%) x 1.72; [c]: Colony forming unit determined by the microbiology department at HLS prior to test substance application.

Findings

The recovery of radioactivity from irradiated soil plates was in the range of 92.8 – 110% applied radioactivity, and from dark control plates in the range of 91.8 – 112% applied radioactivity. After 10 days of irradiation UR-50601 accounted for 73.1 – 77.9% of applied radioactivity, the amount of $^{14}CO_2$ evolved from either radiolabelled form during the 10 day period represented a maximum of 5.7% applied radioactivity and on non-irradiated soil <0.5% (see Table B.8.1-12).

The quantitiy of unchanged test substance remaining in irradiated soil declined in a bi-phasic manner. Data were fitted to a two compartment model described by a bi-exponential equation of the form:

$$C_t = A \cdot e^{-a \cdot t} + B \cdot e^{-b \cdot t}$$

where Ct is the % UR-50601 at time t and A,B,a and b are constants describing the decay curve.

On irradiated soil, UR-50601 was degraded with a DT_{50} and DT_{90} equivalent to 324 days and 1271 days of natural sunlight at latitude 40°N assuming 12 hours of daylight. Correlation coefficient 0.9733. There was essentially no degradation of UR-50601 on non-irradiated soil (UR-50601 after 10 days: 93.7%).

The major degradation product extracted from irradiated soil treated with [ring-U-^{14}C-phenoxy]UR-50601 was identified as phenoxybutanamide (UR-50624). After 10 days irradiation this represented 7.3 % of applied radioactivity. A minor component (UR-50604) representing 1.1% applied radioactivity was also detected. In irradiated soil treated with [ring-U-^{14}C-benzylamine]UR-50601 minor polar compounds were detected none of which represented more than 6.0% applied radioactivity (see Table B.8.1-13). A proposed degradation pathway for UR-50601 is shown in Figure B.8.1-3. Non extractable radioactivity after 10 days irradiation accounted for a maximum of 6.0% applied radioactivity from either radiolabelled forms and 3.1% in non irradiated soils

Table B.8.1-12: Recovery of radioactivity from irradiated soil following application of UR-50601

Nominal duration of irradiation (days)	Results are expressed as % applied radioactivity							
	[Ring-U-^{14}C-phenoxy]				[Ring-U-^{14}C-benzylamine]			
	Extracts	Volatiles	Residue	Total recovery	Extracts	Volatiles	Residue	Total recovery
0[a]	101	-	1.0	102	95.4	-	1.8	97.2
0[a]	98.0	-	0.8	98.8	94.7	-	2.1	96.8
1	92.2	0.4	2.5	95.1	106	0.4	3.5	110
1	93.0	0.4	2.8	96.2	94.0	0.4	3.3	97.7
2	94.5	0.9	5.6	101	91.3	0.9	4.3	96.5
2	93.6	0.9	6.8	101	102	0.9	4.7	108
3	95.5	1.1	6.5	103	91.6	1.5	3.7	96.8
3	99.7	1.1	7.9	109	91.3	1.5	4.7	97.5
5	96.3	1.8	4.8	103	84.8	2.7	5.7	93.2
5	95.9	1.8	3.8	102	91.0	2.7	4.9	98.6
7	86.5	2.5	3.8	92.8	85.7	3.8	5.6	95.1
7	92.1	2.5	3.7	98.3	86.6	3.8	5.4	95.8
10	93.9	5.7	4.0	104	87.7	5.2	6.0	98.9
10	92.4	5.7	4.0	102	83.3	5.2	6.0	94.5

[a]: Day 0 samples were not irradiated.

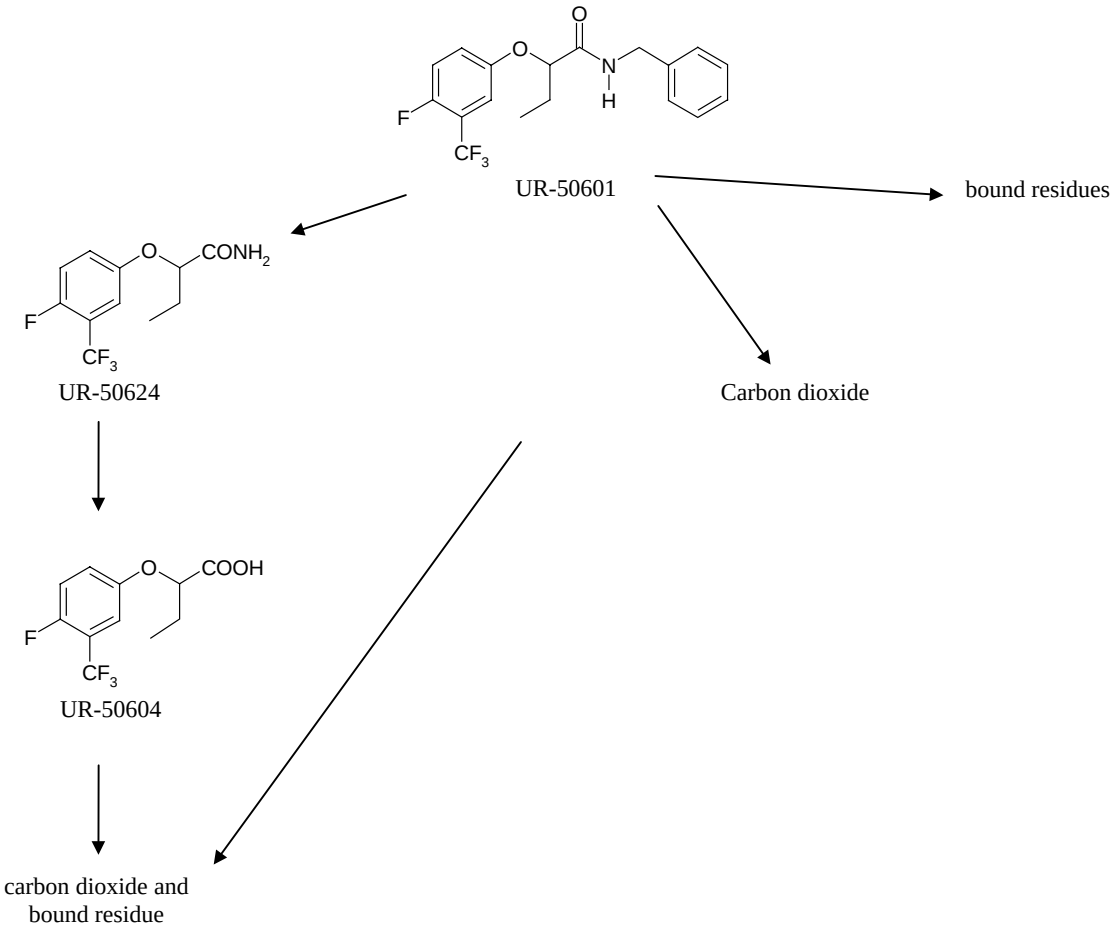
Table B.8.1-13: Quantities of radioactive components from irradiated soil after application of UR-50601

Radioactive component	Results are expressed as % applied radioactivity													
	Time after application in days													
	0[a]	0[a]	1	1	2	2	3	3	5	5	7	7	10	10
[Ring-U-^{14}C-phenoxy]														
P1	0.1	0.1	0.3	0.2	0.4	0.4	0.6	0.5	0.6	0.6	0.9	0.7	0.8	1.0
P2	0.4	0.3	0.4	0.4	0.5	0.4	0.5	0.5	0.5	0.4	0.4	0.5	0.4	0.5
UR-50604	<0.1	<0.1	0.6	0.5	0.9	0.8	1.0	1.0	1.1	1.1	1.0	1.0	0.9	1.2
UR-50624[b]	<0.1	<0.1	2.6	2.6	5.2	4.8	6.8	6.6	8.7	7.8	9.0	9.4	9.2	11.3
P3	0.4	0.4	1.5	1.4	2.3	2.2	2.6	2.4	2.3	1.8	1.8	1.6	1.0	1.4
UR-50601	99.2	96.2	85.8	86.8	83.9	83.6	82.7	87.2	82.1	83.1	72.0	77.6	80.4	75.4
P4	0.1	0.1	0.2	0.2	0.2	0.3	0.2	0.2	0.1	0.2	0.3	0.2	0.1	0.3
Others	<0.1	<0.1	0.8	1.0	1.2	1.2	1.2	1.4	0.9	1.0	1.2	1.1	1.0	1.4
[Ring-U-^{14}C-benzylamine]														
B1	0.1	<0.1	1.9	1.0	1.4	1.2	1.4	2.0	3.7	3.3	2.1	3.2	4.3	1.7
B2	0.7	0.8	2.3	2.5	3.6	3.8	3.9	3.9	5.0	4.7	6.0	5.5	4.8	7.2
B3	0.4	0.2	0.4	0.7	1.2	1.3	1.2	1.2	0.8	1.2	1.7	1.4	0.7	1.7
B4	0.2	0.2	1.6	1.2	1.5	1.4	0.8	1.2	1.7	1.3	0.8	1.0	0.5	0.7
B5	0.1	<0.1	0.4	0.3	0.5	0.5	0.4	0.3	0.3	0.5	0.3	0.4	0.2	0.3
B6	0.6	0.6	0.8	0.9	0.7	0.7	0.7	0.8	0.8	0.7	0.5	0.5	0.5	0.5
UR-50601	92.0	92.0	97.3	85.8	81.3	91.7	81.9	80.8	71.3	78.1	72.8	73.1	75.9	70.2
B7	0.6	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.4	0.3	0.5	0.4	0.2
Others	0.9	0.5	0.7	1.1	0.8	0.7	0.8	0.7	0.8	0.9	1.1	0.9	0.4	<0.1

[a]: Time 0 samples were not irradiated; [b]: Comparative TLC has indicated that this peak may contain UR-50624 (mean 7.3%) and one other compound; Others: Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks

Comment: The study is acceptable although the duration of study (10 days) is short. The calculation of DT_{50}/DT_{90} is not reliable because the DT50 is much longer double the duration of study.

Figure B.8.1-3: Proposed degradation pathway for UR-50601 by soil photolysis



B.8.1.2 Rate of degradation

B.8.1.2.1 Laboratory studies

The studies referred to under point B.8.1.1, Route of degradation , were evaluated with regard to the rate of degradation in soil, too. For overview see Table B.8.1-14

Table B.8.1-14: Results of rate of degradation (Laboratory) / DT50/DT90 values of Beflubutamid and metabolite UR-50604

Conditions	soil	temperature (°C)	moisture	Beflubutamid		Metabolite UR-50604		Reference
				DT_{50} (d)	DT_{90} (d)	DT_{50} (d)	DT_{90} (d)	
aerobic	Arrow sandy loam	20 °C	40 % mwhc	5	179	--	--	BOD2000-1132
aerobic	Wick	20 °C	40 % mwhc	5	16	6	--	BOD2000-1135
aerobic	Speyer 2.2	20 °C	40 % mwhc	118	>365	nc	nc	BOD2000-1135
aerobic	Speyer 2.2	20 °C	40 % mwhc	12	>365	nc	nc	BOD2000-1135
aerobic	Evesham3	20 °C	40 % mwhc	8	62	5	--	BOD2000-1135
aerobic	Evesham 3	10 °C	40 % mwhc	20	182	80	265	BOD2000-1135
soil photolysis	sandy loam	20 °C	---	*)	*)	--	--	BOD2000-1134
anaerobic	sandy loam	20°C	----	water phase: 4 soil: 260	12 ----	--	--	BOD2000-1133

*) calculation not reliable; 73.1 – 77.9% of beflubutamid after 10 days (dark control : 91.8 – 112% in 10 days)

B.8.1.2.2 Field studies

Soil dissipation studies

An overview is given in Table B.8.1-27.

A. Wilson (2000): UR-50601: Terrestrial field dissipation study with ASU 95 510 H (85 g/l UR-50601 + 500 g/l Isoproturon) applied to bare soil in Spain, United Kingdom and Germany in 1998/1999; report no. UBE 099/002143; BOD2000-1332

Guidelines: SETAC Procedure for assessing the environmental fate and ecotoxicity of pesticides ;Decision-making scheme for the environmental risk assessment of plant protection products. OEPP/EPPO Bulletin 23, 27-49, 1993; BBA-Richtlinie Teil IV, 4-1 (Dez. 1986); EC 91/414/EEC and subsequent amendment 96/68/EC

Deviations – none

GLP: Yes

Test system
Product: ASU 95 510 H, Batch no. 9814, Composition: UBH 820 (UR-50601) 87 g ai/l and Isoproturon 520 g ai/l formulated as a suspension concentrate.
Four terrestrial field dissipation trials were carried out from November 1998 to May 2000 on bare soil in Spain, United Kingdom and Germany to establish decline of residue of UR-50601 and its metabolite UR-50604.
The trials were located in important small cereal production regions. Trial UBE/099-01 (clay sand, Spain) and UBE/099-02 (clayey sand, United Kingdom) were sprayed in autumn 1998. Trial UBE/099-03 (sandy clay, Spain) and UBE/099-04 (loamy sand, Germany) were sprayed in spring 1999. Details of the soil characteristics and microbial biomass are given in Table B.8.1-15. The trial design consisted of a non-treated control plot and two replicated treated plots. ASU 95 510 H was applied to the bare soil of each plot once at a nominal rate of 3000 ml/ha (255 g UR-50601/ha) by backpack boom sprayer. The treatment rate was verified by the analysis of spray target deposition cards placed on the test site prior to treatment. Adequate herbicides were applied to each plot to maintain bare soil conditions for the duration of the study.
Soil cores were taken at predetermined intervals (see Table B.8.1-16, Table B.8.1-17, Table B.8.1-18 and Table B.8.1-19) and maintained frozen until analysis using a hydraulic zero contamination soil corer for 50 cm cores and a manual zero contamination soil corer for 30 cm cores. Each sampling point consisted of twenty cores (5 cm diameter x 50 cm length acetate tubes) except for soil cores taken from day 210 at UBE/099-03 and UBE/099-04 which were taken with 30 cm acetate tubes. Soil samples for microbial biomass evaluation were collected prior to test substance application and 120 days post application. Soil was sampled to a depth of 20 cm from ten locations across each treated plot and combined to give a single sample. Similarly soil from twenty locations within the non treated plots were combined to give one sample.
Prior to analysis for UR-50601 and UR-50604 the soil cores were cut into 0-10, 10-20 and 20-30 cm horizons. Levels of UR-50601 and its metabolite UR-50604 were quantified in the soil from 0-10 and 10-20 cm horizons. Soil sample analysis comprised mixing and sieving of soil prior to extraction with methanol/water. Clean-up using an acidic liquid/liquid partition using ethyl acetate, followed by quantitation by liquid chromatography using mass spectrometric detection (LC-MS). Spray target deposition cards were analysed by extraction with

methanol/water, dilution of an aliquot with acetonitrile/water and subsequent LC-MS determination. The LOQ for UR-50601 and UR-50604 residues in all soils was 10 ng/g.

Table B.8.1-15: Characteristics of the soils from ASU 95 510 H dissipation sites

	UBE/099-01 Spain	**UBE/099-02 UK**	**UBE/099-03 Spain**	**UBE/099-04 Germany**
pH	7.5	6.6	7.3	4.6
Organic carbon (%)	0.3	0.7	0.7	0.6
Water holding capacity (at 0.001 bar suction (pF0) % w/w of dry soil)	39.1	40.4	48.8	42.4
Clay (%) Silt (%) Sand (%)	19 8 73	14 12 74	30 15 55	9 19 72
Classification (BBA)	Clay sand	Clayey sand	Sandy clay	Loamy sand
Microbial biomass (mgC/100g soil) (-1 DAT) [(1)]	5.266	7.487	50.327	9.785
Microbial biomass (mgC/100g soil) (120 DAT) [(1)]	10.1065	12.201	11.152	3.258

[(1)]Mean value for the treated plots

Findings

Analysis of the deposition cards from the treated plots during application showed a mean value of 0.74 mg which compared favourably to the theoretical value of 0.81 mg confirming the efficient application of ASU 95 510 H to the plots.

With the exception of two batches, all procedural recoveries for UR-50601 lay within the acceptable range of 70-110%, showing the methodology to be working within its requirements on the days of analysis. The value of recoveries that were outside the range were 112 and 114%. All the procedural recoveries for UR-50604 were within the 70-110% range.

No significant residues of UR-50601 and UR-50604 were detected in the 10-20 cm horizons, therefore, no analyses were performed on the 20-30 cm horizons. For summary of findings see Table B.8.1-16, Table B.8.1-17, Table B.8.1-18 and Table B.8.1-19.

UBE/99-01: no UR-50601 or UR-50604 residues were found in samples taken prior to treatment or in any samples taken from the control plot. Mean residues of UR-50601 declined from 121 ng/g at time of application to less than the limit of quantitation at day 240 in the 0-10 cm horizon. Residues of UR-50601 detected in the 10-20 cm horizon reached a maximum after 119 days at 17 ng/g and was not seen at later sampling occasions. Residues of UR-50604 slightly above the limit of quantitation of 10 ng/g in the top soil horizon after 92 and 119 days, but then declined to below the limit of quantitation by 181 days.

UBE/99-02: no UR-50601 or UR-50604 residues were found in samples taken prior to treatment or in any samples taken from the control plot. Mean residues of UR-50601 declined from 108 ng/g at time of application to less than the limit of quantitation at day 182 in the 0-10 cm horizon. No UR-50601 residues were detected in lower horizons at any sampling

occasion after the day of application. UR-50604 was detected at 12 ng/g in the top soil horizon at 60 days.
UBE/99-03: no UR-50601 or UR-50604 residues were found in samples taken prior to treatment or in any samples taken from the control plot. Mean residues of UR-50601 declined from 140 ng/g at time of application to less than the limit of quantitation at day 214 in the 0-10 cm horizon. No UR-50601 residues were detected in lower horizons at any sampling occasion after the day of application. Quantifiable residues of UR-50604 were detected up to 21 ng/g in the top horizon of soils sampled at 59, 92 and 126 days, but then declined to less than the limit of quantitation in this horizon by day 154. No residues of UR-50604 were detected in any of the lower horizon samples in this trial.
UBE/099-04: no residues of UR-50601 or UR-50604 were found in samples taken prior to treatment or in any samples taken from the control plot. Mean residues declined from 126 ng/g at time of application to 28 ng/g at day 366 in the 0-10 cm horizon. No UR-50601 residues were detected in lower horizons at any sampling occasion. Quantifiable residues of UR-50604 were detected up to 11 ng/g in the top horizon of soils sampled at days 14 and 29, but then declined to less than the limit of quantitation in this horizon by day 60. No residues of UR-50604 were detected in any of the lower horizon samples in this trial.

Simple exponential decline curves, $y = m.exp(-b.t)$ were fitted to each trial using pooled data from both treated plots in order to calculate the DT_{50} and the DT_{90} values. Two methods of fitting were used; non-linear curve fitting of y versus t, since this is the statistically optimal method and ordinary (unweighted) linear regression of ln(y) versus t, since this is required for regulatory authorities. For the non linear curve fitting of y versus t, the DT_{50} values were 103 days for trial UBE/099-01, 51 days for trial UBE/099-02, 86 days for trial UBE/099-03 and 89 days for trial UBE/099-04. The calculated DT_{90} values were 343 days for trial UBE/099-01, 169 days for trial UBE/099-02, 285 days for trial UBE/099-03 and 295 days for trial UBE/099-04 (Table B.8.1-20).
From the unweighted linear regression of ln(y) versus t, the DT_{50} values were 56 days (UBE/099-01), 44 days (UBE/099-02), 55 days (UBE/099-03) and 138 days (UBE/099-04). The corresponding DT_{90} values were 185 days (UBE/099-01), 146 days (UBE/099-02), 183 days (UBE/099-03) and 457 days (UBE/099-04) (Table B.8.1-20).

Table B.8.1-16: Summary UBE/099-01 (Autumn application Spain) findings

Plot number	Soil sample	Amount of UR-50601 (ng/g) 0-10 cm	Amount of UR-50601 (ng/g) 10-20 cm	Amount of UR-50604 (ng/g) 0-10 cm	Amount of UR-50604 (ng/g) 10-20 cm
Plot 2+3	-1 DAT	ND	ND	ND	ND
Plot 2+3	0 DAT	121	14	ND	ND
Plot 2+3	3 DAT	94	ND	ND	ND
Plot 2+3	7 DAT	124	NQ	ND	ND
Plot 2+3	14 DAT	105	NQ	ND	ND
Plot 2+3	28 DAT	106	NQ	NQ	NQ
Plot 2+3	62 DAT	96	NQ	NQ	ND
Plot 2+3	92 DAT	86	11	12	ND
Plot 2+3	119 DAT	62	11	15	ND
Plot 2+3	181 DAT	12	ND	NQ	ND
Plot 2+3	241 DAT	NQ	ND	NQ	ND

DAT = days after treatment
Plot 2 + 3 = replicated treated plots
ND = not detected (<2.5 ng/g)
NQ = not quantifiable (<10 ng/g)

Table B.8.1-17: Summary UBE/099-02 (Autumn application United Kingdom) findings

Plot number	Soil sample	Amount of UR-50601 (ng/g) 0-10 cm	Amount of UR-50601 (ng/g) 10-20 cm	Amount of UR-50604 (ng/g) 0-10 cm	Amount of UR-50604 (ng/g) 10-20 cm
Plot 2+3	-1 DAT	ND	ND	ND	ND
Plot 2+3	0 DAT	108	ND	ND	ND
Plot 2+3	3 DAT	91	NQ	ND	ND
Plot 2+3	7 DAT	89	NQ	ND	ND
Plot 2+3	14 DAT	89	ND	ND	ND
Plot 2+3	28 DAT	73	ND	NQ	ND
Plot 2+3	60 DAT	49	NQ	NQ	ND
Plot 2+3	90 DAT	28	NQ	NQ	ND
Plot 2+3	119 DAT	19	NQ	NQ	ND
Plot 2+3	182 DAT	NQ	ND	ND	ND
Plot 2+3	242 DAT	ND	ND	ND	ND

DAT = days after treatment
Plot 2 + 3 = replicated treated plots
ND = not detected (<2.5 ng/g)
NQ = not quantifiable (<10 ng/g)

Table B.8.1-18: Summary UBE/099-03 (Spring application Spain) findings

Plot number	Soil sample	Amount of UR-50601 (ng/g) 0-10 cm	Amount of UR-50601 (ng/g) 10-20 cm	Amount of UR-50604 (ng/g) 0-10 cm	Amount of UR-50604 (ng/g) 10-20 cm
Plot 2+3	-1 DAT	ND	ND	ND	ND
Plot 2+3	0 DAT	140	19	ND	ND
Plot 2+3	3 DAT	109	NQ	ND	ND
Plot 2+3	7 DAT	126	ND	ND	ND
Plot 2+3	14 DAT	128	NQ	ND	ND
Plot 2+3	28 DAT	87	NQ	ND	ND
Plot 2+3	59 DAT	116	ND	19	ND
Plot 2+3	92 DAT	65	ND	12	ND
Plot 2+3	126 DAT	61	ND	16	ND
Plot 2+3	154 DAT	34	ND	NQ	ND
Plot 2+3	185 DAT	14	ND	NQ	ND
Plot 2+3	214 DAT	NQ	ND	ND	ND

DAT = days after treatment
Plot 2 + 3 = replicated treated plots
ND = not detected (<2.5 ng/g)
NQ = not quantifiable (<10 ng/g)

Table B.8.1-19: Summary UBE/099-04 (Spring application Germany) findings

Plot number	Soil sample	Amount of UR-50601 (ng/g) 0-10 cm	Amount of UR-50601 (ng/g) 10-20 cm	Amount of UR-50604 (ng/g) 0-10 cm	Amount of UR-50604 (ng/g) 10-20 cm
Plot 2+3	-1 DAT	ND	ND	ND	ND
Plot 2+3	0 DAT	126	ND	ND	ND
Plot 2+3	3 DAT	167	ND	ND	ND
Plot 2+3	7 DAT	161	ND	ND	ND
Plot 2+3	14 DAT	110	ND	NQ	ND
Plot 2+3	29 DAT	127	ND	NQ	ND
Plot 2+3	60 DAT	66	ND	ND	ND
Plot 2+3	91 DAT	44	ND	ND	ND
Plot 2+3	121 DAT	49	ND	ND	ND
Plot 2+3	153 DAT	40	ND	ND	ND
Plot 2+3	184 DAT	33	ND	NQ	ND
Plot 2+3	210 DAT	24	ND	NQ	ND
Plot 2+3	238 DAT	40	ND	NQ	ND
Plot 2+3	270 DAT	29	ND	ND	ND
Plot 2+3	297 DAT	23	ND	ND	ND
Plot 2+3	329 DAT	40	ND	NQ	ND
Plot 2+3	366 DAT	28	ND	NQ	ND
Plot 2+3	366 DAT	28	ND	NQ	ND
Plot 2+3	424 DAT	11	ND	NQ	ND

DAT = days after treatment
Plot 2 + 3 = replicated treated plots
ND = not detected (<2.5 ng/g)
NQ = not quantifiable (<10 ng/g)

Table B.8.1-20: Calculated DT_{50} and DT_{90} values

Field location	**Application**	**No transformation (non-linear)**			**Ln-transformation (linear)**		
		DT_{50} (days)	**DT_{90} (days)**	**r^2**	**DT_{50} (days)**	**DT_{90} (days)**	**r^2**
UBE/099-01 Spain	Autumn 1998	103	343	0.97	56	185	0.88
UBE/099-02 UK	Autumn 1998	51	169	0.99	44	146	0.99
UBE/099-03 Spain	Spring 1999	86	285	0.97	55	183	0.86
UBE/099-04 Germany	Spring 1999	89	295	0.95	138	457	0.81

Comment: The studies conducted in Spain and United Kingdom are acceptable whereas the study in Germany with the low soil pH of 4.6 does not represent typical agricultural use (pH > 5) and therefore, these results are not taken into account for risk assessment.

V. Schneider (2001); Determination of residue of UR-50601 (Beflubutamid) in soil dissipation study with Herbaflex in Germany; UBE Industries, Ltd.; unpublished report no. PR00/018, Amendment 4 April 2000, BOD2001-323, BOD2001-324.

Field trial part:
P. Reh (2001); Soil dissipation study with Herbaflex in Germany; UBE Industries, Ltd.; unpublished report no. VP00-1-35, BOD-2001-325.

Guidelines: "Guideline: Residue analytical methods for post-registration control purposes", compiled by Ralf Haenel and Johannes Siebers; Reports from the Federal Biological Research Center for Agriculture and Forestry, 21 July 1998 (book 43, 1998); "Residues: Guidelinefor generating data requirement for Annex II (part A, Section 4) and Annex III (part A, section 5) of Directive 91/414", working document, SANCO/3029/99, rev. 4, 07 July 2000; Guideline Biologische Bundesanstalt IV, 3-3; Braunschweig, December 1986; Guideline Society of Environmental Toxicology and Chemistry (SETAC), Brussels, March 1995.

Deviations – none

GLP: yes

Test system
Product: ASU 95 510 H, Batch no. 0003, composition: UBH 820 (UR-50601) 85 g ai/l and Isoproturon 500 g ai/l formulated as a suspension concentrate.

Each one site was selected in north (Hilgermissen) and south (Baiertal) of Germany, respectively. Trial VP00-1-35D1 (clayey loam, south Germany) was sprayed on 17.07.2000 and VP00-1-35D2 (sandy loam, North Germany) was sprayed on 08.07.2000. Details of the soil characteristics and microbial biomass are given in Table B.8.1-21 . The trial design consisted of each two plots for non-treated control and for treated trial. ASU 95 510 H was applied to the bare soil of each plot once at a nominal rate of 3000 ml product/ha (255 g UR-50601 /ha) by handheld boom sprayer. For VP00-1-35D1 glyphosate was applied to maintain bare soil conditions for the duration of the study and for VP00-1-35D2 spring barley was sown to keep the plots under vegetation 5 days before application and the trial was kept under vegetation.

Table B.8.1-21: Characteristics of soils

	VP00-1-35D1 South Germany	VP00-1-35D2 North Germany
soil type	sandy loam	clayey loam
pH	7.5	6.4
organic matter (%)	1.75	1.05
water holding capacity (at 0.001 bar suction (pF 0) % w/w of dry soil)	30.2	39.7
Clay (%)	23.3	26.3
Silt (%)	66.8	35.0
Sand (%)	9.9	38.7

Soil cores were taken at predetermined intervals and maintained frozen until analysis using a coremastor soil auger with plastic cores (30 cm length and 5 cm diameter). Each sampling point consisted of ten cores. Soil samples for microbial biomass evaluation were collected prior to test substance. Soil samples were taken for analysis at 0, 3, 7, 14, 28, 60, 90 and 120 days after application of Herbaflex. The cores were put in plastic bags and stored frozen in deep freezers. Samples were shipped in cardboard boxes.

For weather data see Table B.8.1-22 and Table B.8.1-23.

Table B.8.1-22: Weather data VP00-1-35D1

Month	Temperature average (°C)	Precipitation (mm)
July	17.6	42.1
August	20.4	43.6
September	16.0	92.6
October	11.4	48.6
November	7.5	62.9
December	4.8	34.8
January	7.2	21.2

Reference: Deutscher Wetterdienst; Weather station: Mannheim; Distance to the trial site: 25 km

Table B.8.1-23: Weather data VP00-1-35D2

Month	Temperature average (°C)	Precipitation (mm)	Sun radiation (hr)
July	15.3	72.7	68.9
August	17.0	69.5	207.4
September	14.2	71.5	118
October	10.9	42.1	99.2
November	7.1	26.6	67.6
December	3.9	50.3	55.6
January (5d)	5.0	18.0	2.7

Reference: Deutscher Wetterdienst; Weather station: Bremen; Distance to the trial site: 30 km

The wet soil is extracted several times with methanol:water (70:30). Methanol is removed from the extract by rotary evaporation. Then NaCl-solution is added to the extract. The extract is acidified with hydrochloric acid and extracted two times with ethyl acetate. The organic phase is evaporated to dryness and dissolved in a defined volume of toluene. The determination is performed by means of GC-MS with selective mass-fragments. The limit of determination was 10 µg/kg and the limit of detection was 1.4 µg/kg. The method is specific under investigation, because three typical fragment ions (m/z=176, 193 and 221) are used for detection with an m/z ratio of > 100. Evaluation of UR-50601 was performed on fragment ion m/z = 176 which is the most intensive of the three characteristic masses.

Findings
The recovery experiment showed the range of 90-96% for the fortification of 10-1000 µg/g, and procedural recoveries were conducted for the sample of south Germany at day 0 of application to be 45.7 µg/kg +/- 3.9 % to show that homogenization of soil samples is sufficient. Due to the irregular analysis of samples (DAT 0-28: 0-30 cm soil depth; DAT 60-120: 0-10 / 10-20 cm soil depth) analytical results of DAT0-28 were multiplied by 3 to get comparable values. For summary of findings see Table B.8.1-24 and Table B.8.1-25.

No UR-50601 residue was found in samples taken prior to treatment or in any samples taken from the control plot in both of two trials.

Mean residues of UR-50601 declined from 137.1 and 103.5 µg/kg at time of application for South Germany and North Germany respectively. From the best fit to the decay curves, DT_{50} values of 15 (South Germany) and 20 days (North Germany) and DT_{90} values of 49 and 65 days, respectively, were calculated (see Table Table B.8.1-26).

No significant beflubutamid residues were measured in the lower soil segment (10-20cm).

Table B.8.1-24: Results of South Germany

Soil sample	Amount of UR-50601 (µg/kg)
0 DAT	137.1
3 DAT	169.2
7 DAT	81.3
14 DAT	67.2
28 DAT	15.6
60 DAT	3.4(0-10cm) n.d.(10-20cm)
90 DAT	3.3 (0-10cm) n.d. (10-20cm)

Remark: Analytical results of DAT 0-28 were multiplied with 3
DAT = days after treatment
n.d. = not detected (< 1.4 µg/kg)

Table B.8.1-25: Results of North Germany

Soil sample	Amount of UR-50601 (µg/kg)
0 DAT	103.5
3 DAT	142.2
7 DAT	122.4
14 DAT	123.9
28 DAT	57.6
60 DAT	7.2(0-10cm) n.d.(10-20cm)
90 DAT	5.2 (0-10cm) n.d. (10-20cm)
120 DAT	2.9 (0-10cm) n.d. (10-20cm)

Remark: Analytical results of DAT 0-28 were multiplied with 3
DAT = days after treatment
n.d. = not detected (< 1.4 µg/kg)

Table B.8.1-26: Calculated DT_{50}/DT_{90} values

Place	**DT_{50} (d)**	**DT_{90} (d)**	**Kinetic**	**r^2**
South Germany	15	49	First order	0.7967
North Germany	20	65	First order	0.8585

Comment: The study is acceptable.

Summary soil dissipation studies
For overview see Table B.8.1-27. .

Table B.8.1-27: Results of field dissipation studies/ DT_{50}/DT_{90} values of Beflubutamid

Country	**Application**	**soil type**	**Beflubutamid**		**Reference**
			DT_{50} (d)	**DT_{90} (d)**	
Spain	Autumn 1998	clay sand	103	343	BOD2000-1332
United Kingdom	Autumn 1998	clayey sand	51	169	BOD2000-1332
Spain	Spring 1999	sandy clay	86	285	BOD2000-1332
Germany - North - South	 Summer 2000 Summer 2000	 clayey sand sandy loam	 20 15	 65 49	 BOD2001-323, 324, 325

Soil residue studies

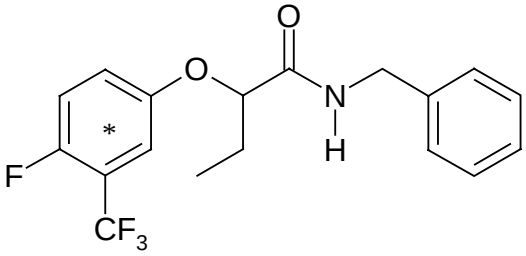
S.J. Mellor, B.C. Mayo (1999); UR-50601 Confined accumulation in rotational crops; UBE Industries, Ltd.; unpublished report no. UBE 083/992872, RIP2000-2897

Guidelines: 91/414/EEC directive as amended by 96/68/EC and working document 7521/v1/95 rev 2 Appendix C; Testing of plant protection products in rotational crops (1997)

Deviations – none

GLP: Yes

Test material



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601:
Batch number: CFQ 9801, Radiochemical purity: >98%, Specific activity: 1.59 GBq/mmol.
Loamy sand soil (Speyer 2.2) in pots was treated with formulated [ring-U-^{14}C -phenoxy]UR-50601 at a nominal application rate of 255g a.i./ha and left to age for a period of 30 days after which wheat and carrots at ± 15°C were sown and grown to maturity. The total radioactive residue concentrations (TRR's) were determined in soil and plants.

Sampling: Application, sowing, immature sampling, earliest possible harvest and normal harvest in soil.

Analysis: Chromatography: HPLC and TLC for quantification and identification. Radioactivity was measured by LSC.

Findings:

Total radioactive residues (TRR) in soil used for growing carrots was 0.218 ppm at application, declining to 0.071 ppm at normal harvest.

In soil used for growing wheat, the TRR concentration after application was 0.237 ppm, and declined to 0.057 ppm at normal harvest. TRR concentrations in untreated soils were less than twice the background at all sampling intervals. Individual results are shown in Table B.8.1-28.

At normal harvest, the TRR concentrations in carrots were 0.033 ppm in the foliage and 0.009 ppm in the root. The results are summarised in Table B.8.1-28.

At normal harvest, the TRR concentrations in wheat grain, husk and straw were 0.018 ppm, 0.105 ppm, and 0.131 ppm respectively. The results are summarised in Table B.8.1-28.

The transition factors for carrot at normal harvest were 0.46 for foliage and 0.13 for roots. Transition factors for wheat grain, husks and straw were 0.32, 1.8 and 2.3 respectively. These values are summarised in Table B.8.1-28.

The route of degradation in soil was the same as observed in the laboratory aerobic soil metabolism studies. The major degradation products were confirmed to be UR-50604

(phenoxybutyric acid) and UR-50624 (phenoxybutanamide) (see Table B.8.1-29). The unknown minor product U1 was present at the sowing of the rotational crops. In carrots at harvest only the unknown minor product detected in soil, U1, was present in foliage and root extracts (see Table B.8.1-29). In wheat at harvest a minor degradate was shown to be UR-50604 and U1 was the major degradate in grain, husks and straw (see Table B.8.1-29). U1 was shown to be a single polar, water soluble component.

Table B.8.1-28: Total radioactive residues in Speyer 2.2 soil after application of [ring-U-^{14}C-phenoxy]UR-50601 at an application rate of 255 g ai/ha

Results expressed as µg equivalents UR-50601/g soil dry weight (% TRR)

(a) Soil samples (planted with carrot)

Time after application (days)	Total radioactive residue	Extractable residue		Non-extractable residue	
0	0.218	0.201	(92.1)	0.017	(7.9)
30	0.158	0.116	(73.6)	0.042	(26.4)
105	0.089	0.014	(16.2)	0.075	(83.8)
161	0.071	0.009	(12.1)	0.062	(87.9)

(b) Soil samples (planted with wheat)

Time after application (days)	Total radioactive residue	Extractable residue		Non-extractable residue	
0	0.237	0.224	(94.4)	0.013	(5.6)
30	0.121	0.085	(70.2)	0.036	(29.8)
82	0.106	0.015	(13.8)	0.091	(86.2)
193	0.057	0.006	(10.8)	0.051	(89.2)

Table B.8.1-29: Quantities of radioactive components in soil after application of [ring-U-^{14}C-phenoxy]UR-50601 at an application rate of 255 g ai/ha

Results expressed as µg equivalents UR-50601/g soil dry weight (% TRR)

(a) Soil samples (planted with carrot)

Radioactive component	Approximate retention time (minutes)	Time after application in days			
		0		30	
U1	4.5	<0.001	(<0.1)	0.002	(1.0)
UR-50604	10.0	0.001	(0.6)	0.024	(15.0)
UR-50624	24.0	<0.001	(<0.1)	0.002	(1.0)
UR-50601	42.0	0.197	(90.2)	0.083	(52.5)
Others[a]	-	0.003	(1.3)	<0.001	(<0.4)

(b) Soil samples (planted with wheat)

Radioactive component	Approximate retention time (minutes)	Time after application in days			
		0		30	
U1	4.5	0.001	(0.4)	0.002	(1.3)
UR-50604	10.0	<0.001	(<0.1)	0.019	(15.6)
UR-50624	24.0	<0.001	(<0.1)	0.002	(1.6)
UR-50601	42.0	0.220	(92.8)	0.056	(46.5)
Others[a]	-	0.002	(1.0)	0.006	(5.1)

[a]: Radioactivity distributed through regions of the chromatogram other than those specified and which did not contain any discrete peaks

Comment: The study is acceptable.

Soil accumulation studies

In field dissipation studies conducted with ASU 95 510 H with autumn, spring and summer applications at a rate equivalent to 255 g UR-50601/ha, the DT_{90}'s were found to be in the range of 49 - 343 .

Comment: According to the results of the acceptable field dissipation studies in Spain , United Kingdom and Germany the DT_{90f} values don't exceed one year and therefore it is not necessary to conduct an accumulation study for autumn use in southern and northern part of European Union nor for spring use in the southern part.

B.8.2 Adsorption, desorption and mobility in soil (Annex IIA 7.1.2, 7.1.3; Annex IIIA 9.1.2)

B.8.2.1 Adsorption and desorption

P.J. Aikens, A.J. Millais, D. Kirkpatrick (1997); UR-50601: Adsorption/Desorption on soil; report no. UBE 42/971616, BOD2000-1129

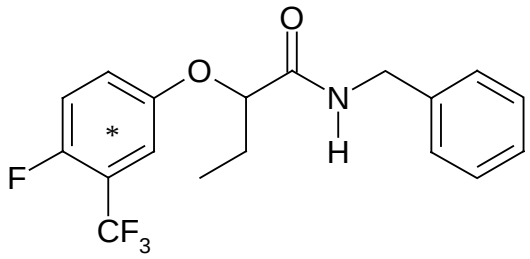
Guidelines: OECD No. 106.

Deviations – none

GLP: Yes

Test system

The soil leaching potential of UR-50601 was measured using the adsorption/desorption batch equilibration method to determine the Freundlich adsorption constants (K_a) and desorption constants in four different soil types. UR-50601 was labelled uniformly in the phenyl ring as indicated below. Details of the soils used are provided in Table B.8.2-1.



* position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >99%, Specific Activity: 1.63 GBq/mmole.

In the definitive study, four concentrations of ^{14}C-UR-50601 in aqueous calcium chloride solution (0.01M) was used 0.06, 0.2, 0.6 and 2 mg/L. For the adsorption phase all four soils and solutions were equilibrated for 24 hours at 20°C in the dark. Soil samples were then desorbed twice with fresh calcium chloride solution for 24 hours on each occasion. Solutions and soil extracts were analysed by TLC and HPLC to determine the actual concentration of ^{14}C-UR-50601 present in solutions and soil extracts during the equilibration phases.

Findings

^{14}C-UR-50601 was moderately well adsorbed to the four soils tested. Freundlich adsorption constants (K_a) and desorption constants (K_{d2}, second desorption) are shown in Table B.8.2-2. Based on these results ^{14}C-UR-50601 can be classified as having a low potential for mobility in soil. K_{oc} values calculated from the Freundlich adsorption constants for the four soils generally correlate with the organic carbon content of the soil, but suggest that other mechanisms were important in the adsorption of ^{14}C-UR-50601 to soil.

Recoveries of radioactivity after adsorption and two desorption equilibrations ranged between 91.95 - 94.72 % of the amounts initially applied (see Table B.8.2-3).

Table B.8.2-1: Characteristics of the test soil

Soil	**Arrow**	**Wick**	**Speyer 2.2**	**Evesham 3**
Textural class	Sandy loam	Sandy loam	Loamy sand	Clay loam
Particle size distribution (%):				
To 63 µm				
63 µm – 2 mm (sand)	65.30	69.42	80.54	33.61
2-63 µm (silt)	22.76	18.39	13.19	34.31
<2 µm (clay)	11.93	12.19	6.26	32.08
To 53 µm				
53 µm – 2 mm (sand)	68.61	69.95	81.73	34.19
2-53 µm (silt)	19.98	17.82	12.09	33.08
<2 µm (clay)	11.41	12.23	6.18	32.74
pH	6.4	5.8	6.0	7.1
Organic carbon (%)	2.0	0.8	2.4	1.9
Organic matter (%)[a]	3.4	1.4	4.1	3.3

[a]: Organic matter calculated as organic carbon (%) x 1.72.

Table B.8.2-2: Adsorption/desorption constants of UR-50601

Soil	Soil type	Organic carbon content %	Freundlich adsorption constant k_a	Organic carbon normalised adsorption constant k_{oc}	Slope of the Freundlich isotherm 1/n
Arrow	Sandy loam	2.0	26.7	1335	0.93
Wick	Sandy loam	0.8	8.49	1061	0.92
Speyer 2.2	Loamy sand	2.4	43.0	1793	0.92
Evesham 3	Clay loam	1.9	16.2	852	0.86

Table B.8.2-3: Recovery of radioactivity and proportions of radioactive components after adsorption and two desorption equilibrations

Soil	Results are expressed as % applied radioactivity			
	Arrow	Wick	Speyer 2.2	Evesham 3
Recovery				
Adsorption solution	25.67	49.22	17.67	32.78
Desorption solution 1	17.44	19.70	11.72	15.56
Desorption solution 2	11.97	9.97	9.11	9.60
Soil extract	39.09	14.00	52.82	34.20
Non-extractable	0.55	0.21	0.63	2.08
Total recovery	94.72	93.10	91.95	94.22
Components soil extract				
UR-50601	97.82	95.36	98.82	98.24
Others	2.18	4.64	1.18	1.76
Components aqueous solution				
UR-50601	79.11	92.43	75.64	83.15
Others	20.89	7.57	24.36	16.85

Comment: The study is acceptable.

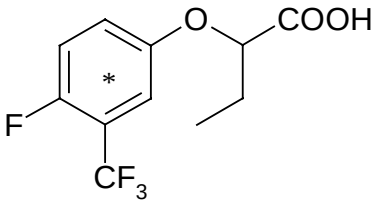
P.J. Aikens, D. Kirkpatrick (1999); UR-50604: Adsorption/Desorption on soil report no. UBE 086/992243, BOD2000-1130

Guidelines: OECD No. 106.

Deviations – none.
GLP: Yes

Test system

The soil leaching potential of UR-50604, a soil metabolite of the herbicide UR-50601, was measured using the adsorption/desorption batch equilibration method to determine the Freundlich adsorption constants (K_a) and desorption constants in three different soil types. UR-50604 was labelled uniformly in the phenyl ring as indicated below. Details of the soils used are provided in Table B.8.2-4.



* position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50604

[Ring-U-^{14}C-phenoxy]UR-50604: Batch number: CFQ10694, Radiochemical purity: >99%, Specific activity: 1.74 GBq/mmol.

In the definitive study, four concentrations of ^{14}C-UR-50604 in aqueous calcium chloride solution (0.01M) were used 0.06, 0.2, 0.6 and 2 mg/L. For the adsorption phase all three soils and solutions were equilibrated for 24 hours at 20°C in the dark. Soil samples were then desorbed twice with fresh calcium chloride solutions for 24 hours on each occasion. Aqueous solutions and soil extracts were analysed by TLC to determine the actual concentration of ^{14}C-UR-50604 present during the equilibration phases.

Findings

^{14}C-UR-50604 was poorly adsorbed to the three soils tested. Freundlich adsorption constants (K_a) and desorption constants (K_{d2}, second desorption) are shown in Table B.8.2-5. Based on these results ^{14}C-UR-50604 can be classified as being mobile to very mobile in soil. K_{oc} values calculated from the Freundlich adsorption constants for the three soils generally correlate with the organic carbon content of the soil, but suggest that other mechanisms were important in the adsorption of ^{14}C-UR-50604 to soil.

Recoveries of radioactivity after adsorption and two desorption equilibrations ranged between 94.1 - 100.9% of the amounts initially applied (see Table B.8.2-6).

Table B.8.2-4: Characteristics of the test soil

Soil	**Wick**	**Speyer 2.2**	**Evesham 3**
Textural class	Sandy loam	Loamy sand	Clay loam
Particle size distribution (%):			
To 63 µm			
63 µm – 2 mm (sand)	69.42	80.54	33.61
2-63 µm (silt)	18.39	13.19	34.31
<2 µm (clay)	12.19	6.26	32.08
To 53 µm			
53 µm – 2 mm (sand)	69.95	81.73	34.19
2-53 µm (silt)	17.82	12.09	33.08
<2 µm (clay)	12.23	6.18	32.74
pH	5.8	6.0	7.1
Organic carbon (%)	0.8	2.4	1.9

Table B.8.2-5: Adsorption/desorption constants of UR-50604

Soil	Soil type	Organic carbon content %	Freundlich adsorption constant k_a	Organic carbon normalised adsorption constant k_{oc}	Slope of the Freundlich isotherm 1/n
Wick	Sandy loam	0.8	0.17647	22	0.93
Speyer 2.2	Loamy sand	2.4	0.21956	9	0.81
Evesham 3	Clay loam	1.9	0.11511	6	0.57

Table B.8.2-6: Recovery of radioactivity and proportions of radioactive components after adsorption and two desorption equilibrations

Soil	Results are expressed as % applied radioactivity		
	Wick	**Speyer 2.2**	**Evesham 3**
Recovery			
Adsorption solution	71.9	67.8	75.2
Desorption solution 1	18.3	21.4	14.5
Desorption solution 2	4.8	6.1	5.3
Soil extract	2.4	4.1	3.7
Non-extractable	0.5	0.8	2.2
Total recovery	97.9	94.1	100.9
Components soil extract			
UR-50604	84.2	86.7	60.3
Others	15.8	13.3	39.7
Components aqueous solution			
UR-50604	97.8	99.9	95.7
Others	2.2	0.1	4.3

Comment: The study is acceptable.

B.8.2.2 Mobility

B.8.2.2.1 Column leaching studies

Under point B.8.2.1 reliable adsorption coefficient values have been determined for the active substance UR-50601 and metabolite UR-50604 in several soil types. Therefore, a column leaching study is not considered necessary.

B.8.2.2.2 Aged residue column leaching studies

A separate adsorption/desorption study for the major soil metabolite UR-50604 has been performed (point B.8.2.1), therefore an aged column leaching study is not considered necessary.

B.8.2.2.3 Lysimeter or field leaching studies

The mobility of the active substance UR-50601 has been shown to be low in soil (point B.8.2.1). The major metabolite UR-50604, however may be classified as having a high potential for mobility in soil having a DT_{50} of 5-17 days and K_{oc} of 6-22 . Furthermore, Pelmo modelling used for risk assessment shows that concentrations in groundwater are expected to be >0.1 µg/l. However, the metabolite has been shown to be non-relevant in terms of ecotoxicological concern and biological activity (see appropriate sections). Toxicological relevance of metabolite UR-50604 is not yet assessed. Therefore, the need to perform a

lysimeter or field leaching study to demonstrate the probable leaching of the metabolite is yet not clear.

B.8.3 Predicted environmental concentrations in soil (Annex IIIA 9.1.3)

PEC_S for UR-50601

Comment: The notifier presented a non-realistic worst case calculation (e.g. no relevant DT_{50} values) .The rapporteur recalculated the PECs-values based on the following assumption:
Soil depth 5 cm, DT_{50f} 103 days , first order kinetic, maximum dose per season 0.255 kg as/ha, no process other than degradation considered, no multiple application because DT50 much lower than interval for next application.

	PEC_{soil} **Distribution to 5-cm depth**	
	PEC_{soil}	
Time (days)	**Actual concentration (mg/kg)**	**Time weighted average (mg/kg)**
0	0.340	0.340
1	0.338	0.339
2	0.335	0.338
4	0.331	0.335
7	0.324	0.332
28	0.282	0.310
50	0.243	0.289
100	0.173	0.247

PEC_S for metabolite UR-50604

Comment: The notifier presented a calculation based on a DT50 which was not considered valid (see below). The rapporteur presents the following calculation:

The metabolite UR-50604 accumulated to maximum values of 9.0-26.1% of applied radioactivity in six aerobic soil degradation studies with UR-50601. Maximum accumulation was observed seven days after application of the parent compound in five soils incubated at 20ºC and thirty days after treatment in a single soil incubated at 10ºC. The largest accumulation of UR-50604 (26.1% AR) was used for PEC_S calculations to give a worst-case situation. The initial, maximum PEC_S values for UR-50601 were 0.340 mg/kg evenly distributed to 5-cm depth. Taking the molecular weights of UR-50601 (355.3 g/mol) and UR-50604 (266.2 g/mol) into account, this gives **initial, maximum PEC_S for UR-50604** of

0.066 mg/kg for an even distribution to 5-cm depth;

These values are larger than data on formation and dissipation of UR-50604 in soil after application of the parent compound to four field sites in Europe. The maximum concentration of UR-50604 in any single sample at 0-10 cm depth was 0.021 mg/kg which is equivalent to

0.042 mg/kg evenly distributed to 0-5 cm depth . This concentration was determined after spring application of UR-50601 in Spain to bare soil at a rate of 0.255 kg a.s./ha.

In all laboratory studies the metabolite UR-50604 was formed and degraded during the study period. Only the calculated values of 5 and 6 days in the Wick and Evesham3 soils are considered as valid although they may not represent worst case values. Therefore, no further PEC values after day 0 are calculated. The non-relevance of the metabolite regarding toxicology, ecotoxicology and biological activity was demonstrated.

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

Active substance

M.H. Chalker; A.K. Kaur; L.F. Elsom; D. Kirkpatrick (1997); UR-50601: Hydrolysis under laboratory conditions; report no. UBE 58/971769, WAS2000-554

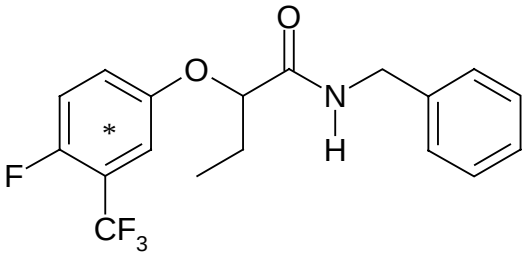
Guidelines: SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 9.

Deviations – none.

GLP: Yes

Test system

The hydrolytic stability of UR-50601 was studied in buffered aqueous solution at pH values of 5, 7 and 9. The solutions were incubated at *ca* 50ºC for up to 5 days under aseptic conditions. Radiolabelled ^{14}C-UR-50601 was used, as shown below, at a solution concentration of 1.0 mg/L.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ 9257, Radiochemical purity: >98%, Specific activity: 1.63 GBq/mmole.

Solutions were analysed at zero time and after five days to determine the rate of hydrolysis. The incubated solutions were analysed by HPLC and TLC to determine proportions of UR-50601 and its radiolabelled hydrolysis products.

Findings
Recoveries of radioactivity from test solutions were in the range 100.8 – 101.8% applied radioactivity at time 0 and 92.9 – 99.0% at Day 5 for the three pH buffers.

HPLC analysis of the test solutions indicated that UR-50601 was the major component representing 91.3 – 97.3% applied radioactivity after five days for the three buffers. Of the remaining components none accounted for more than 0.8% applied radioactivity (see Table B.8.4-1). These findings were confirmed by TLC.
Under the experimental conditions used, UR-50601 was stable at pH 5, 7 and 9 at 50°C and therefore no extended study at 20°C was considered necessary.

Table B.8.4-1: Proportions of radioactivity components in aqueous solutions at various pH's after addition of [ring-U-^{14}C-phenoxy]UR-50601

Component	Approx. R_t (minutes)	Results are expressed as % applied radioactivity					
		pH 5		pH 7		pH 9	
		Time 0*	Day 5	Time 0*	Day 5	Time 0*	Day 5
UR-50601	41-42	97.2	97.3	97.9	94.7	96.1	91.3
	36-37	0.2	nd	0.2	nd	0.2	nd
	22-23	nd	nd	nd	nd	nd	0.2
	6-7	0.4	0.8	0.4	0.4	1.1	0.4
	3-5	nd	0.2	nd	nd	1.1	nd
	Others[a]	2.2	0.7	1.5	1.4	1.5	0.8
	Total	100	99.0	100	96.5	100	92.7

[a]: Others refers to radioactivity not associated with specific components; nd: Not detected; *: Normalised data.

Comment: The study is acceptable.

Metabolite UR-50604

Remark: The dark controls from the aqueous photolysis study with the metabolite UR-50604 show that the metabolite is hydrolytically stable over the relevant pH range (UR-50604 after 7 days: 95.4-99.2%). Therefore, hydrolysis will not be a significant route of degradation of UR-50604 and it is not considered necessary to perform a separate hydrolytic degradation test for this metabolite.

Comment: The statement is agreed on.

B.8.4.2 Photochemical degradation

Active substance

L.F. Elsom; A.K. Kaur; D. Kirkpatrick (1998a); UR-50601: Photolytic degradation in water; report no. UBE 57/973942, LUF2000-464.

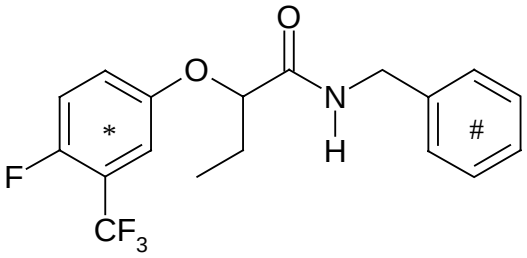
Guidelines: US EPA §161-2 ; SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 10.

Deviations – none.

GLP: Yes

Test system

The photolytic degradation of UR-50601 was studied in aqueous pH 7 buffer. Two different radiolabelled forms of ^{14}C-UR-50601 were used, as shown below.



*Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601
Position of radiolabel in [ring-U-^{14}C-benzylamine]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

[Ring-U-^{14}C-benzylamine]UR-50601: Batch number: CFQ9258, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

Each form of ^{14}C-UR-50601 was added to pH 7 buffer to obtain a solution at a concentration of 1.0 mg/L. A xenon arc light source apparatus was used to provide continuous irradiation of these test solutions for periods up to 15 days. Irradiated test solutions and non-irradiated control solutions (incubated) were maintained at *ca* 25°C at all times. Volatile radioactivity liberated from the test vessels was trapped, via a series of trapping solutions.
Additional solutions of a chemical actinometer were irradiated/incubated to determine quantum yield.
The photodegradation products of UR-50601 were quantified by HPLC and confirmed by TLC at each sampling point.

Findings

Recoveries of radioactivity from all test solutions (irradiated and non-irradiated controls) were >92.2% of applied radioactivity for both radiolabelled forms (except one sample of [ring-U-^{14}C-phenoxy]UR-50601 which was 86.1%). Volatile radioactivity trapped accounted for a maximum of 1.5% of the applied radioactivity (see **Table B.8.4-2**).

The photolysis of active substance was modelled assuming first order kinetics. The half-life (DT_{50}) of UR-50601 (mean of two radiolabelled forms) under the artificial light source was 48 days which was equivalent to 126 days of natural summer sunlight at latitude 40°N, assuming 12-hours of daylight.

At the final analysis time (355.3 hours irradiation), UR-50601 accounted for 77.6% of the applied radioactivity (mean of both radiolabelled forms) (see Table B.8.4-3). No single

photodegradate in either label was detected representing greater than 3.5% of the applied radioactivity when using different HPLC methods. In the corresponding non-irradiated control samples UR-50601 accounted for 96.4% of the applied radioactivity (mean of both radiolabelled forms).

The quantum yield of UR-50601 was 0.044.

Table B.8.4-2: Recovery of radioactivity from irradiated test solutions following application of UR-50601

Analysis time (days)	Results expressed as % applied radioactivity							
	Ring-U-^{14}C-phenoxy				Ring-U-^{14}C-benzylamine			
	Aqueous solution	Vessel rinse	Volatiles	Total recovery	Aqueous solution	Vessel rinse	Volatiles	Total recovery
0	92.0	4.4	-	96.4	96.1	3.0	-	99.1
2	96.0	2.3	<0.1	98.3	96.1	2.7	<0.1	98.8
5	83.3	2.6	0.2	86.1	97.4	2.1	<0.1	99.5
8	91.8	3.3	0.3	95.4	95.8	3.7	<0.1	99.5
10	89.8	3.7	0.5	94.0	95.0	2.5	<0.1	97.5
13	89.2	1.5	1.5	92.2	96.0	2.4	<0.1	98.4
15	92.6	2.8	1.3	96.7	97.5	2.0	<0.1	99.5

Table B.8.4-3: Proportions of radioactive components in irradiated test solutions after application of UR-50601

Component	Approx R_t (min)	Results are expressed as % applied radioactivity						
		Analysis time (hours)						
		0*	44.30	118.72	187.75	237.49	311.00	355.30
[Ring-U-^{14}C-phenoxy]								
UR-50601	38-39	94.4	89.7	78.8	86.8	73.8	72.4	75.7
	34-35	nd	<0.1	0.2	nd	0.7	0.5	0.5
	29-30	nd	nd	0.2	0.2	0.8	nd	0.5
	27-28	nd	nd	0.2	0.2	0.8	0.6	0.6
	24-25	nd	nd	nd	nd	nd	0.5	nd
	19-20	nd	0.4	nd	nd	1.4	nd	nd
	17-19	nd	nd	0.3	0.3	0.8	nd	0.9
	13-14	0.3	nd	nd	nd	0.4	nd	0.6
	10-13	nd	nd	nd	nd	nd	0.6	0.4
	9-10	nd	nd	nd	nd	0.7	0.5	0.5
	7-8	nd	nd	0.4	nd	1.8	1.1	1.4
	6-7	0.5	2.4	1.5	2.3	2.6	2.9	3.1
	3-5	0.6	2.5	2.3	4.0	8.6	9.1	9.6
	Others	0.7	3.3	2.0	1.4	1.0	2.3	1.8

Component	Approx R_t (min)	Results are expressed as % applied radioactivity						
		Analysis time (hours)						
		0*	44.30	118.72	187.75	237.49	311.00	355.30
[Ring-U-^{14}C-benzylamine]								
	42-43	0.3	nd	0.4	0.3	0.3	0.4	0.3
UR-50601	38-39	97.4	94.0	90.6	90.0	85.1	81.6	79.4
	34-35	nd	nd	nd	0.2	0.2	nd	0.5
	29-30	nd	nd	nd	0.2	nd	nd	0.4
	27-28	nd	nd	nd	0.2	0.2	0.2	0.6
	24-25	nd	nd	nd	nd	nd	0.2	nd
	17-19	nd	<0.1	nd	nd	nd	nd	nd
	13-14	nd	nd	0.2	0.2	nd	nd	0.4
	10-13	nd	nd	0.3	0.3	0.4	0.4	0.6
	9-10	nd	nd	0.5	0.7	0.5	0.7	1.1
	7-8	nd	nd	1.7	1.4	1.7	2.5	3.1
	6-7	nd	2.1	2.3	2.7	3.7	5.1	5.3
	3-5	0.9	1.3	1.8	2.3	3.5	6.0	6.6
	Others	0.6	1.3	1.8	1.1	1.9	1.5	1.3

*: Time 0 samples were not irradiated; Others: Refers to radioactivity not associated with specific components; nd Not detected.

Comment: The study is acceptable.

Metabolite UR-50604

A.J. Millais, D. Kirkpatrick (1999); UR-50604: Aqeous photolysis; report no. UBE 087/992694, LUF2000-465

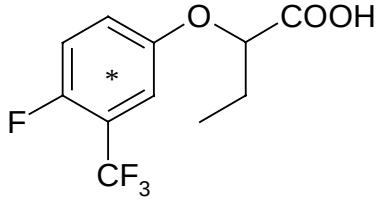
Guidelines: US EPA §161-2 ≅ SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides, Section 10.

Deviations – none.

GLP: Yes

Test system

The photolytic degradation of UR-50604, a major degradate of UR-50601, was studied in aqueous pH 9, 7 and 5 buffer at ca. 20 °C, because it may be of environmental significance in aquatic systems. Radiolabelled ^{14}C-UR-50604 was used, as shown below.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50604

[Ring-U-^{14}C-phenoxy]UR-50604: Batch number: CFQ10694, Radiochemical purity: >97%, Specific activity: 1.74GBq/mmole.

^{14}C-UR-50604 was added to pH 9, 7 and 5 buffer to obtain a solution at a concentration of 1.0 mg/L. A xenon arc light source apparatus was used to provide continuous irradiation of these test solutions for periods up to 168 hours (equivalent to a maximum of 21 days of summer sunlight equivalents at latitude 40°N). Irradiated test solutions and non-irradiated control solutions (incubated) were maintained at *ca* 20°C at all times. Volatile radioactivity liberated from the test vessels was trapped, via a series of trapping solutions.
Additional solutions of a chemical actinometer were irradiated/incubated to determine quantum yield.
The photodegradation products of UR-50604 were quantified by HPLC and confirmed by TLC at each sampling point.

Findings
Recoveries of radioactivity from all test solutions (irradiated and non-irradiated controls) were ≥91.7% of applied. Volatile radioactivity trapped accounted for <1.2% of the applied radioactivity (see Table B.8.4-4).
The photolysis of metabolite UR-50604 was modelled assuming first order kinetics. The half-life (DT_{50}) of UR-50604 at pH 9, 7 and 5 under the artificial light source was 20, 24 and 21 d respectively, which was equivalent to 60.3, 64.7 and 61.1 days of natural summer sunlight at latitude 40°N, assuming 12-hours of daylight.
At the final analysis time (7 d irradiation), UR-50604 accounted for 78.7%-80.4% of the applied radioactivity in the different buffers (see Table B.8.4-5). No single photodegradate in any buffer was detected representing greater than 10% of the applied radioactivity. Two regions of polar material and three metabolites were detected. In the corresponding non-irradiated control samples UR-50604 accounted for 95.4%-99.2% of the applied radioactivity in the different buffers.
The quantum yields for UR-50604 were 8.8 x 10^{-5} at pH 9, 1.9 x10^{-4} at pH 7 and 1.8 x10^{-4} at pH 5.

Table B.8.4-4: Recovery of radioactivity from irradiated test solutions following application of UR-50604

Equivalent time of latitude 40°N summer sunlight (days)	Analysis time (hours)	Results expressed as % applied radioactivity		
		Aqueous solution	Traps	Total recovery
pH 9.0 buffer				
5.74	48	96.9	nd	96.9
12.60	96	96.5	nd	96.5
17.64	144	94.1	0.2[b]	94.3
21.07	168	94.0	0.2[b]	94.2
pH 7.0 buffer				
6.30	48	98.0	0.3[a]	98.3
12.04	96	96.2	0.1[b]	96.3
16.38	144	95.3	0.2[b]	95.5
19.11	168	95.7	0.2[b]	95.9
pH 5.0 buffer				

Equivalent time of latitude 40°N summer sunlight (days)	Analysis time (hours)	Results expressed as % applied radioactivity		
		Aqueous solution	Traps	Total recovery
5.32	48	96.8	nd	96.8
10.64	96	93.7	0.2[b]	93.9
17.22	144	90.5	1.2[a]	91.7
20.09	168	93.0	0.2[b]	93.2

nd: Not detected; [a]: Detected in the ethyl digol trap; [b]: Detected in the KOH trap.

Table B.8.4-5: Proportions of radioactive components in irradiated test solutions after application of UR-50604

Component	Results are expressed as % applied radioactivity			
	Analysis time (hours)			
	48	96	144	168
pH 9.0 buffer				
Polar 1[a]	5.1	4.2	14.8	8.7
Polar 2[a]	nd	3.8	0.4	4.0
A1	nd	nd	0.2	nd
UR-50602	nd	nd	nd	nd
UR-50604	90.0	85.9	76.1	78.7
A2	nd	0.3	0.5	nd
Others	1.7	2.3	2.2	2.4
pH 7.0 buffer				
Polar 1[a]	0.5	1.3	2.4	2.5
Polar 2[a]	1.3	3.7	6.4	5.7
A1	2.7	2.5	3.3	4.3
UR-50602	nd	1.5	1.6	0.4
UR-50604	90.9	84.9	80.5	80.2
A2	0.9	0.5	nd	0.4
Others	2.1	1.8	1.0	2.2
pH 5.0 buffer				
Polar 1[a]	0.3	0.5	1.7	1.3
Polar 2[a]	0.6	0.8	1.3	1.3
A1	3.6	5.2	6.6	8.0
UR-50602	0.9	2.3	3.5	2.8
UR-50604	89.5	83.6	77.3	78.7
A2	nd	0.3	nd	0.2
Others	1.8	1.0	0.1	0.7

Nd: Not detected; [a]: Region containing more than one component.

Comment: The study is acceptable.

B.8.4.3 Biological degradation

B.8.4.3.1 Ready biodegradability

In the water/sediment study (point 7.2.1.3.2) it was shown that the active substance UR-50601 is not biodegradable (<70% in 28 days according to Directive 93/21/EEC). Therefore, a ready biodegradability study is not considered necessary.

Comment: The statement is agreed on.

B.8.4.3.2 Water/sediment study

Active substance

L.F. Elsom, A.K. Kaur, D. Kirkpatrick (1998b): UR-50601: Aerobic aquatic degradation study; report no. UBE 069/983037, WAS2000-555

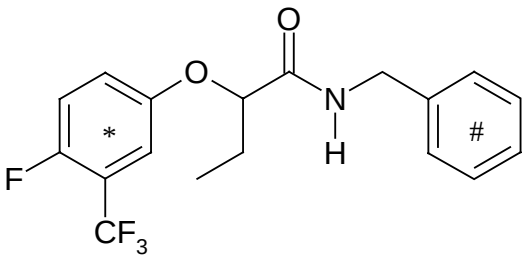
Guidelines: SETAC Procedures for assessing the environmental fate and ecotoxicity of pesticides.

Deviations – none.

GLP: Yes

Test system

The metabolism and degradation of UR-50601 was studied in Bury Pond and Houghton Meadow water/sediment systems in darkness at a temperature of *ca* 20°C(see Table B.8.4-6). Prepared water/sediment systems were incubated under study conditions for two to five weeks prior to test substance application, in order to achieve stable conditions with respect to water pH, water oxygen concentration and redox potentials in the water and sediment. Two labelled forms of UR-50601, [ring-U-^{14}C-phenoxy]UR-50601 and [ring-U-^{14}C-benzylamine]UR-50601 (see below) were used. These were applied separately to the water /sediment test systems at a rate of 0.25 ppm.



* Position of radiolabel in [ring-U-^{14}C-phenoxy]UR-50601
# Position of radiolabel in [ring-U-^{14}C-benzylamine]UR-50601

[Ring-U-^{14}C-phenoxy]UR-50601: Batch number: CFQ9257, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

[Ring-U-^{14}C-benzylamine]UR-50601: Batch number: CFQ9258, Radiochemical purity: >98%, Specific activity: 1.63GBq/mmole.

Following test substance application, test systems were incubated in darkness at *ca* 20°C for up to 100 days. Test systems were taken for analysis at 0, 1, 3, 7, 14, 30, 59 and 100 days for

each water/sediment and each radiolabel form of the test substance. Water and sediment were separated and analysed separately by HPLC and TLC to assess the proportions and nature of any degradation products. Radiolabelled volatile degradation products were trapped and quantified. Additional sediment/water systems were set up to determine microbial biomass at the beginning and end of the study.

Table B.8.4-6: Characteristics of the water/sediment systems

	Parameter	Location			
		Bury Pond		Houghton Meadow	
		German	USDA	German	USDA
Sediment	% sand	45.94	47.93	39.05	39.56
	% silt	29.98	29.03	19.36	18.89
	% clay	24.07	23.04	41.60	41.55
	Classification	Clay loam	Loam	Clay	Clay
	pH (1:5) in water	8.3		8.2	
	pH (1:5) in 1M KCl	7.8		7.6	
	pH (1:5) in 0.01 M $CaCl_2$	7.9		7.7	
	Organic carbon (%)	1.7		2.4	
	Total nitrogen (mg/kg)	1042.8		1070.8	
	Total phosphorus (mg/kg)	1000.5		1436.5	
Water	Hardness (mg/l calcium carbonate)	473.0		291.0	
	pH*	6.93		7.06	
	Dissolved organic carbon (mg/l)	18.0		22.6	
	Total nitrogen (mg/l)	<0.05		<0.05	
	Total phosphorus (mg/l)	3.1		0.4	
Microbial biomass (µg C/g soil)					
Day 0		386		263	
Day 101		13		-	
Day 104		-		486	
Day 168		71.8		-	

Characterisation of the soil was carried out by Soil Survey and Land Research Centre; Determination of the microbial biomass was performed by Chemex International plc and by SSLRC; *: measured as source.

Findings

For either water/sediment system the recovery of radioactivity was in the range of 92.1 – 112.4% applied radioactivity whichever radiolabel form of the test substance was used (see Table B.8.4-7and Table B.8.4-8).

Pseudo-first order reaction kinetics were assumed for the decline of UR-50601 in the water and water/sediment with time. The mean quantities of UR-50601 at each time point in the water and water/sediment have been used to calculate the kinetics parameters. In the Bury Pond system, the DT_{50} for UR-50601 in the water and sediment was 64 days and the corresponding DT_{90} was 212 days. In the water only, UR-50601 had a DT_{50} and a DT_{90} of 20 days and 66 days respectively. In the Houghton Meadow system, the DT_{50} for UR-50601 in the water and sediment was 49 days and the corresponding DT_{90} was 164 days. In the water only, UR-50601 had a DT_{50} and a DT_{90} of 16 days and 53 days respectively.

The major degradation product of [ring-U-^{14}C-phenoxy]UR-50601 was UR-50604 in water and sediment extracts. This accounted for 45.5% applied radioactivity at day 100 from the Bury Pond sediment system (Table B.8.4-9), with a large proportion (36.1% applied radioactivity) in the water phase (Table B.8.4-11, Table B.8.4-12). In the Houghton Meadow system (Table B.8.4-10) after 100 days UR-50604 accounted for 54.9% applied radioactivity of which 34.6% applied radioactivity was associated with the water (Table B.8.4-13, Table B.8.4-14). Another minor component corresponding to UR-50624 accounted for 5.3 and 6.4% applied radioactivity in the Bury Pond and Houghton Meadow systems respectively at day 100. These degradates were only observed in the [ri (ng-U-^{14}C-phenoxy]UR-50601 treatment due to cleavage of UR-50601 and further degradation to $^{14}CO_2$. - No significant degradates were found in the water or sediment extracts from samples treated with [ring-U-^{14}C-benzylamine]UR-50601 as extensive mineralisation to $^{14}CO_2$ occurred (32.1% applied radioactivity in Bury Pond and 41.6% applied radioactivity in Houghton Meadow at day 100). Non-extractable radioactivity for Bury Pond and Houghton Meadow reached a maximum of 28.8% and 19.7% applied radioactivity after 100 days.

A proposed degradation pathway for UR-50601 is shown in Figure B.8.4-1

The relative proportions of the UR-50604 optical isomers in the Houghton Meadow water/sediment system were 25.6% S-isomer at 14 days and 83.3% S-isomer at 100 days. This increase could be due to selective degradation of the R-isomer or isomerisation of the R-isomer to the S-isomer in the aqueous phase.

Table B.8.4-7: Recovery of radioactivity from Bury Pond water/sediment system following application of UR-50601

Analysis time (days)	Results are expressed as % applied radioactivity					
	Water	Sediment			Volatiles	Total recovery
		Extracts	Residue	Total		
[Ring-U-^{14}C-phenoxy]						
0	100.9	-	2.6	2.6	-	103.5
1	89.1	15.5	4.1	19.6	0.0	108.7
3	72.7	20.8	7.8	28.6	0.0	101.3
7	52.7	45.5	4.5	50.0	0.1	102.8
14	49.8	48.3	5.5	53.8	0.2	103.8
30	38.4	62.6	6.3	68.9	0.6	107.9
59	40.7	60.2	9.3	69.5	2.2	112.4
100	44.8	37.7	11.9	49.6	7.6	102.0
[Ring-U-^{14}C-benzylamine]						
0	103.2	-	1.8	1.8	-	105.0
1	81.4	16.4	1.4	17.8	<0.1	99.2
3	66.3	28.2	2.8	31.0	0.2	97.5
7	50.1	44.6	5.0	49.6	1.3	101.0
14	41.8	50.5	6.3	56.8	2.3	100.9
30	27.3	56.2	9.3	65.5	6.7	99.5
59	11.4	49.6	17.6	67.2	14.1	92.7
100	1.9	30.7	28.8	59.5	32.1	93.5

Table B.8.4-8: Recovery of radioactivity from Houghton Meadow water/sediment system following application of UR-50601

Analysis time (days)	Results are expressed as % applied radioactivity					
	Water	Sediment			Volatiles	Total recovery
		Extracts	Residue	Total		
[Ring-U-^{14}C-phenoxy]						
0	104.0	-	1.8	1.8	-	105.8
1	86.2	17.0	6.2	23.2	<0.1	109.4
3	64.1	33.1	4.3	37.4	0.1	101.6
7	58.7	44.0	6.2	50.2	0.1	109.0
14	40.8	52.8	7.0	59.8	2.0	102.6
30	49.0	44.6	6.0	50.6	3.1	102.7
59	36.3	54.9	7.7	62.6	5.2	104.1
100	40.1	39.8	12.4	52.2	10.7	103.0
[Ring-U-^{14}C-benzylamine]						
0	107.7	-	1.4	1.4	-	109.1
1	82.4	16.8	5.7	22.5	<0.1	104.9
3	63.6	34.4	4.3	38.7	0.2	102.5
7	47.4	43.3	7.0	50.3	2.2	99.9
14	31.3	55.1	5.5	60.6	4.6	96.5
30	18.5	53.8	11.7	65.5	11.9	95.9
59	7.8	40.2	19.1	59.3	27.4	94.5
100	1.3	29.5	19.7	49.2	41.6	92.1

Table B.8.4-9: Proportions of radioactive components in the water and sediment (sum) extracts of Bury Pond after application of UR-50601

Component	Approx R_t (min)	Results are expressed as % applied radioactivity							
		Analysis time (days)							
		0	1	3	7	14	30	59	100
[Ring-U-^{14}C-phenoxy]									
	42-43	nd	nd	<0.1	nd	0.1	nd	nd	nd
UR-50601	38-39	97.8	99.5	86.0	85.0	82.5	81.2	62.4	26.5
	37-38	nd	nd	1.0	1.6	1.7	nd	nd	nd
	36-37	nd	nd	0.1	0.1	0.4	0.3	0.2	0.2
	35-36	nd	nd	0.7	1.3	0.8	nd	nd	nd
	29-30	nd	nd	nd	0.2	0.2	0.1	0.2	0.1
	27-28	nd	nd	nd	0.4	0.2	0.7	nd	0.1
	19-20	nd	nd	<0.1	nd	0.2	nd	nd	nd
UR-50624	17-19	0.3	0.3	0.5	1.0	0.8	1.3	2.2	5.3
	15-16	nd	nd	nd	0.3	nd	nd	nd	nd
	9-10	nd	0.3	nd	0.4	0.3	0.3	nd	nd
UR-50604	7-8	nd	0.7	1.5	3.9	7.8	14.3	33.3	45.5
	6-7	0.5	0.9	0.7	1.2	0.7	0.4	0.4	0.5
	3-5	1.5	1.2	0.4	0.8	0.4	0.6	1.1	2.5
	Others	0.8	1.7	2.5	2.1	2.0	1.8	1.2	2.0
Total		100.9	104.6	93.4	98.3	98.1	101.0	100.9	82.7

Component	Approx R_t (min)	Results are expressed as % applied radioactivity							
		Analysis time (days)							
		0	1	3	7	14	30	59	100
[Ring-U-^{14}C-benzylamine]									
	42-43	0.3	0.3	0.1	0.3	0.2	0.2	0.2	0.1
UR-50601	38-39	100.1	95.7	91.9	92.9	87.4	79.9	57.3	30.8
	36-37	nd	0.1	0.1	0.1	0.3	0.3	0.2	nd
	34-35	nd	nd	nd	nd	nd	nd	nd	<0.1
	29-30	nd	nd	nd	nd	0.7	0.3	0.3	<0.1
	27-28	nd	nd	nd	nd	nd	0.1	0.3	<0.1
	24-25	nd	nd	nd	nd	nd	nd	<0.1	<0.1
	19-20	nd	nd	nd	nd	nd	nd	0.1	0.1
	17-19	nd	nd	nd	nd	nd	nd	0.1	<0.1
	15-16	nd	nd	nd	nd	nd	nd	<0.1	nd
	13-14	nd	nd	nd	nd	0.1	nd	nd	<0.1
	10-13	nd	nd	nd	nd	nd	nd	0.1	<0.1
	9-10	0.2	nd	nd	0.2	0.4	0.4	0.2	0.1
	7-8	nd	nd	nd	nd	0.5	0.5	0.1	0.1
	6-7	1.0	0.7	0.6	0.3	0.6	0.6	0.1	0.1
	3-5	0.4	0.2	0.3	0.2	0.3	0.1	0.2	0.2
	Others	1.1	0.7	1.6	0.8	2.0	1.0	2.0	1.1
Total		103.1	97.7	94.6	94.8	92.5	83.4	61.2	32.6

Others: Refers to radioactivity not associated with specific components; nd: Not detected.

Table B.8.4-10: Proportions of radioactive components in the water and sediment (sum) extracts of Houghton Meadow after application of UR-50601

Component	Approx R_t (min)	Results are expressed as % applied radioactivity							
		Analysis time (days)							
		0	1	3	7	14	30	59	100
[Ring-U-^{14}C-phenoxy]									
UR-50601	38-39	99.3	98.3	90.8	91.1	73.6	46.3	42.8	14.7
	37-38	nd	0.2	0.3	0.2	1.1	0.3	nd	nd
	36-37	nd	nd	nd	0.2	0.2	nd	nd	nd
	35-36	nd	0.1	nd	0.4	1.9	0.6	0.2	nd
	34-35	nd	0.1	0.6	nd	nd	nd	nd	nd
	29-30	nd	nd	nd	0.6	nd	nd	0.2	nd
	27-28	nd	nd	nd	0.7	nd	nd	nd	nd
	19-20	nd	nd	nd	nd	0.1	nd	nd	nd
UR-50624	17-19	0.4	0.4	0.6	0.6	0.6	1.9	2.7	6.4
	9-10	nd	nd	nd	0.4	0.3	0.5	0.6	nd
UR-50604	7-8	nd	1.2	2.4	5.2	14.1	40.8	40.6	54.9
	6-7	0.8	1.3	0.9	1.1	0.3	0.5	0.8	0.6
	3-5	1.8	0.3	0.4	0.4	0.4	0.4	1.1	1.3
	Others	1.7	1.4	1.4	1.8	1.2	2.2	2.3	1.7
Total		104.0	103.3	97.4	102.7	93.8	93.5	91.2	79.6

Component	Approx R_t (min)	Results are expressed as % applied radioactivity							
		Analysis time (days)							
		0	1	3	7	14	30	59	100
[Ring-U-^{14}C-benzylamine]									
	42-43	nd	nd	0.2	nd	nd	nd	0.2	0.1
UR-50601	38-39	105.4	96.0	94.0	87.3	82.7	68.0	45.5	27.8
	37-38	nd	0.4	0.7	0.8	0.4	nd	nd	nd
	36-37	nd	0.1	0.2	0.3	0.3	0.4	0.2	0.3
	35-36	nd	0.6	0.9	1.1	0.7	nd	nd	nd
	29-30	nd	nd	nd	nd	nd	0.3	0.2	0.2
	27-28	nd	nd	nd	nd	nd	0.3	0.2	0.2
	24-25	nd	nd	nd	nd	nd	nd	nd	<0.1
	19-20	nd	nd	nd	nd	nd	nd	<0.1	0.1
	17-19	nd	nd	nd	nd	nd	nd	nd	<0.1
	15-16	nd	nd	nd	nd	nd	nd	nd	<0.1
	13-14	nd	nd	nd	nd	nd	nd	nd	<0.1
	10-13	nd	nd	nd	nd	nd	nd	nd	<0.1
	9-10	0.2	nd	nd	nd	nd	nd	0.1	0.1
	7-8	1.2	nd	nd	nd	0.2	0.3	0.2	0.3
	6-7	nd	0.5	0.5	0.3	0.1	0.1	0.3	0.2
	3-5	0.3	0.6	nd	nd	0.1	0.2	0.3	0.3
	Others	0.5	0.9	1.5	0.9	1.9	2.6	0.9	0.9
Total		107.6	99.1	98.0	90.7	86.4	72.2	48.1	30.5

Others: Refers to radioactivity not associated with specific components; nd: Not detected.

Table B.8.4-11: Proportions of radioactive components in the water and sediment of Bury Pond water/sediment system after application of [ring-U-14C-phenoxy]UR-50601 (as % of applied radioactivity)

WATER PHASE									
		Analysis time (days)							
Component	Approx. Rf (minutes)	0d	1d	3d	7d	14d	30d	59d	100d
UR-50601	38-39	97.8	84.7	67.9	43.8	39.9	23.7	10.2	3.2
	29-30	nd	nd	nd	0.2	0.1	nd	nd	nd
	27-28	nd	nd	nd	0.4	nd	0.3	nd	nd
UR-50624	17-19		0.3	0.5	1.0	0.8	0.9	1.2	2.2
	15-16	nd	nd	nd	0.3	nd	nd	nd	nd
	9-10	nd	0.3	nd	0.4	0.3	0.2	nd	nd
UR-50604	7-8	nd	0.5	1.3	3.5	6. 6	11.7	27.6	36.1
	6-7	0.5	0.9	0.6	1.1	0.6	0.4	0.4	0.4
	3-5	1.5	1.2	0.3	0.7	0.4	0.6	1.0	2.0
	Others[1]	0.8	1.2	2.1	1.4	1.1	0.6	0.4	0.9
Total		100.9	89.1	72.7	52.8	49.8	38.4	40.7	44.8
SEDIMENT									
Component		Analysis time (days)							
	42-43	----	nd	<0.1	nd	0.1	nd	nd	nd
UR-50601	38-39	----	14.8	18.1	41.2	42.6	57.5	52.2	23.3
	37-38	----	nd	1.0	1.6	1.7	nd	nd	nd
	36-37	----	nd	0.1	0.1	0.4	0.3	0.2	0.2
	35-36	----	nd	0.7	1.3	0.8	nd	nd	nd
	29-30	----	nd	nd	nd	0.1	0.1	0.2	0.1
	27-28	----	nd	nd	nd	0.2	0.4	nd	0.1
	19-20	----	nd	<0.1	nd	0.2	nd	nd	nd
UR-50624	17-19	----	nd	nd	nd	nd	0.4	1.0	3.1
	9-10	----	nd	nd	nd	nd	0.1	nd	nd
UR-50604	7-8	----	0.2	0.2	0.4	1.2	2.6	5.7	9.4
	6-7	----	nd	0.1	0.1	0.1	nd	nd	0.1
	3-5	----	nd	0.1	0.1	nd	nd	0.1	0.5
	Others[1]	----	0.5	0.4	0.7	0.9	1.2	0.8	1.1
Total		----	15.5	20.7	45.5	48.3	62.6	60.2	37.9

[1] Others refers to radioactivity not associated with specific components

nd not detected

Table B.8.4-12: Proportions of radioactive components in the water and sediment of Bury Pond water/sediment system after application of [ring-U-14C-benzylamine]UR-50601 (as % applied radioactivity)

WATER PHASE									
		Analysis time (days)							
Component	Approx. Rf (minutes)	0d	1d	3d	7d	14d	30d	59d	100d
	42-43	0.3	0.2	nd	nd	nd	nd	nd	<0.1
UR-50601	38-39	100.1	79.9	64.7	49.1	38.7	24.5	10.2	1.3
	36-37	nd	nd	nd	nd	nd	0.1	nd	nd
	34-35	nd	nd	nd	nd	nd	nd	nd	<0.1
	29-30	nd	nd	nd	nd	0.3	0.1	0.1	<0.1
	27-28	nd	nd	nd	nd	nd	0.1	0.1	<0.1
	24-25	nd	nd	nd	nd	nd	nd	<0.1	<0.1
	19-20	nd	nd	nd	nd	nd	nd	0.1	0.1
	17-19	nd	nd	nd	nd	nd	nd	0.1	<0.1
	15-16	nd	nd	nd	nd	nd	nd	<0.1	nd
	13-14	nd	nd	nd	nd	0.1	nd	nd	<0.1
	10-13	nd	nd	nd	nd	nd	nd	0.1	<0.1
	9-10	0.2	nd	nd	0.2	0.3	0.4	0.2	0.1
	7-8	nd	nd	nd	nd	0.4	0.5	0.1	0.1
	6-7	1.0	0.7	0.5	0.3	0.6	0.5	0.1	0.1
	3-5	0.4	0.2	0.3	0.2	0.3	0.1	0.2	0.2
	Others[1]	1.1	0.3	0.8	0.4	1.2	0.9	0.3	<0.1
Total		103.1	81.3	66.3	50.2	41.9	27.2	11.6	1.9
SEDIMENT									
Component		Analysis time (days)							
	42-43	----	0.1	0.1	0.3	0.2	0.2	0.2	0.1
UR-50601	38-39	----	15.8	27.2	43.8	48.7	55.4	47.1	29.5
	36-37	----	0.1	0.1	0.1	0.3	0.2	0.2	nd
	29-30	----	nd	nd	nd	0.4	0.2	0.2	nd
	27-28	----	nd	nd	nd	nd	nd	0.2	nd
	9-10	----	nd	nd	nd	0.1	nd	nd	nd
	7-8	----	nd	nd	nd	0.1	nd	nd	nd
	6-7	----	nd	0.1	nd	nd	0.1	nd	nd
	Others[1]	----	0.4	0.8	0.4	0.8	0.1	1.7	1.1
Total		----	16.4	28.3	44.6	50.6	56.2	49.6	30.7

[1] Others refers to radioactivity not associated with specific components

nd not detected

Table B.8.4-13: Proportions of radioactive components in the water and sediment of Houghton Meadow water/sediment system after application of [ring-U-14C-phenoxy]UR-50601 (as % applied radioactivity)

WATER PHASE									
		Analysis time (days)							
Component	Approx. Rf (minutes)	0d	1d	3d	7d	14d	30d	59d	100d
UR-50601	38-39	99.3	82.1	59.2	49.7	28.0	12.6	3.6	1.0
	37-38	nd	nd	nd	nd	nd	0.3	nd	nd
	36-37	nd	nd	nd	0.2	nd	nd	nd	nd
	35-36	nd	nd	nd	nd	nd	0.4	nd	nd
	29-30	nd	nd	nd	0.4	nd	nd	nd	nd
	27-28	nd	nd	nd	0.5	nd	nd	nd	nd
UR-50624	17-19	0.4	0.4	0.6	0.6	0.6	1.3	1.6	1.9
	9-10	nd	nd	nd	0.4	0.3	0.2	0.3	nd
UR-50604	7-8	0.0	1.1	2.1	4.2	11.1	32.4	27.7	34.6
	6-7	0.8	1.3	0.9	1.1	0.3	0.5	0.8	0.6
	3-5	1.8	0.3	0.4	0.4	0.4	0.4	0.8	0.8
	Others[1]	1.7	1.0	1.0	1.1	0.2	0.8	1.5	1.0
Total		104.0	86.2	64.2	58.6	40.9	48.9	36.3	39.9
SEDIMENT									
Component		Analysis time (days)							
UR-50601	38-39	----	16.2	31.6	41.4	45.6	33.7	39.2	13.7
	37-38	----	0.2	0.3	0.2	1.1	nd	nd	nd
	36-37	----	nd	nd	nd	0.2	nd	nd	nd
	35-36	----	0.1	nd	0.4	1.9	0.2	0.2	nd
	34-35	----	0.1	0.6	nd	nd	nd	nd	nd
	29-30	----	nd	nd	0.2	nd	nd	0.2	nd
	27-28	----	nd	nd	0.2	nd	nd	nd	nd
	19-20	----	nd	nd	nd	0.1	nd	nd	nd
UR-50624	17-19	----	nd	nd	nd	nd	0.6	1.1	4.5
	9-10	----	nd	nd	nd	nd	0.3	0.4	nd
UR-50604	7-8	----	0.1	0.3	1.0	3.0	8.4	12.8	20.3
	3-5	----	nd	nd	nd	nd	nd	0.2	0.5
	Others[1]	----	0.4	0.4	0.7	1.0	1.4	0.8	0.7
Total		----	17.1	33.2	44.1	52.9	44.6	54.9	39.7

[1] Others refers to radioactivity not associated with specific components

nd not detected

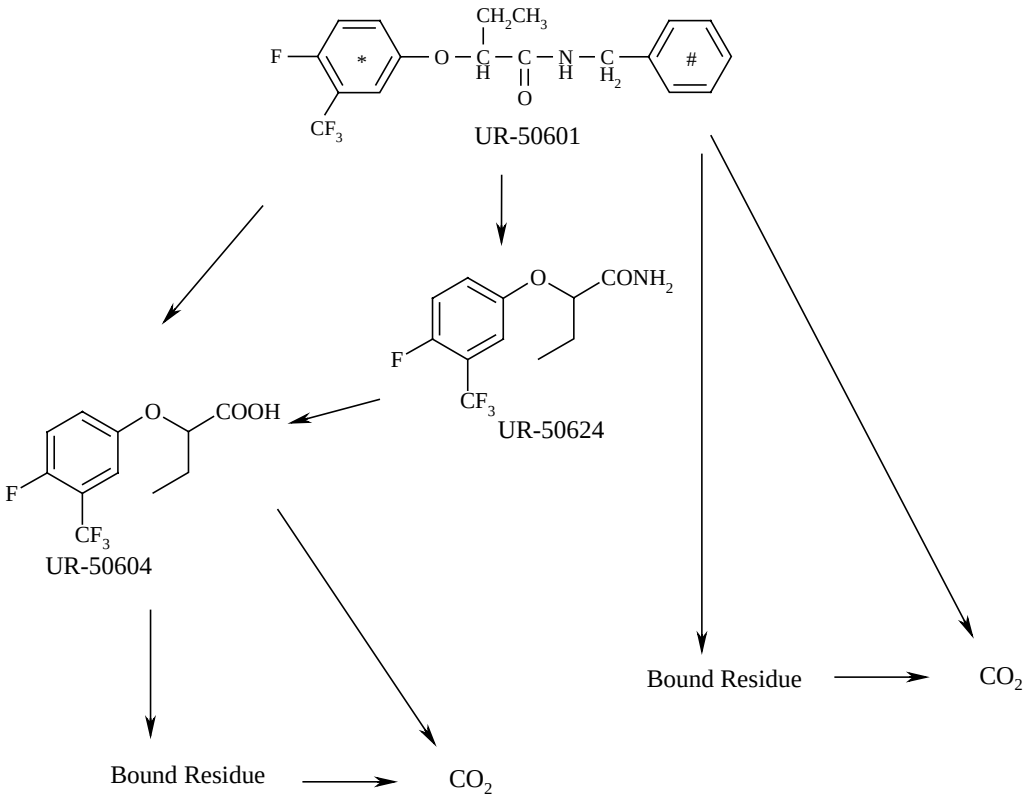
Table B.8.4-14: Proportions of radioactive components in the water and sediment of Houghton Meadow water/sediment system after application of [ring-U-14C-benzylamine]UR-50601 (as % applied radioactivity)

WATER PHASE									
		Analysis time (days)							
Component	Approx. Rf (minutes)	0d	1d	3d	7d	14d	30d	59d	100d
	42-43	nd	nd	0.2	nd	nd	nd	nd	<0.1
UR-50601	38-39	105.4	80.6	62.3	46.8	30.5	17.2	7.2	0.8
	36-37	nd	nd	nd	nd	nd	nd	nd	<0.1
	29-30	nd	nd	nd	nd	nd	nd	<0.1	<0.1
	27-28	nd	nd	nd	0.5	nd	nd	nd	<0.1
	24-25	nd	nd	nd	nd	nd	nd	nd	<0.1
	19-20	nd	nd	nd	nd	nd	nd	<0.1	<0.1
	17-19	nd	nd	nd	nd	nd	nd	nd	<0.1
	15-16	nd	nd	nd	nd	nd	nd	nd	<0.1
	13-14	nd	nd	nd	nd	nd	nd	nd	<0.1
	10-13	nd	nd	nd	nd	nd	nd	nd	<0.1
	9-10	0.2	nd	nd	nd	nd	nd	0.1	<0.1
	7-8	1.2	nd	nd	nd	0.2	0.3	0.1	0.1
	6-7	nd	0.5	0.5	0.3	nd	nd	0.1	0.1
	3-5	0.3	0.6	nd	nd	nd	0.1	0.1	0.1
	Others[1]	0.5	0.7	0.6	0.3	0.6	0.9	0.2	<0.1
Total		107.6	82.4	63.6	47.4	31.3	18.5	7.8	1.1
SEDIMENT									
Component		Analysis time (days)							
	42-43	----	nd	nd	nd	nd	nd	0.2	0.1
UR-50601	38-39	----	15.4	31.7	40.5	52.2	50.8	38.3	27.0
	37-38	----	0.4	0.7	0.8	0.4	nd	nd	nd
	36-37	----	0.1	0.2	0.3	0.3	0.4	0.2	0.3
	35-36	----	0.6	0.9	1.1	0.7	nd	nd	nd
	29-30	----	nd	nd	nd	nd	0.3	0.2	0.2
	27-28	----	nd	nd	nd	nd	0.3	0.2	0.2
	19-20	----	nd	nd	nd	nd	nd	nd	0.1
	9-10	----	nd	nd	nd	nd	nd	nd	0.1
	7-8	----	nd	nd	nd	nd	nd	0.1	0.2
	6-7	----	nd	nd	nd	0.1	0.1	0.2	0.1
	3-5	----	nd	nd	nd	0.1	0.1	0.2	0.2
	Others[1]	----	0.2	0.9	0.6	1.3	1.7	0.7	0.9
Total		----	16.7	34.4	43.3	55.1	53.7	40.3	29.4

[1] Others refers to radioactivity not associated with specific components
nd not detected

Comment: The study is acceptable.

Figure B.8.4-1: Proposed route of degradation of UR-50601 in aerobic water/sediment systems



Metabolite UR-50604

Most of the metabolite UR-50604 produced in the sediment after exposure to UR-50601 moves into the water phase (see point 7.2.1.3.2/01) and degrades by photolysis [DT_{50} 60-65 days (point 7.2.1.2/02)]. Furthermore, there is only one application/year and therefore, the metabolite will not accumulate in the water and a separate water/sediment study for this metabolite is not considered necessary.

Comment: The statement is agreed on.

B.8.4.3.3 Degradation in the saturated zone

The field soil dissipation study and the adsorption/desorption study have shown that the active substance UR-50601 is not likely to leach through the soil profile and reach the saturated zone.

Based on the available data the metabolite UR-50604 could be found in the saturated zone. UR-50604 may be classified as being mobile to very mobile in soil (K_{oc} 6-22) and hence UR-50604 is likely to leach through the soil profile. The degree of persistence of UR-50604 in the saturated zone will be dependent upon the extent of leaching of UR-50604 through to the groundwater system and upon the soil microflora degradation to non-extractable bound residues and CO_2. The DT_{50} for UR-50604 in soil is 5 to 17 days under aerobic conditions, while under anaerobic conditions data indicate that the DT_{50} will be greater. The potential for soil microflora degradation in a saturated environment may be reduced however. Furthermore, data indicate that most of the UR-50604 exists in the water phase instead of the sediment phase. UR-50604 is hydrolytically stable in the pH range 5 to 9 and therefore

hydrolysis will not represent a mechanism for removal. Given these factors it is unlikely that UR-50604 will stay in the saturated zone but will enter the ground water. Furthermore, the non-relevance of UR-50604 in terms of biological activity, ecotoxicological and toxicological concern have been demonstrated (see the appropriate sections).

Comment: No study was submitted but only this statement. According to the rapporteur opinion a corresponding study is not required because the calculation of PECgw show that there is no potential of groundwater contamination and therefore no further studies regarding degradation in the saturated zone are necessary.

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 environmental concentrations in surface water (PEC_{sw})

Standard references (not submitted):

ECPA (1994). Estimation of initial exposure for environmental safety/risk assessment of pesticides. Guideline document, December 1994.

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JENE, B. (1998). SLFA Projektbericht: Weiterentwicklung des Simulationsmodells PELMO 2.01 zu PELMO 3.00. SLFA, D-67435 Neustadt/Wstr., Germany.

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KLOSKOWSKI, R.; FISCHER, R. UND BINNER, R., WINKLER, R. (1999). Draft guidance on the calculation of predicted environmental concentration values of plant protection products for soil, groundwater, surface water and sediment. Proceedings of the XI Symposium Pesticide Chemistry, Cremona, Italy, 11-15 September 1999, 835-850.

MERSIE, W, SEYBOLD, C.A., MCNAMEE, C. AND HUANG, J. (1999). Effectiveness of switchgrass fiter strips in removing dissolved atrazine and metolachlor from runoff. *Journal of Environmental Quality*, **28**, 816-821.

MISRA, A.K., BAKER, J.L., MICKELSON, S.K. AND SHANG, H. (1996). Contributing area and concentration effects on herbicide removal by vegetative buffer strips. *Transactions of the ASAE*, **39**, 2105-2111.

PATTY, L., REAL, B. AND GRIL, J.J. (1997). The use of grassed buffer strips to remove pesticides, nitrate and soluble phosphorous compounds from runoff water. *Pesticide Science*, **49**, 243-251.

WAUCHOPE, R.D. (1978). The pesticide content of surface waters draining from agricultural fields – a review. *Journal of Environmental Quality* **7**, 459-472.

Reference (submitted):

BEULKE, S. (2000): Estimation with PRZM-3.12 of expected concentrations of UR-50601 in surface waters (PECsw) arising from losses via surface runoff and erosion, SSLRC No. JF 4290V, WAS2000-561

PEC_{SW} for UR-50601 from overspray

PEC_{SW} calculations for UR-50601 can be made on the basis of the following assumptions:

- Direct overspray of a static ditch of 1 m width and 30 cm depth.
- Maximum use rate of 0.255 kg a.s./ha.
- One application per year.

Loading to the ditch via overspray for an application of UR-50601 at the rate of 0.255 kg a.s./ha is 25.5 mg/m^2. The resulting initial PEC_{SW} value is 85.0 µg/l.

Short- and long-term PEC_{SW} values were calculated on the basis of first-order dissipation. Only concentrations in the water phase are of relevance to non-sediment dwelling aquatic organisms. In natural waters, UR-50601 degrades to the metabolites UR-50624 and UR-50604 and partitions into sediment. Two first-order half-lives were reported for dissipation from the water phase of water-sediment systems (19.9 and 16.0 days). The longer of these half-lives was used for PEC_{SW} calculations.

Actual PEC_{SW} values and time-weighted average concentrations for UR-50601 are given below.

Time (days)	**Actual concentration (µg/l)**	**Time-weighted average (µg/l)**
0	85.0	85.0
1	82.1	83.5
2	79.3	82.1
4	73.9	79.3
7	66.6	75.4
14	52.2	67.3
21	40.9	60.3
28	32.1	54.3
42	19.7	44.6

It should be noted that direct overspray contravenes Good Agricultural Practice.

PEC_{SW} for UR-50601 from drift

PEC_{SW} calculations for UR-50601 were made on the basis of the following assumptions:

- Drift to a static ditch of 1 m width and 30 cm depth.
- Drift from 1, 5 or 10 m distance with drift values of 4.0, 0.6 and 0.4% respectively, selected as a worst-case (95^{th} percentile) for application to field crops (Ganzelmeier *et al.*, 1995).
- Maximum use rate of 0.255 kg a.s./ha.
- One application per year.

Loading to the ditch and the initial PEC_{SW} value via drift for an application of UR-50601 at the rate of 0.255 kg a.s./ha are given below.

Distance (m)	Drift (%)	Loading to ditch (mg/m^2)	Initial PEC_{SW} (µg/l)
1	4.0	1.02	3.40
5	0.6	0.15	0.51
10	0.4	0.10	0.34

Short- and long-term PEC_{SW} values were calculated on the basis of first-order dissipation using the longer of two first-order half-lives reported for dissipation from the water phase of water-sediment systems (19.9 days).

Actual PEC_{SW} values and time-weighted average concentrations for UR-50601 are given below.

Time	1 m drift distance		5 m drift distance		10 m drift distance	
	Actual concentration	Time-weighted average	Actual concentration	Time-weighted average	Actual concentration	Time-weighted average
(days)	(µg/l)	(µg/l)	(µg/l)	(µg/l)	(µg/l)	(µg/l)
0	3.40	3.40	0.51	0.51	0.34	0.34
1	3.28	3.34	0.49	0.50	0.33	0.33
2	3.17	3.28	0.48	0.49	0.32	0.33
4	2.96	3.17	0.44	0.48	0.30	0.32
7	2.66	3.02	0.40	0.45	0.27	0.30
14	2.09	2.69	0.31	0.40	0.21	0.27
21	1.64	2.41	0.25	0.36	0.16	0.24
28	1.28	2.17	0.19	0.33	0.13	0.22
42	0.79	1.79	0.12	0.27	0.08	0.18

Apart from any initial input to surface waters via direct overspray or spray drift, two other major sources of input are possible:

1. Drainflow – The modelling with PELMO 3.00 demonstrates extremely limited potential for vertical movement of UR-50601 through soil because of its strong sorption to soil. It can be concluded that inputs to surface waters via drainflow will be negligible.
2. Surface runoff and erosion – A simple, worst-case estimate of potential concentrations in surface water arising from losses via runoff was made according to ECPA guidelines (Wauchope, 1978; ECPA, 1994). This is based upon the assumption that 0.5% of the pesticide loading to soil in a 1 ha field moves to a 0.2 ha static pond which is 1 m in depth. On the basis of the maximum application rate of 0.255 kg a.s./ha and no interception by the crop, a 0.5% loss equates to 1.28 g/ha. The volume of the 0.2 ha pond is 2×10^6 l, giving a worst-case initial PEC_{SW} value from runoff of 0.64 µg/l. As a consequence of this relatively large concentration estimated at step 1, higher tier simulation of losses via this pathway was undertaken.

PEC_{SW} for UR-50601 from surface runoff and erosion

A higher tier assessment of the potential for UR-50601 to enter surface waters via surface runoff and erosion was carried out using the simulation model PRZM-3.12. The model was preferred over PELMO-3.00 which was used for simulations of PEC_{GW} because PELMO-3.00 has an inherent tendency to over-estimate pesticide losses in surface runoff. In addition, errors occurred during test simulations of losses via runoff and erosion with PELMO 3-00.

Simulations with PRZM-3.12 were made for three soils to represent northern and southern European conditions:

a) a sandy soil with low organic carbon content from Germany (Borstel soil);
b) a slowly permeable, seasonally wet loam over clay from the UK with a high runoff potential (Brockhurst series);
c) a river-terrace soil from Italy with a relatively impermeable layer at 40-cm depth resulting in significant lateral movement of water and solutes to surface waters (soil LGP2).

Two climate scenarios were selected from those provided with the simulation model PELMO (Klein, 1995; Jene, 1998) and adapted for use with PRZM-3.12. These were 'Hamburg wet' and 'Hamburg normal' with total volumes of annual rainfall of 872 mm and 776 mm, respectively. Behaviour of UR-50601 was assessed following application to winter cereals in autumn or to spring cereals in spring at the maximum rate (0.255 kg a.s./ha). Application was made to a 100 x 100 m field exclusive of an untreated 10-m buffer strip along one side of the field which resulted in an effective application rate of 0.230 kg a.s./ha.

The DT_{50} value for UR-50601 in soil was set to 144 days (the longest of first-order values determined following autumn or spring application of UR-50601 to four field sites). The mean of four reported K_{oc} values (1260 ml/g) was used for modelling the behaviour of UR-50601. PRZM-3.12 does not allow to simulate sorption according to the Freundlich equation, but assumes that the sorption isotherm is linear (Freundlich exponent = 1).

Simulated loadings of UR-50601 were discharged daily into a 100 x 20 m pond of 1 m depth (= 2 x 10^6 litres). Pesticide lost via erosion was assumed to be completely and instantaneously desorbed from the eroded sediment and dissolved in the pond water, thus giving a worst-case estimate for concentrations in the aqueous phase. Degradation within the pond occurred according to first-order kinetics. The longer of two first-order half-lives reported for dissipation of UR-50601 from the water phase of water-sediment systems (19.9 days) was used for calculations of daily concentrations of UR-50601 in the pond. Calculations were made using the ModelMaker software (Version 3.1, Cherwell Scientific Ltd, Oxford, UK) over one year following application of UR-50601.

Losses of UR-50601 via runoff for a full year after application ranged from 0.02 to 0.13% of the applied amount according to the scenario selected. Annual losses via erosion did not exceed 0.01% of the applied amount for any of the scenarios.

Soil	**Maximum daily concentrations of UR-50601 in surface waters arising from runoff and erosion (µg/l)**			
	Hamburg wet		**Hamburg normal**	
	Autumn application	**Spring application**	**Autumn application**	**Spring application**
Borstel	0.025	0.052	0.020	0.023
Brockhurst	0.040	0.078	0.031	0.031
LGP2	0.077	0.082	0.062	0.018

Maximum concentrations of UR-50601 in the pond at any time within the simulation period were between 0.018 µg/l and 0.082 µg/l for the twelve scenarios. In general, concentrations were larger for the Italian soil LGP2 than for the Borstel soil (Germany) and the Brockhurst series (UK).

The results of this study are based on a number of worst-case assumptions:

- DT_{50} values for dissipation of UR-50601 in the field following application in autumn or spring at four sites ranged from 51 to 103 days and from 44 to 144 days according to the methodology used for parameter estimation. The longest of these DT_{50} values (144 days) was used for modelling with PRZM-3.12.
- Two first-order half-lives were reported for dissipation of UR-50601 from the water phase of water-sediment systems (19.9 and 16.0 days). The longer of these values was used to calculate concentrations of the compound in the pond.
- UR-50601 sorbed to the eroded sediment was considered to be completely and instantaneously desorbed and dissolved in the pond water.
- The amount of UR-50601 which was lost from the treated area of the field via runoff and erosion was fully discharged into the pond. A possible decrease of pesticide losses as runoff and erosion passed through the untreated 10-m buffer strip was ignored. The 10-m buffer strip could be expected to significantly attenuate the amount of pesticide entering the water body by capturing a fraction of surface runoff and eroded sediment, particularly when cropped. Strong effects have been measured for grass buffers with typical reductions of 30 to 100% (Misra *et al.*, 1996; Patty *et al.*, 1997; Mersie *et al.*, 1999). This effect was ignored here as PRZM cannot simulate the reduction.

The concentrations of UR-50601 in surface water arising from losses via runoff and erosion presented in this report are thus likely to over-estimate actual concentrations under the conditions of use.

UR-50601 has a limited potential to reach surface waters via surface runoff and erosion. Peak concentrations in the water body are unlikely to exceed 0.082 µg/l under the conditions considered. This maximum value is only ca. 24% of the initial PEC_{SW} estimated for inputs of UR-50601 to surface waters via drift from a distance of 10 m. **It can be concluded that drift is the major potential route for entry of UR-50601 to surface waters.**

PEC_{SW} for the metabolite UR-50604

Two aerobic aquatic degradation studies demonstrated that the metabolite UR-50604 accumulated throughout the 100-day studies to a maximum of 45.5-54.9% of applied radioactivity. It was thus not possible to establish an absolute maximum level of accumulation in the two studies, nor the rate of subsequent dissipation. The initial, maximum concentration of UR-50604 in surface water was thus calculated assuming 100% conversion of the parent compound to the metabolite. Calculations were made assuming (1) direct overspray and (2) drift from a distance of 1 m, 5 m or 10 m. The initial PEC_{SW} for the parent compound was 85.0 µg/l for direct overspray. Initial PEC_{SW} values for the parent compound arising from drift were 3.4 µg/l, 0.51 µg/l and 0.34 µg/l for drift distances of 1 m, 5 m and 10 m, respectively. Taking the molecular weights of UR-50601 (355.3 g/mol) and UR-50604 (266.2 g/mol) into account, the assumption of 100% conversion results in initial, maximum PEC_{SW} values for UR-50604 of:

63.70 µg/l	arising from direct overspray;
2.55 µg/l	arising from drift from 1 m;
0.38 µg/l	arising from drift from 5 m;
0.26 µg/l	arising from drift from 10 m.

It should be noted that direct overspray contravenes Good Agricultural Practice.

Apart from any initial input to surface waters via direct overspray or spray drift, two other major sources of input are possible:

1. Drainflow – An estimate of concentrations of UR-50604 in surface waters arising from drainflow has been made according to draft German recommendations (Kloskowski *et al.*, 1999). Two scenarios were considered (winter and summer):

Winter

Volumes of drainflow were assumed to be 50% of total precipitation during a 20 mm rainfall event (100,000 litres). Losses of the pesticide in drainflow are 0.25% of the initial amount. The initial predicted environmental concentration in soil for the metabolite UR-50604 was 0.066 mg/kg (see Section 9.1.3) which is equivalent to 50.0 g UR-50604/ha. A 0.25% loss of UR-50604 thus equates to 0.125 g/ha. Drainflow is discharged into a water body of 100-m length, 1-m width and 30-cm depth (30,000 litres). The total volume of water is 130,000 litres giving a worst-case initial PEC_{SW} value from drainflow for the winter scenario of 0.96 µg UR-50604/l.

Summer

Volumes of drainflow were assumed to be 5% of 20 mm rainfall (10,000 litres). Losses of UR-50604 were 0.025% of the initial amount (50.0 g/ha) giving 0.0125 g. These were discharged into a surface water body of 100-m length, 1-m width and 30-cm depth (30,000 litres). The total volume of water is 40,000 litres which results in a worst-case initial PEC_{SW} value from drainflow for the summer scenario of 0.31 µg UR-50604/l.

2. Surface runoff and erosion –A simple, worst-case estimate of potential concentrations in surface water arising from losses via runoff was made according to ECPA guidelines (Wauchope, 1978; ECPA, 1994). This is based upon the assumption that 0.5% of the pesticide loading to soil in a 1 ha field moves to a 0.2 ha static pond which is 1 m in depth. The initial predicted environmental concentration in soil for the metabolite UR-50604 was 0.066 mg/kg (see point 9.1.3) which is equivalent to 50.0 g UR-50604/ha. A 0.5% loss of UR-50604 thus equates to 0.25 g/ha. The volume of the 0.2 ha pond is 2×10^6 l, giving a worst-case initial PEC_{SW} value from runoff of 0.12 µg UR-50604/l.

Drift was shown to be the main pathway for entry of UR-50604 into surface waters under Good Agricultural Practice with initial, maximum concentration of 0.26-2.55 µg/l depending upon drift distance (1-10 m). Largest predicted concentrations arising from drainflow or surface runoff and erosion were much smaller (0.96 and 0.12 µg/l, respectively). The initial, maximum PEC_{SW} of UR-50604 can thus be taken to be 2.55 µg/l.

Comment: Acceptable. It is agreed on that spray drift is the main entry route in surface water for both the active substance and the metabolite UR-50604.

B.8.6.2 Predicted environmental concentrations in sediment (PEC_{sed})

Standard references (not submitted):

EC (1998). Draft working document. Draft guidance document on aquatic ecotoxicology in the frame of the directive 91/414/EEC. EU Document 8075/VI/97 rev4.

GANZELMEIER, H., RAUTMANN, D., SPANGENBERG, R., STRELOKE, M., HERRMANN, M., WENZELBURGER H.-J. & WALTER, H.-F. (1995). Untersuchungen zur Abtrift von Pflanzenschutzmitteln. Mitteilungen aus der Biologischen Bundesanstalt für Land- und ForstwirtschaftBerlin-Dahlem,30

Initial, maximum PEC_{SED} values for UR-50601 in sediment arising from direct overspray or drift have been calculated based on the method proposed by DGVI of the European Commission (EC, 1998).

PEC_{SED} for UR-50601 from direct overspray

The following assumptions were made:

- Direct overspray of a static ditch of 1 m width and 1 m length.
- Sediment depth of 5 cm.
- Sediment bulk density of 1.5 g/cm^3.
- Maximum use rate of 0.255 kg a.s./ha.
- One application per year.

The maximum accumulation of UR-50601 in sediment at any interval during aerobic aquatic degradation studies with two water/sediment systems and two radiolabelled forms of UR-50601 was 57.5% and 52.2% of applied radioactivity, respectively. The larger of these values was used to calculate the loading of UR-50601 to the sediment. Sediment was assumed to be 5 cm deep and to have a bulk density of 1.5 g/cm^3, giving a total mass of 75 kg/m^2 ditch. Dividing the sediment loading equally throughout the sediment resulted in an initial estimate for PEC_{SED}. Results of the calculations of PEC_{SED} for UR-50601 arising from direct overspray are given below.

Loading to ditch (mg/m^2)	**Resulting loading to sediment** (mg/m^2)	**Initial PEC_{SED}** (mg/kg)
25.5	14.7	0.20

It should be noted that direct overspray contravenes Good Agricultural Practice.

PEC_{SED} for UR-50601 from drift

The following assumptions were made:

- Drift to a static ditch of 1 m width and 1 m length.
- Drift from 1, 5 or 10 m distance with drift values of 4.0, 0.6 and 0.4% respectively, selected as a worst-case (95th percentile) for application to field crops (Ganzelmeier *et al.*, 1995).
- Sediment depth of 5 cm.
- Sediment bulk density of 1.5 g/cm^3.
- Maximum use rate of 0.255 kg a.s./ha.
- One application per year.

The longer of two values for maximum accumulation of UR-50601 in sediment at any interval during aerobic aquatic degradation studies (57.5% of applied radioactivity) was used to calculate the loading of UR-50601 to the sediment. Sediment was assumed to be 5 cm deep and to have a bulk density of 1.5 g/cm^3, giving a total mass of 75 kg/m^2 ditch. Dividing the sediment loading equally throughout the sediment resulted in an initial estimate for PEC_{SED}. Results of the calculations of PEC_{SED} for UR-50601 arising from drift are given below.

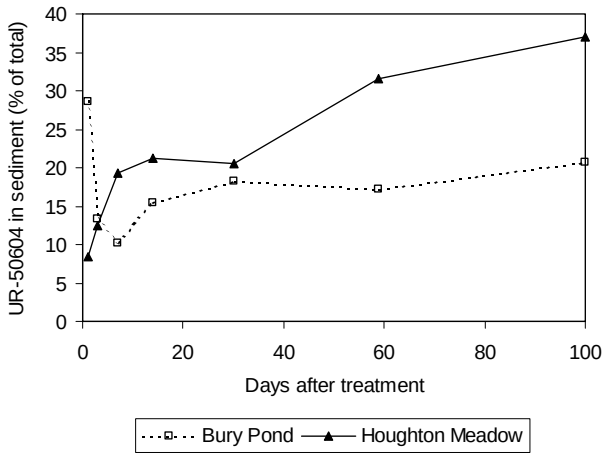
Distance (m)	Drift (%)	Resulting loading to ditch (mg/m^2)	Resulting loading to sediment (mg/m^2)	Initial PEC_{SED} (mg/kg)
1	4.0	1.02	0.59	0.0078
5	0.6	0.15	0.09	0.0012
10	0.4	0.10	0.06	0.00078

PEC_{SED} for UR-50604

An initial, maximum PEC_{SED} value for UR-50604 in sediment was calculated on the basis of inputs of the parent compound via overspray or drift from a distance of 1 m, 5 m or 10 m and 100% conversion of the parent compound to the metabolite. Taking the molecular weights of UR-50601 (355.3 g/mol) and UR-50604 (266.2 g/mol) into account, this results in a loading to the ditch of

19.1 mg/m^2	arising from direct overspray;
0.764 mg/m^2	arising from drift from 1 m;
0.115 mg/m^2	arising from drift from 5 m;
0.076 mg/m^2	arising from drift from 10 m.

Aerobic aquatic degradation studies with two water/sediment systems demonstrated that the proportion of the metabolite UR-50604 in the sediment did not exceed 40% of the amount of UR-50604 present in the total system (water + sediment) at any time within the 100-day study period.



It was thus assumed that the loading of UR-50604 to the sediment equals 40% of the total loading to the 1 m wide ditch. This gave a loading of UR-50604 to the sediment of 7.64 mg/m^2 for direct overspray. Loadings to the sediment via drift from 1 m, 5 m and 10 m distance were calculated to be 0.306 mg/m^2, 0.046 mg/m^2 and 0.031 mg/m^2, respectively. Dividing the sediment loading equally throughout the sediment (75 kg/m^2) resulted in initial estimates for PEC_{SED} of

0.1019 mg/kg	arising from direct overspray;
0.0041 mg/kg	arising from drift from 1 m;
0.0006 mg/kg	arising from drift from 5 m;
0.0004 mg/kg	arising from drift from 10 m.

It should be noted that direct overspray contravenes Good Agricultural Practice.

Comment: Acceptable.

B.8.6.3 Predicted environmental concentrations in ground water (PEC_{gw})

Reference: Anonymous, "UR-50601 (Beflubutamid), Evaluation of groundwater contamination by the metabolite UR-50604 in soil (refined risk assessment)", Revised report, 12 April 2002, BOD2002-280

Remark: The earlier submitted simulation is not reported here because it was not based on the recommendations of the FOCUS group (Reference: S. Beulke; C.D. Brown (2000): Estimation with PELMO-3.00 of expected concentrations of UR-50601 and UR-50604 in the groundwater (PEC_{GW}), report no. JF4290V, WAS2000-1137)

In the degradation studies conducted with UR-50601 in the laboratory, half-life times of the metabolite UR-50604 have been overestimated, because the linear regression of logarithmically transformed data during the respective decline period ignores the concurrent formation of the degradation product. Therefore the degradation rate of UR-50604 was re-calculated from data of the same laboratory soil degradation studies using the modelling software "ModelMaker" (version 4.0, FamilyGenetix Limited the Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA, United Kingdom).

The computer model ModelMaker uses the Marquardt iterative numerical method of optimisation Model parameters systematically adjusted to find the best agreement between the model and the experimental data.

The software required that the degradation pathway ("the model") be defined by the user with two degradation products of UR-50624 and UR-50604, possible four models were examined, based on the known degradation pathway. Since in the field dissipation studies, the metabolite UR-50604 was only found temporally in small amounts, and the DT_{50} of the metabolite could not be determined, the calculation half-life times as well as the simulation of groundwater contamination has to be based on laboratory data.

From three possible models, the one was chosen, which gave the best statistically significance of individual parameters were satisfied the best. Taken the statistically significance and the fitness into account, five soils (out of six) delivered satisfactory DT_{50} and DT_{90} values using the computer software ModelMaker, however, one soil was tested at 10°C. In addition to estimating rate constants for UR-50604, the software calculated constants for UR-50601 and UR-50624. The errors associated with the rate constants for UR-50624 were large, therefore the data are shown for the active substance and metabolite UR-50604 only.

Soil	Temp.	Data set (day)	UR-50601		UR-50604	
			DT_{50}(days)	DT_{90}(days)	DT_{50}(days)	$DT_{9}0$(days)
Arrow	20°C	0-152	15.8	52.6	18.0	59.8
Wick	20°C	0-120	5.3	17.4	0.9	3.2
Speyer 2.2 (1^{st} experiment)	20°C	0-30	31.7	105.4	3.1	10.2
Evesham 3	20°C	0-120	8.7	29.1	3.1	10.3
Evesham 3	10°C	0-120	30.5	101.3	17.2	57.0
Speyer 2.2 (2^{nd} experiment)	20°C	0-30	14.5	48.2	2.8	9.3

The results of the optimisation analysis and individual parameters significance are shown as follows:

Soil	Temp.	Data set (days)	Optimisation statistics of entire models			P values of T-test for individual parameters		
			r^2	F	P	d1	k1	k2
Arrow	20°C	0-152	0.8526	49	$2.7x10^{-11}$	<0.01	<0.01	<0.01
Wick	20°C	1-120	0.99	641	0.00046	<0.01	<0.01	<0.01
Speyer 2.2 (1^{st} experiment)	20°C	0-30	0.9936	702	0.0016	<0.01	<0.01	<0.05
Evesham 3	20°C	0-120	0.9785	295	$4.3x10^{-5}$	<0.01	<0.01	<0.01
Evesham3	10°C	0-120	0.9796	313	$1.9x10^{-5}$	<0.01	<0.01	<0.01
Speyer 2.2 (2^{nd} experiment)	20°C	0-30	0.9895	424	0.00043	<0.01	<0.01	<0.01

A statistically good optimisation of the both Speyer 2.2 groups could only be achieved by using the 0-30 days. The agreement was less good for Arrow soil and so in this case the model has been less reliable in estimating the rate constants. In addition, the rate of degradation in Arrow soil declined markedly during the later stages of the incubation period. This is in contrast to Wick and Evesham 3 soils in particular in which degradation of UR-50601 continued throughout the incubation. This suggests a decline in microbial activity in Arrow soil during this time, and consequently the use of DT_{50} values from Arrow soil will be inappropriate.

For further evaluation for the input in the computer model FOCUS-Pelmo the DT_{50} obtained at 20°C data were normalized to the reference moisture content of 10 kPa (pF2) as recommended by the Guidance paper of the FOCUS group. Normalized DT_{50} were as follows:

Soil	UR-50601	UR-50604 DT_{50} (days)
Wick	3.6	0.6
Speyer 2.2 (1st experiment)	24.3	2.4
Evesham 3	5.0	1.8
Speyer 2.2 (2nd experiment)	11.1	2.2
Average	11.0	1.7

The simulation of groundwater contamination was conducted with FOCUS PELMO 2.2.2 for EU registration with nine location scenarios for winter cereals and six location scenarios for spring cereals.

As crop scenarios, defaults values were used as proposed fro the model of winter cereals and spring cereals. As mentioned before, average DT_{50} (normalised data) and average K_{oc} values were used both for UR-50601 and UR-50604 according to the recommendations of the FOCUS guidance. Other input parameters as volatilisation and degradation parameters were taken from the correponding reports.

Input data of UR-50601 and UR-50604 to FOCUS-PELMO:

Crop		Winter and spring cereals
	Crop specific values (emergence etc.)	default
Application	Rate	0.255 kg a.s. /ha
	Time	default
Active substance	**UR-50601**	
	Molecular mass	355.3
Volatilisation	Henry-constant	1.08×10^{-2} Pa m^3 /mol
	vapour pressure	1.1×10^{-5} Pa
	water solubility	3.290 mg/L
	diffusion coefficient	4320
	depth of surface layer for volatilisation	0.1 cm
	plant uptake factor	0.5 (default)

Sorption parameter	average K_{oc}	1260
	pKa	20
	pH	7.1
	Freundlich-exponent	0.92
Transformation to UR-50604	normalised DT_{50}	11.0 days
	Temp. corr. factor (Q10)	2.2
Metabolite	**UR-50604**	
	Molecular mass	266.2
	plant uptake factor	0.5 (default)
Sorption parameter	K_{oc}	12.3
	pKa	20
	pH	6.0
	Freundlich-exponent	0.87
Transformation to CO_2	normalised DT_{50}	1.7 days
	Temp. corr. factor (Q10)	2.2

The calculation showed that the contamination of the parent compound UR-50601 and the metabolite UR-50604 is less than 0.1 µg/L in groundwater.

Crop	Winter cereal		Spring cereal	
Substance	UR-50601	UR-50604	UR-50601	UR-50604
Weather/soil scenario:	Maximum long-term concentration in groundwater (µg/L) (80^{th} percentile value of UR-50604 in the percolate at 1 m soil depth)			
Chateaudun	0.000	0.000	0.000	0.000
Hamburg	0.000	0.000	0.000	0.000
Jokioinen	0.000	0.000	0.000	0.000
Kremsmunster	0.000	0.000	0.000	0.000
Okehampton	0.000	0.000	0.000	0.000
Piacenza	0.000	0.009	-	-
Porto	0.000	0.000	0.000	0.000
Sevilla	0.000	0.000	-	-
Thiva	0.000	0.000	-	-

Comment: **Not acceptable**. The DT_{50} values from "Arrow" soil are also to be taken into account because the microbial biomass is in the same order as for the other soils and these values are not evaluated as outliers. The Rapporteur conducted a new simulation taking into account all these results for the scenario "Hamburg" and "Piacenza" which resulted in concentrations for the metabolite UR-50604 of 0.113 and 0.224 µg/L (DT_{50} 12 d (active substance) and 5d (metabolite UR-50604)). Therefore, the notifier has to submitt a new FOCUS-PELMO calculation with these parameters. Furthermore, it is unclear why different intervalls (Speyer 2.2. 0-30 days, Wick and Evesham 0-120 days) were selected for the determination of DT_{50} values.

It is up to the notifier to show the non-relevance of the metabolite or to conduct lysimeter and field leaching studies, respectively.

B.8.7 Fate and behaviour in air (Annex IIA 7.2.2; Annex IIIA 9.3)

The low vapour pressure of the parent compound UR-50601 (1.1×10^{-5} Pa at 25°C) indicates little potential for volatilisation from either soil or plant surfaces. This is not a likely route of environmental contamination.
For the determination of beflubutamid in air the following calculation was carried out:
The maximal intended field application rate is 3 l/ha x 85 g a.i./ha = 255 g a.i./ha. This equals a concentration of 25.5 mg/m^2. If one assumes a worst-case situation in which the entire concentration of beflubutamid evaporates into 1 m^3 of air, this would lead to a concentration of 0.0255 mg/l air or 25.5 µg/l air (Table B.8.7-1). Furthermore, the acute inhalation toxicity of beflubutamid was measured and indicated no potential risk of beflubutamid via air contamination (LC_{50} rat > 5.00 mg/l air). The acute inhalation median lethal concentration of the formulated product Herbaflex (85 g/l beflubutamid + 500 g/l isoproturon) in the rat was greater than 3.2 mg/l of air. This was the highest attainable practical concentration under the test conditions. The exposure levels achieved with the active ingredient beflubutamid and the formulated product Herbaflex in the inhalation toxicity studies are far in excess of any exposure level that could be generated in reality even by accident. However, comparing the predicted environmental concentration 0.0255 mg beflubutamid/l air under the assumption that the entire application rate escapes into air with the toxicity values obtained in the acute inhalation toxicity studies, no potential risk of beflubutamid via air contamination can be identified.
Therefore, a further study to determine the fate of beflubutamid in air was not considered to be necessary.

Table B.8.7-1: Concentrations of beflubutamid in air compared to inhalation toxicity

Maximum application rate	255 g beflubutamid/ha, equivalent to 25.5 mg/m^2
Beflubutamid concentration in air assuming a worst-case of all applied product vapourising (PEC_{air}).	25.5 mg beflubutamid/m^3, equivalent to 0.0255 mg beflubutamid/l of air
Acute inhalation toxicity of beflubutamid (UR-50601), LC_{50} rat (4 hours)	> 5.0 mg beflubutamid/l air
Acute inhalation toxicity of Herbaflex (ASU 95 510 H), LC_{50} rat (4 hours)	> 3.2 mg beflubutamid/l air
TER for beflubutamid in air based on active substance	> 196
TER for beflubutamid in based on formulation	> 125

Comment: This risk assessment is based on human exposure. The following risk assessment for the environment was conducted by the rapporteur:

Risk assessment:
The active substance is a semivolatile substance due to the vapour pressure of 1.1 x 10^{-5} Pa at 25°C . Volatilization from soil and/or plants should occur only in minor amounts. Once in the atmosphere beflubutamid is degraded with DT_{50} of 3.5 hours (12 h day) and 15.7 hours (24 h day), respectively, by photochemical oxidative degradation and therefore no long range transport is expected.

B.8.8 Predicted environmental concentrations in air (Annex IIIA 9.3)

The active substance is a semivolatile substance due to the vapour pressure of 1.1 x 10^{-5} Pa at 25°C . Volatilization from soil and/or plants should occur only in minor amounts. Once in the atmosphere beflubutamid is degraded with DT_{50} of 3.5 hours by photochemical oxidative degradation and therefore no long range transport is expected.

Therefore, the calculation of predicted environmental concentrations in air are deemed to be not necessary.

B.8.9 Definition of the residue (Annex IIA 7.3)

The residue can be defined as beflubutamid and its major metabolite UR-50604 (soil (aerobic, anaerobic), water/sediment). Metabolite UR-50604 is non-relevant regarding ecotoxicology and biological activity.

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; AIIIA-9.1	Dean, G.M. and Mayo, B.C.	1997	Aerobic soil metabolism (Pilot study). UBE 036/97729 GLP, unpublished BOD2000-1131	Y	UBE
AIIA-7.1.1.1.1; AIIA-7.1.1.2.1; AIIIA-9.1	Dean, G.M. et al.	1999	Aerobic soil metabolism (Main study). UBE 67/983000 GLP, unpublished BOD2000-1132	Y	UBE
AIIA-7.1.1.1.2	Dean, G.M. et al.	1998	Soil photolysis. UBE 077/983818 GLP, unpublished BOD2000-1134	Y	UBE
AIIA-7.1.1.1.2; AIIA-7.1.1.2.1; AIIIA-9.1	Dean, G.M. et al.	1998	Anaerobic soil metabolism. UBE 076/982926 GLP, unpublished BOD2000-1133	Y	UBE
AIIA-7.1.1.2.1; AIIIA-9.1	Dean, G.M. and Mayo, B.C.	1999	Rate of degradation in three soils. UBE 071/982852 GLP, unpublished BOD2000-1135	Y	UBE
AIIA-7.1.1.2.2	Heydkamp, I.	2001	Soil dissipation study with Herbafles in Germany. Rep.No. VP00-1-35 GLP, unpublished BOD2001-325	Y	ASU
AIIA-7.1.1.2.2	Schneider, V.	2001	Determination of residue od UR 50601 (Beflubutamid) in soil dissipation study with Herbaflex in Germany. Rep.No. PR00/018 GLP, unpublished BOD2001-395	Y	ASU
AIIA-7.1.1.2.2; AIIA-7.1.3.3	Takamura, S.	2002	Evaluation of groundwater contamination by the metabolite UR-50604 in soil. - not GLP, unpublished BOD2002-280	Y	TSU

[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-7.1.1.2.2	Wilson, A.	2000	Terrestrial field dissipation study with ASU 95510 H (85 g/l UR + 500 g/l Isoproturon) applied to bare soil in Spain, United Kingdom and Germany in 1998/1999. UR-50601 not GLP, unpublished BOD2000-1332	Y	UBE
AIIA-7.1.1.2.2; AIIIA-9.1	Wilson, A.	1999	Terrestrial field dissipation study with ASU 95 510 H (85 g/l UR-50601+500 g/l Isoproturon) applied to bare soil in Spain, United Kingdom and Germany in 1998/1999. UBE 099/002143 GLP, unpublished BOD2000-1136	Y	UBE
AIIA-7.1.2	Aikens, P.J. et al.	1999	Adsorption/desorption on soil. UBE 086/992243 GLP, unpublished BOD2000-1130	Y	UBE
AIIA-7.1.2	Aikens, P.J. et al.	1997	Adsorption/desorption on soil. UBE 42/971616 GLP, unpublished BOD2000-1129	Y	UBE
AIIA-2.9; AIIA-7.2.1.1	Chalker, M.H. et al.	1997	Hydrolysis under laboratory conditions. UBE 58/971769 GLP, unpublished WAS2000-554	Y	UBE
AIIA-2.9; AIIA-7.2.1.2	Elsom, L.F. et al.	1998	Photolytic degradation in water. UBE 57/973942 GLP, unpublished LUF2000-464	Y	UBE
AIIA-7.2.1.2	Millais, A.J. and Kirkpatrick, D.	1999	Aqueous photolysis. UBE 087/992694 GLP, unpublished LUF2000-465	Y	UBE
AIIA-7.2.1.3.2	Elsom, L.F. et al.	1999	Aerobic aquatic degradation study. UBE 069/983037 GLP, unpublished WAS2000-555	Y	UBE
AIIIA-9.1.3	Takamura, S.	2002	Evaluation of groundwater contamination by the metabolite UR-50604 in soil (Refined risk assessment) Appendix 1-3. - not GLP, unpublished BOD2002-382	Y	TSU

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-9.1.3	Takamura, S.	2002	PELMO simulation of UR-50601 and UR-50604 in groundwater, detailed information. - not GLP, unpublished BOD2002-281	Y	TSU
AIIIA-9.2.1	Beulke, S. and Brown, C.D.	2000	Estimation with PELMO-3.00 of expected concentrations of UR-50601 and UR-50604 in the groundwater (PECgw). - not GLP, unpublished BOD2000-1137	Y	ASU
AIIIA-9.2.3	Beulke, S. and Brown, C.D.	2000	Estimation with PRZM-3.12 of expected concentrations of UR-50601 in surface waters (PECsw) arising from losses via surface runoff and erosion. - not GLP, unpublished WAS2000-561	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

Annex B

Beflubutamid

B-9: Ecotoxicology

B.9 Ecotoxicology

B.9.1 Effects on birds (Annex IIA 8.1; Annex IIIA 10.1)

B.9.1.1 Acute Oral Toxicity (Annex IIA 8.1, Annex IIIA 10.1.1)

Title:	**UR-50601: Acute toxicity (LD_{50}) to the bobwhite quail**
Author:	Johnson, A.J., Cameron, D.M. and Dawe, I.S. (1997)
BBA-Ref.-No.:	AVS2000-117
Test substance:	technical beflubutamid
Purity:	97.46 %
Guideline:	EPA 71-1
Test species:	Bobwhite quail (*Colinus virginianus*)
Age:	ca. 8 mo
Birds per treatment:	5 M + 5 F
Administration:	intubation
Solvent / vehicle:	methylcellulose
Dose levels:	0/500/1000/2000 mg/kg
Findings:	No mortalities or signs of intoxication have been observed. Over days 1 to 3 post-dosing food consumption was slightly reduced in groups 1000 and 2000 mg/kg; group mean body weight was slightly decreased at 2000 mg/kg.
LD_{50}:	>2000 mg/kg bw
Lowest lethal dose:	>2000 mg/kg bw
NOED:	500 mg/kg bw
valid:	yes
GLP compliance:	yes

B.9.1.2 Dietary toxicity (Annex IIA 8.1.2)

Title:	**UR-50601: Dietary LC_{50} to the bobwhite quail**
Author:	Rodgers, M.H., Cameron, D.M. and Dawe, I.S. (1997)
BBA-Ref.-No.:	AVS2000-118
Test substance:	technical beflubutamid
Purity:	97.46 %
Guideline:	EPA 71-2 / OECD 205
Test species:	Bobwhite quail (*Colinus virginianus*)
Age:	14 d
Birds per treatment:	10 unsexed
Solvent / vehicle:	none

Exposure period:	5 d
Conc. levels (nom.):	0/163/325/650/1300/2600/5200 ppm
Conc. levels (meas.):	0/162/321/645/1290/2550/5120 ppm
Homogeneity:	satisfactory
Stability:	satisfactory
Achieved doses:	-/34/123/248/568/970 mg/kg bw/d
Findings:	There have been observed no effects up to and including the top dose level.
LC_{50}:	>5200 ppm
Lowest lethal conc.:	>5200 ppm
NOEC:	5200 ppm
valid:	yes
GLP compliance:	yes

B.9.1.3 Effects on reproduction (Annex IIA 8.1.3)

Title:	**UR-50601: Effects on reproduction in bobwhite quail**
Author:	Johnson, A.J. and Cameron, D.M. (1998)
BBA-Ref.-No.:	AVS2000-119
Test substance:	technical beflubutamid
Purity:	97.46 %
Guideline:	EPA 71-4 / OECD 206
Test species:	Bobwhite quail (*Colinus virginianus*)
Age:	ca. 9 mo
Birds per treatment:	20 pairs
Solvent / vehicle:	none
Exposure period:	22 wk
Conc. levels (nom.):	0/100/500/1000 ppm
Conc. levels (meas.):	0/94/472/921 ppm
Homogeneity:	satisfactory
Stability:	satisfactory
Achieved doses:	-/8/44/88 mg/kg bw/d
Findings:	There were observed no effects up to and including the top dose level. The number of 14-day survivors per female for 0 / 100 / 500 / 1000 ppm was 31.2 / 32.7 / 35.6 / 34.7.
NOEC:	1000 ppm
valid:	yes
GLP compliance:	yes

Table 9.1-1: Summary of avivan toxicity data

Test material	Species	Test	NOEL	LD_{50}/LC_{50}	Unit
Beflubutamid	Bobwhite quail	Acute	500	>2000	mg/kg bw
Beflubutamid	Bobwhite quail	5-day-dietary	5200	>5200	ppm
Beflubutamid	Bobwhite quail	Reproduction	1000		ppm

B.9.1.4 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 beflubutamid formulations are to be applied exclusively as sprays.

B.9.1.5 Risk assessment for birds

Birds may be exposed to beflubutamid 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 0.255 kg as/ha that is intended for cereals.

Exposure assessment: Residues are estimated according to Hoerger and Kenaga (1972)[1]. 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. Then the maximum daily intake is 7 mg/kg bw.

Table 9.1-2: Exposure assessment for birds

Use	Maximum application rate (kg/ha)	Feed	Typical maximum residue[1] (mg/kg)	Initial residue (mg/kg)	Relative feed demand (%)	Maximum daily intake (mg/kg bw)
Cereals	0.255	Cereal shoots	112·R	28	25	7
Cereals	0.255	Insects	29·R	8	40	3

[1] according to Hoerger and Kenaga (1972): Pesticide residues on plants: Correlation of representative data as a basis for estimation of their magnitude in the environment. Environmental Quality I. New York: Academic Press, 9-28.

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 well above the Annex-VI-triggers; so the risk to birds is considered as low.

Table 9.1-3: Toxicity/exposure ratios for birds

Use	Feed	Time-scale	Toxicity/Exposure ratio
Cereals	Cereal shoots	acute	TER_a = >2000/7 = >285
Cereals	Cereal shoots	short-term	TER_{st} = >5200/28 = >185
Cereals	Cereal shoots	long-term	TER_{lt} = 1000/28 = 36
Cereals	Insects	acute	TER_a = >2000/3 = >660
Cereals	Insects	short-term	TER_{st} = >5200/8 = >650
Cereals	Insects	long-term	TER_{lt} = 1000/8 = 125

B.9.2 Effects on aquatic organisms (Annex IIA 8.2; Annex IIIA 10.2)

B.9.2.1 Toxicity and bioaccumulation tests

B.9.2.1.1 Fish - acute toxicity

Title: **UR-50601: Acute toxicity to Bluegill sunfish Determination of 96-hour LC_{50}**
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-576
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: OECD 203
Test species: *Lepomis macrochirus*
Exposure mode: semi-static
Conc. levels (nom.): 0; 1.3; 2.16; 3.6; 6; 10 mg/L
Conc. levels (meas.): 0; 1.03; 1.66; 2.69; 4.44; 5.56 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	1.66			2.69

valid: yes
GLP compliance: yes

Title: **UR-50601: Acute toxicity to Rainbow trout Determination of 96-hour LC_{50}**

Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-575
Test substance: technical beflubutamid
Guideline: EPA 72-1
Test species: *Oncorhynchus mykiss*

Exposure mode: semi-static
Conc. levels (nom.): 0; 0.622; 1.04; 1.73; 2.88; 4.8; 8 mg/L
Conc. levels (meas.): 0; 0.552; 0.898; 1.48; 2.46; 3.55; 5.16 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	n.d.			1.86

valid: yes
GLP compliance: yes

Title: **UR-50604: Acute toxicity to Fish (Rainbow trout)**
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-577
Test substance: metabolite UR-50604
Guideline: OECD 203
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 1.94; 4.27; 9.39; 20.7; 45.5; 100 mg/L
Conc. levels (meas.): 0; 1.77; 3.92; 8.68; 18.9; 42.6; 93.0 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	3.92	93.0	43	>93.0

valid: yes
GLP compliance: yes

Title: **ASU 95 510 H (UBH-820-IPU Formulation) Acute Toxicity to Fish (Rainbow trout)**
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-574
Test substance: formulation ASU 95510 H
beflubutamid 86.83 g/L
isoproturon 500.53 g/L
Guideline: OECD 203
Test species: *Oncorhynchus mykiss*
Exposure mode: static
Conc. levels (nom.): 0; 3.42; 7.51; 16.5; 36.4; 80 mg/L
Conc. levels (meas.): 0; 3.14; 6.57; 14.3; 32.6; 68.7 mg/L

Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
96 h	Mortality	3.14			39.1

valid: yes

GLP compliance: yes

B.9.2.1.2 Fish - ELS

Title: **UR-50601: Fish Early Life Stage Toxicity Test for Fathead minnow (*Pimephales promelas*)**
Author: Bell, G. and Hargreaves, T.L. (2000)
BBA-Ref.-No.: WAT2000-578
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: OECD 210
Test species: *Pimephales promelas*
Exposure mode: flow-through
Conc. levels (nom.): 0.1; 0.22; 0.46; 1.0; 2.2 mg/L
Conc. levels (meas.): 0.11; 0.22; 0.45; 0.85; 1.4 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
28 d	Mortality	0.85	1.4	45	
28 d	Hatch rate	1.4			
28 d	Growth	0.11	0.22	21	
28 d	Behaviour	0.45	0.85		

Remarks: at highest test concentration precipitation; 0.05 mg/L tetrahydrofuran as solvent; 28 d plus 3 d pre-hatch
valid: yes
GLP compliance: yes

B.9.2.1.3 Invertebrates - acute toxicity

Title: **UR-50601: Acute toxicity to *Daphnia magna* Determination of 48-hour EC_{50} under static conditions**

Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-580
Test substance: technical beflubutamid
Purity: 97.46 %

Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 0.233; 0.389; 0.648; 1.08; 1.8; 3; 5 mg/L
Conc. levels (meas.): 0; 0.186; 0.335; 0.516; 0.939; 1.47; 2.7; 3.57 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}

48	h	Mortality			1.64

valid: yes
GLP compliance: yes

Title: **UR-50604 Acute toxicity to *Daphnia magna***
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-581
Test substance: metabolite UR-50604
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 100 mg/L
Conc. levels (meas.):
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	91.8			>91.8

valid: yes; limit-test
GLP compliance: yes

Title: **ASU 95 510 H (UBH-820-IPU Formulation) Acute toxicity to *Daphnia magna***
Author: Jenkins, W.R. (1999)
BBA-Ref.-No.: WAT2000-589
Test substance: formulation ASU 95 510 H
beflubutamid 86.83 g/L
isoproturon 500.53 g/L
Guideline: OECD 202 I
Test species: *Daphnia magna*
Exposure mode: static
Conc. levels (nom.): 0; 3.75; 7.5; 15; 30; 60 mg/L
Conc. levels (meas.): 0; 3.23; 6.73; 13.7; 27.3; 44.7 mg/L

Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
48 h	Mortality	6.73			17.3

valid: yes
GLP compliance: yes

B.9.2.1.4 Invertebrates - long-term toxicity

Title: **UR-50601: *Daphnia magna* Reproduction Test**
Author: Jenkins, C.A. (1999)

BBA-Ref.-No.: WAT2000-582
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: OECD 202 II
Test species: *Daphnia magna*
Exposure mode: semi-static
Conc. levels (nom.): 0.0853; 0.188; 0.413; 0.908; 2.0 mg/L
Conc. levels (meas.): 0.1; 0.223; 0.455; 1.09; 2.29 mg/L

Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
21 h	Mortality	0.455	1.09	13	1.43
21 h	Growth	0.455	1.09		
21 h	Reproduction	0.455	1.09	71	

valid: yes
GLP compliance: yes

B.9.2.1.5 Sediment dwellers

Title: **UR-50601 To assess the toxicity to the sediment dwelling phase of the midge *Chironomus riparius***
Author: Bell, G. (2000)
BBA-Ref.-No.: WAT2000-586
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: BBA
Test species: *Chironomus riparius*
Exposure mode: spiked water
Conc. levels (nom.): 0.056; 0.18; 0.56; 1.8; 5.6 mg/L
Results (mg/L) related to nominal concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
28 d	Development	0.56	5.6	4	
28 d	Emergence	1.8	5.6	50	6,5

Remarks: labelled material was used; additional vessels for analytical measurements; measured concentrations in overlying water 86 - 39 % at the start and 32 - 27 % at the end; in pore water 0.14 and 0.239 mg/L on day 3 and 7 for 5.6 mg/L and 32/36 mg/kg for sediment respectively; on day 28 amount in sediment and overlying water comparable, whereas in porewater 0.3 %
valid: yes
GLP compliance: yes

B.9.2.1.6 Algae

Title: **UR-50601: Determination of 120-hour EC_{50} to Anabaena**
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-584
Test substance: technical beflubutamid
Guideline: EPA 123-2 / 122-2
Test species: *Anabaena flos-aquae*
Exposure mode: static
Conc. levels (nom.): 0; 0; 10 mg/L
Conc. levels (meas.): 0; 0; 6.01 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass				>6.01
72 h	Growth				>6.01

Remarks: test concentration is in the range of the water solubility; highest concentration considered practicable to prepare
valid: yes
GLP compliance: yes

Title: **UR-50601: Determination of 72-hour EC_{50} to *Selenastrum capricornutum***
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-583

Test substance: technical beflubutamid
Guideline: OECD 201
Test species: *Selenastrum capricornutum*
Exposure mode: static
Conc. levels (nom.): 0; 0; 0.000485; 0.00107; 0.00235; 0.00517; 0.0114; 0.025 mg/L
Conc. levels (meas.): 0; 0; 0.000448; 0.00113; 0.00244; 0.00537; 0.0104; 0.0258 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass	0.00244			0.00445
72 h	Growth	0.00244			0.0055

valid: yes
GLP compliance: yes
Title: **UR-50604 Algal growth inhibition assay**
Author: Jenkins, C.A. (1999)
BBA-Ref.-No.: WAT2000-585
Test substance: metabolite UR-50604

Guideline: OECD 201
Test species: *Selenastrum capricornutum*
Exposure mode: static
Conc. levels (nom.): 0; 4.27; 9.39; 20.7; 45.5; 100 mg/L
Conc. levels (meas.): 0; 4.15; 9.38; 20.1; 43.4; 94.7 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass	20.1			69.2
72 h	Growth	43.4			>94.7

valid: yes
GLP compliance: yes

Title: **ASU 95 510 H (UBH-820-IPU Formulation) Algae growth inhibition assay (*Selenastrum capricornutum*)**
Author: Jenkins, W.R. (1999)
BBA-Ref.-No.: WAT2000-590
Test substance: formulation ASU 95 510 H
beflubutamid 86.83 g/L
isoproturon 500.53 g/L
Guideline: OECD 201 (Green algae))
Test species: *Selenastrum capricornutum*
Exposure mode: static
Conc. levels (nom.): 0; 0.00938; 0.0188; 0.0375; 0.075; 0.150 mg/L
Conc. levels (meas.): 0; 0.0112; 0.0188; 0.0367; 0.069; 0.136 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
72 h	Biomass	0.0188			0.0527

valid: yes
GLP compliance: yes

B.9.2.1.7 Aquatic plants

Title: **UR-50601 Higher Plant (LEMNA) Growth inhibition test**
Author: Kelly, C. (1998)
BBA-Ref.-No.: WAT2000-587
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: EPA 122-2 / EPA 123-2
Test species: *Lemna minor*
Exposure mode: semi-static

Conc. levels (nom.): 0; 0.0022; 0.0046; 0.01; 0.022; 0.046 mg/L

Conc. levels (meas.): 0; 0.0023; 0.0046; 0.0088; 0.02; 0.036 mg/L
Results (mg/L) related to measured concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
14 d	Fronds	0.02			0.029
14 d	Growth	0.0046	0.0088		

Remarks: after 14 d exposure five groups of three fronds from the solvent control, the lowest and the highest test concentration were placed in fresh medium (recovery period); this procedure was repeated after 4 days of the recovery period; recovery occured only in the lowest test concentration; due to a considerable difference between control and solvent control the growth (weight) measurements are difficult to evaluate; at 0.0088 mg/l a lower number of roots were observed
valid: yes
GLP compliance: yes

B.9.2.1.8 Bacteria

Title: **UR-50601 Activated sludge - Respiration inhibition test**
Author: Jenkins, W.R. (1998)
BBA-Ref.-No.: WAT2000-588
Test substance: technical beflubutamid
Purity: 97.46 %
Guideline: OECD 209
Test species:
Exposure mode:
Conc. levels (nom.): 0; 100 mg/L
Conc. levels (meas.):
Results (mg/L) related to nominal concentrations:

Time	End point	NOEC	LOEC	Effect (%) at LOEC	EC_{50}
3 h	Respiration rate				>100

valid: yes
GLP compliance: yes

B.9.2.1.9 Bioaccumulation

Title: **UR-50601: Bioconcentration in Rainbow trout**
Author: Corden, M.T. (1999)
BBA-Ref.-No.: WAT2000-579
Test substance: technical beflubutamid
Purity: 97 %
Guideline: OECD 305

Test species:	*Oncorhynchus mykiss*
Exposure mode:	flow-through
Conc. levels (nom.):	0.002; 0.020 mg/L
Conc. levels (meas.):	>80 %
Duration exposure phase:	35 d
Duration depuration phase:	14 d
Results related to:	nominal concentrations
Maximum BCF:	230 after 35 d (steady-state achieved)
Depuration:	elimination >90 % after 1 d
valid:	yes
GLP compliance:	yes

Table B.9.2-1: Toxicity values

Summary of aquatic toxicity data

Test material	**Species**	**Duration**		**NOEC (mg/L)**	**EC_{50} (mg/L)**	
beflubutamid	*L. macrochirus*	96 h (ss)	Mortality	1.66	2.69	Meas
beflubutamid	*O. mykiss*	96 h (ss)	Mortality	n.d.	1.86	Meas
beflubutamid	*P. promelas*	28 d (fl)	Mortality	0.85		Meas
			Hatch rate	1.4		Meas
			Growth	0.11		Meas
			Behaviour	0.45		Meas
beflubutamid	*D. magna*	48 h (st)	Mortality		1.64	Meas
beflubutamid	*D. magna*	21 h (ss)	Mortality	0.455	1.43	Meas
			Growth	0.455		Meas
			Reproduction	0.455		Meas
beflubutamid	*C. riparius*	28 d (st)	Development	0.56		Nom
			Emergence	1.8	6.5	Nom
beflubutamid	*A. flos-aquae*	72 h (st)	Biomass		>6.01	Meas
			Growth		>6.01	Meas
beflubutamid	*S. capricornutum*	72 h (st)	Biomass	0.00244	0.00445	Meas
			Growth	0.00244	0.0055	Meas
beflubutamid	*L. minor*	14 d (ss)	Fronds	0.02	0.029	Meas
			Growth	0.0046		Meas
beflubutamid	*Act.Sludge*	3 h (st)	Respiration rate		>100	Nom
UR-50604	*O. mykiss*	96 h (st)	Mortality	3.92	>93.0	Meas
UR-50604	*D. magna*	48 h (st)	Mortality	91.8	>91.8	Meas
UR-50604	*S. capricornutum*	72 h (st)	Biomass	20.1	69.2	Meas
			Growth	43.4	>94.7	Meas
ASU 95 510 H	*D. magna*	48 h (st)	Mortality	6.73	17.3	Meas
ASU 95 510 H	*S. capricornutum*	72 h (st)	Biomass	0.0188	0.0527	Meas
ASU 95 510 H	*O. mykiss*	96 h (st)	Mortality	3.14	39.1	Meas

fl = flow-through; st = static; ss = semi-static; sm = special method

Table B.9.2-2 Bioaccumulation:

Species	(Exp. + Dep.)	BCF	Elimination	Wat-Nr.
Oncorhynchus mykiss	35 + 14 d	230	>90 % after 1 d	2000-579

B.9.2.2 Evaluation of toxicity results and data on bioaccumulation

The available data are sufficient for a final assessment. The formulated product and the metabolite are not more toxic than the active substance which is therefore relevant for the risk assessment. Fish and Daphnia are less sensitive than plants and algae. Sediment-dwelling organisms were slightly less sensitive than Daphnia. Algae are the most sensitive group of organisms. The EC_{50} of 0.0045 mg/L for *S. capricornutum* should be used for the risk assessment.

The metabolite UR-50604 is not of ecotoxicological relevance.

Beflubutamid is liable for bioaccumulation. The BCF is higher than the relevant trigger of 100 but the elimination is fast. Furthermore data from an ELS-test indicate that no effects on the reproduction are to be expected under the proposed conditions of use. Therefore, the bioaccumulation potential is regarded as acceptable.

B.9.2.3 Risk assessment

Based on maximum application rates of 170 and 255 g as/ha for single applications the following TER-values are to be calculated:

Table B.9.2-3: TER-values

Distance [m]	PEC [µg/L]	Toxicity [µg/L]	TER
0	56/85	4.5	0.08/0.05
1	2.2/3.4	“	2.04/1.3
5	0.34/0.51	“	13.2/8.8
10	0.22/0.34	“	20.4/13

The TER-values for a distance of 1 m are below the relevant trigger value of 10 indicating an unacceptable risk to aquatic organisms. Additional data to conduct a refined risk assessment were not submitted. Therefore risk mitigation measures are to be set on member state level. For a distance of 5 m/10 m to adjacent waterbodies the TER-values indicate an acceptable risk to aquatic organisms.

Due to the high toxicity of beflubutamid to algae and the low biological degradation the active substance must be labelled with “N” and “R 50/53”.

B.9.3 Effects on other terrestrial vertebrates (Annex IIIA 10.3)

B.9.3.1 Toxicity to mammals (Annex IIIA 10.3)

There were conducted neither wild mammal toxicity studies nor field studies.

The acute oral LD_{50} of beflubutamid for rats is >5000 mg/kg body weight. Regarding the long-term risk the assessment will be based on 200 ppm that was the NOAEL for reproductive effects in a multi-generation study with rats (see section B.06, Toxicology).

B.9.3.2 Risk assessment for mammals

Mammals may be exposed to beflubutamid mainly by the consumption of contaminated feed. Highest residues will be in cereal shoots, therefore herbivorous species are considered as worst-case. The risk assessment will be based on a maximum rate of 0.255 kg as/ha as intended for cereals.

Exposure assessment: Residues on plants are estimated according to Hoerger and Kenaga. 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. Then the maximum daily intake is 7 mg/kg bw.

Exposure assessment for mammals:

Use	Maximum application rate (kg/ha)	Feed	Typical maximum residue[1] (mg/kg)	Initial residue (mg/kg)	Relative feed demand (%)	Maximum daily intake (mg/kg bw)
Cereals	0.255	Cereal shoots	112*R	28	25	7

[1] according to Hoerger and Kenaga (1972); R = application rate in kg/ha

Toxicity/exposure ratios: For the acute TER_a 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; so the risk to mammals is considered as low.

Toxicity/exposure ratios for mammals:

Use	Feed	Time-scale	Toxicity/Exposure ratio
Cereals	cereal shoots	acute	TER_a = >5000/7 = >710
Cereals	cereal shoots	long-term	TER_{lt} = 200/28 = 7

B.9.4 Effects on bees (Annex IIA 8.3.1; Annex IIIA 10.4)

B.9.4.1 Acute toxicity (Annex IIA 8.3.1)

B.9.4.1.1 Acute oral and contact toxicity of beflubutamid (technical)

Title: **UR-50601 - Acute Toxicity to Honey Bees (*Apis mellifera*)**

Author: Gray, A. P. (1999)
BBA-Ref.No.: BIE 2000-45

Guideline: EPPO guideline No. 170
Test species: *Apis mellifera*
Test substance: beflubutamid

Reference substance:	dimethoat
Control:	untreated
Control:	aceton treated

The test was performed as a limit test, i.e. the test substance was applied only in one high concentration.

No. of replicates:	6 with 10 bees/replicate
Administration:	Oral and contact administration 100 µg/bee in terms of test product. For oral uptake the solution was offered in a single dose of 200 µl/cage (20 µl/bee). For contact administration a 1 µl droplet of the solution was placed on the ventral thorax of each bee.

Results:	oral administration	24h LD_{50} > 100 µg/bee
		48h LD_{50} > 100 µg/bee
	contact administration	24h LD_{50} > 100 µg/bee
		48h LD_{50} > 100 µg/bee

GLP compliance: yes

B.9.4.1.2 Acute oral and contact toxicity of formulated beflubutamid to bees

Title: **ASU 95 510 H – Acute toxicity to Honey Bees (*Apis mellifera*)**

Author:	Halsall, N. (1999)
BBA-Ref.-Nr.:	BIE 2000-44
Guideline:	EPPO guideline No. 170
Test species:	*Apis mellifera*
Test substance:	ASU 95 510 H, containing 85 g/L beflubutamid and 500 g/L isoproturon
Reference substance:	dimethoat
Control:	untreated
Control:	aceton treated

The test was performed as a limit test, i.e. the test substance was applied only in one concentration.

No. of replicates:	6 with 10 bees/replicate
Administration:	Oral and contact administration 200 µg/bee in terms of test product. For oral uptake the solution was offered in a single dose of 200 µl/cage (20 µl/bee). For contact administration a 1 µl droplet of the solution was placed on the ventral thorax of each bee.

Results:	oral administation	24h LD_{50} > 200 µg/bee
		48h LD_{50} > 200 µg/bee

	contact administration	24h LD_{50} > 200 µg/bee 48h LD_{50} > 200 µg/bee

GLP compliance: yes

B.9.4.2 Bee brood feeding test (Annex IIA 8.3.1.2)

Tests are not required, as the test substance is not an IGR.

B.9.4.3 Residue test (Annex IIIA 10.4.2)

Tests are not required, as the LD_{50} values for oral and contact toxicity are high.

B.9.4.4 Cage test (Annex IIIA 10.4.3)

Tests are not required, as the test substance is of low toxicity for bees.

B.9.4.5 Field test (Annex IIIA 10.4.4)

Tests are not required, as the test substance is of low toxicity for bees.

B.9.4.6 Tunnel test (Annex IIIA 10.4.5)

Tests are not required, as the test substance is of low toxicity for bees.

B.9.4.7 Risk assessment for honeybees

Risk assessment is done according to the EPPO/Coe risk assessment scheme:

Hazard Quotient = LD_{50}^{-1} x g as/ha

The calculation is based on the highest amount of active substance/ha (255 g).

Beflubutamid technical (UR 50 601)

HQ oral = 2.55
HQ contact = 2.55

Formulation 85 g/L beflubutamid + 500 g/L isoproturon

HQ oral = 1.275
HQ contact = 1.275

All values are clearly below the threshold value of 50. This indicates a negligible risk for honeybees by the use of beflubutamid containing plant protection products.

B.9.5 Effects on other arthropod species (Annex IIA 8.3.2; Annex IIIA 10.5)

The results presented below are considered valid (i.e. quality criteria are fulfilled). The risk assessment is based on the uses and nominal field rates outlined in this monograph. Investigations into the toxicity of beflubutamid are conducted using a representative formulation as suggested in the SETAC/ESCORT "*Guidance document on regulatory testing procedures for pesticides with non-target arthropods*" (Barrett et al., 1994).

B.9.5.1 Acute toxicity (Annex IIA 8.3.2, Annex IIIA 10.5.1)

Investigations of the acute toxicity of formulated beflubutamid in laboratory tests:

Predatory mites

Title:	**UR-50601 - Evaluation of the effects of pesticides on the predacious mite *Typhlodromus pyri* in the laboratory using the Louis & Ufer method**
Author:	Halsall, N. (1999)
BBA-Ref.-No.:	ANA2000-922
Test substance:	formulation ASU 92530 H beflubutamid 500 g/L
Guideline:	Typhlodromus (Louis and Ufer 1995)
Test species:	*Typhlodromus pyri*
Developmental stage:	protonymphs
Substrate:	glass plates
Exposure route:	deposit
Exposure duration:	14 d (7 + 7)

Results:

Appl. rate	Mortality	Sublethal effects
500 mL/ha	8 %	9 % (Fertility)

valid:	yes
GLP compliance:	yes

Title:	**ASU 95 510 H - Evaluation of the effects of pesticides on the predacious mite *Typhlodromus pyri* in the laboratory using the Louis & Ufer method**
Author:	Halsall, N. (1999)
BBA-Ref.-No.:	ANA2000-918
Test substance:	formulation ASU 95 510 H isoproturon 500 g/L beflubutamid 85 g/L
Guideline:	Typhlodromus (Louis and Ufer 1995)
Test species:	*Typhlodromus pyri*
Developmental stage:	protonymphs
Substrate:	glass plates
Exposure route:	deposit

Exposure duration: 14 d (7 + 7)
Results:

Appl. rate	Mortality	Sublethal effects
3000 mL/ha	31 %	0 % (Fertility)

Remarks: Mortality = dead and affected mites
valid: yes
GLP compliance: yes

Parasitoids

Title: **UR-50601 - Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid *Aphidius rhopalosiphi* in the laboratory**
Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-921
Test substance: formulation ASU 92530 H
beflubutamid 500 g/L
Guideline: Aphidius, Lab (Mead-Briggs 1992)
Test species: *Aphidius rhopalosiphi*
Developmental stage: adults
Substrate: glass plates
Exposure route: deposit
Exposure duration: 48 h
Results:

Appl. rate	Mortality	Sublethal effects
500 mL/ha	0 %	44 % (Parasitation capacity)

valid: yes
GLP compliance: yes

Title: **ASU 95 510 H - Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid *Aphidius rhopalosiphi* in the laboratory**
Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-917
Test substance: formulation ASU 95 510 H
isoproturon 500 g/L
beflubutamid 85 g/L
Guideline: Aphidius, Lab (Mead-Briggs 1992)
Test species: *Aphidius rhopalosiphi*
Developmental stage: adults
Substrate: glass plates
Exposure route: deposit
Exposure duration: 48 h
Results:

Appl. rate	Mortality	Sublethal effects

3000 mL/ha	3 %	13 % (Parasitation capacity)

valid: yes
GLP compliance: yes

Plant dwelling species

Title: **UR-50601 - Evaluation of the effects of pesticides on the green lacewing *Chrysoperla carnea* in the laboratory**
Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-923
Test substance: formulation ASU 92530 H
beflubutamid 500 g/L
Guideline: Chrysopa (Bigler 1988)
Test species: *Chrysopa carnea*
Developmental stage: larvae
Substrate: glass plates
Exposure route: deposit
Exposure duration: until 21 d (until hatching)
Results:

Appl. rate	Mortality	Sublethal effects
500 mL/ha	6 %	5 % (Fertility)

valid: yes
GLP compliance: yes

Title: **ASU 95 510 H - Evaluation of the effects of pesticides on the green lacewing *Chrysoperla carnea* in the laboratory**
Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-919
Test substance: formulation ASU 95 510 H
isoproturon 500 g/L
beflubutamid 85 g/L
Guideline: Chrysopa (Bigler 1988)
Test species: *Chrysopa carnea*
Developmental stage: larvae
Substrate: glass plates
Exposure route: deposit
Exposure duration: 21 d (until hatching)
Results:

Appl. rate	Mortality	Sublethal effects
6000 mL/ha	18 %	0 % (Fertility)

Remarks: Mortality = larval and pupal mortality
valid: yes
GLP compliance: yes

Soil dwelling species

Title: **UR-50601 - Evaluation of the effects of pesticides on the carabid beetle *Poecilus cupreus* in the laboratory**

Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-924
Test substance: formulation ASU 92530 H
beflubutamid 500 g/L
Guideline: Poecilus (Heimbach 1992)
Test species: *Poecilus cupreus*
Developmental stage: adults
Substrate: quartz sand
Exposure route: overspray + oral
Exposure duration: 14 d
Results:

Appl. rate	Mortality	Sublethal effects
500 mL/ha	12 %	8 % (Food uptake)

valid: yes
GLP compliance: yes

Title: **ASU 95 510 H - Evaluation of the effects of pesticides on the carabid beetle *Poecilus cupreus* in the laboratory**

Author: Halsall, N. (1999)
BBA-Ref.-No.: ANA2000-920
Test substance: formulation ASU 95 510 H
isoproturon 500 g/L
beflubutamid 85 g/L
Guideline: Poecilus (Heimbach 1992)
Test species: *Poecilus cupreus*
Developmental stage: adults
Substrate: quartz sand
Exposure route: overspray + oral
Exposure duration: 14 d
Results:

Appl. rate	Mortality	Sublethal effects
6000 mL/ha	0 %	9 % (Food uptake)

valid: yes
GLP compliance: yes

Table B.9.5-1: Summary of arthropod toxicity data with two formulations of beflubutamid (ASU 92530 H and ASU 95 510 H)

Test material	Species	Developmental stage	Substrate	Dosage mL/ha	Effects (%) lethal	sublethal
Predatory mites						
ASU 92530 H	*T. pyri*	Protonymphs	I	500	8	9
ASU 95 510 H	*T. pyri*	Protonymphs	I	3000	31	0
Parasitoids						
ASU 92530 H	*A. rhopalosiphi*	Adults	I	500	0	44
ASU 95 510 H	*A. rhopalosiphi*	Adults	I	3000	3	13
Plant dwelling species						
ASU 92530 H	*C. carnea*	Larvae	I	500	6	5
ASU 95 510 H	*C. carnea*	Larvae	I	6000	18	0
Soil dwelling species						
ASU 92530 H	*P. cupreus*	Adults	I	500	12	8
ASU 95 510 H	*P. cupreus*	Adults	I	6000	0	9

I = Inert substrate, N = Natural substrate

B.9.5.2 Risk assessment for non-target terrestrial arthropods

B.9.5.2.1 Details of use patterns

The herbicide Herbaflex ASU 95 510 H (UBH-820/isoproturon) is a suspension concentrate (SC) containing 85 g/L beflubutamid and 500 g/L isoproturon and is used in agriculture. Beflubutamid inhibits the enzyme phytoene desaturase involved in carotenoid biosynthesis thereby causing chlorophyll photooxidation (bleaching). Isoproturon is taken up via the roots and leaves of the weeds and is inhibiting photosynthesis. The product is most effective if applied on young growing dicotyledonous weeds. The product is intended for postemergence use in winter cereals in Northern and Southern Europe and durum wheat in Southern Europe. Herbaflex is applied at dose rates of 2.0 to 3.0 L/ha. The maximum recommended field rate of the product is 3.0 L/ha, corresponding to 255 g/ha beflubutamid and 1500 g/ha isoproturon. The product Herbaflex is applied with standard field crop sprayers at water volumes of 200 to 400 L/ha. Herbaflex is applied as single application with 2.0 to 3.0 L/ha in autumn or spring at BBCH 11-13 (autumn) or BBCH 11-29 (spring) of the weeds and at BBCH 11-29 (autumn) or BBCH 13-29 (spring) of the crop.

B.9.5.2.2 Risk Assessment

Non-target arthropods are likely to be exposed to formulated beflubutamid by direct spray, contact on 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 1 worst-case exposure scenario, the predicted environmental exposure of non-target arthropods is assumed to be equivalent to the maximum nominal field rate.

The field rates tested given in Table B.9.5-1 compare to the intended uses given above. According to the data submitted a low toxicity was demonstrated in basic laboratory tests on a number of species (i.e. *A. rhopalosiphi, T. pyri, C. carnea, P. cupreus*).

The submitted studies fulfil the requirements of Annexes II and III of the Directive. For the intended uses of beflubutamid, the risk for arthropods is acceptable and fulfils the decision criteria mentioned in Annex VI, point 2.5.2.4.

B.9.6 Effects on earthworms (Annex IIA 8.4; Annex IIIA 10.6.1)

B.9.6.1 Acute toxicity (Annex IIA 8.4.1, Annex IIIA 10.6.1.1)

Title:	**UR-50601 Acute toxicity to the earthworm**
Author:	Johnson, A.J.; Cameron, D.M. (1997)
BBA-Ref.-No.:	ARW2000-147
Test substance:	technical beflubutamid
Guideline:	OECD 207
Test species:	*Eisenia fetida*
Exposure duration:	14 d
Worms per treatment:	4 x 10
Conc. levels (nom):	95, 171, 309, 556, 1000 mg/kg
Findings:	
LC_{50}:	732 (666-806) mg/kg
Lowest lethal conc.:	556 mg/kg
NOEC:	171 mg/kg
valid:	yes
GLP compliance:	yes

Title:	**UR-50604 Acute toxicity(LC_{50}) to the earthworm (*Eisenia foetida*)**
Author:	Rodgers, M.H.;Cameron, D.M. (1997)
BBA-Ref.-No.:	ARW2000-148
Test substance:	metabolite UR-50604

Guideline: OECD 207
Test species: *Eisenia fetida*
Exposure duration: 14 d
Worms per treatment: 4 x 10
Conc. levels (nom): 95, 171, 309, 556, 1000 mg/kg

Findings:
LC_{50}: 229 (203-259) mg/kg
Lowest lethal conc.: 95 mg/kg
NOEC: < 95 mg/kg
valid: yes
GLP compliance: yes

Title: **ASU 95 510 H Acute toxicity (LC_{50}) to the earthworm *(Eisenia foetida*)**

Author: Johnson, A.J.; Cameron, D.M. (1998)
BBA-Ref.-No.: ARW2000-150
Test substance: formulation ASU 95 510 H
(beflubutamid 86 g/L, isoproturon 502 g/L)
Guideline: OECD 207
Test species: *Eisenia fetida*
Exposure duration: 14 d
Worms per treatment: 4 x 10
Conc. levels (nom): 0, 95, 171, 309, 556, 1000 mg/kg

Findings:
LC_{50}: > 1000 mg/kg
Lowest lethal conc.: 95 mg/kg
NOEC: 1000 mg/kg
valid: yes
GLP compliance: yes

Table B.9.6-1: Summary of earthworm toxicity data

Test material	**Species**	**Test**	**NOEC (mg/kg)**	**LC_{50} (mg/kg)**	**BBA Ref.- No.**
Beflubutamid UR-50601	*Eisenia fetida*	acute	171	732	ARW 2000-147
Metabolite UR-50604	*Eisenia fetida*	acute	< 95	229	ARW 2000-148
Formulation ASU 95 510 (beflubutamid 86 g/L, isoproturon 502 g/L)	*Eisenia fetida*	acute	1000	> 1000	ARW 2000-150

B.9.6.2 Other studies (Annex IIA 8.4.2, Annex IIIA 10.6.1.2)

Reproduction toxicity

Title: **UR-50601: To determine the effects on reproduction and growth of the earthworm, *Eisenia fetida***

Author: Rodgers, M. H. (2000)
BBA-Ref.-No.: ARW2001-45
Test substance: formulation ASU 92 530 H
(beflubutamid 500.0 g/L)
Guideline: ISO/DIS 11268-2
Test species: *Eisenia fetida*
Application: on soil surface
Exposure duration: 8 w
Worms per treatment: 4 x 10

Findings:

Dose level (kg as/ha)	**Adult mortality (%)**	**Adult weight (% of initial weight)**	**Mean number of juveniles**	**Reduction of juvenile numbers (in % of control)**
Control	0	159.2	169	100
0.255	0	158.4	136 *	80.5
1.275	0	158.5	138.5 *	82.0

* sign. $p < 0.05$

NOEC: < 0.255 kg as/kg (equivalent to < 0.34 mg as/kg; calculated for 5 cm soil depth and a soil bulk density of 1.5 mg/cm^3)
valid: yes
GLP compliance: yes

Title: **ASU 95 510 H: To determine the effects on reproduction and growth of the earthworm (*Eisenia fetida)***

Author: Rodgers, M. H. (2000)
BBA-Ref.-No.: ARW2001-46
Test substance: formulation ASU-95510-H-0-SC
isoproturon 502 g/L
beflubutamid 85.0 g/L
Guideline: ISO/DIS 11268-2
Test species: *Eisenia fetida*
Application: on soil surface
Exposure duration: 8 w
Worms per treatment: 4 x 10

Findings:

Dose level (L/ha)	**Adult mortality (%)**	**Adult weight (% of initial weight)**	**Mean number of juveniles**	**Reduction of juvenile numbers**

				(in % of control)
Control	0	129.5	234.3	100
3 L	0	130.0	191.8 *	82
15 L	0	131.0	183.3 *	78

*sign. $p < 0.05$

NOEC: < 3 L/ha (equivalent to <2.0 mg as isoproturon/kg and < 0.34 mg as beflubutamid/kg; calculated for 5 cm soil depth and a soil bulk density of 1.5 mg/cm^3)
valid: yes
GLP compliance: yes

Title: Herbaflex, Earthworm (*Eisenia fetida*), effects on reproduction

Author: Noack, M. (2001)
BBA-Ref.-No.: ARW2001-163
Test substance: formulation ASU-95510-H-0-SC
isoproturon 500 g/L
beflubutamid 85 g/L
Guideline: ISO/DIS 11268-2
Test species: *Eisenia fetida*
Exposure duration: 8 w
Worms per treatment: 4 x 10

Findings:

Dose level (L/ha)	**Adult mortality (%)**	**Adult weight (% of initial weight)**	**Mean number of juveniles**	**Reduction of juvenile numbers (in % of control)**
Control	0	106.0	95	100
1.5	0	102.0	80	84
3.0	5	110.0	72	76
6.0	0	110.0	67	71
15.0	5	108.0	58*	61
30.0	0	114.0	50*	53

sign. $p < 0.05$

NOEC: 6.0 L/ha (equivalent to 4 mg isoproturon/kg + 0.68 mg beflubutamid/kg)
valid: yes
GLP compliance: yes

Three reproduction tests were submitted and are considered valid. Risk assessment is described in the chapter below.

Two additional reproduction tests were conducted and are considered not valid. One test (Rodgers et al., 2000, ARW2000-149) was done with an SC-formulation containing 500 g/L

beflubutamid (like the test ARW 2001-45). This test is considered not valid. The number of juveniles in the control is in the average 9.5 and the variation coefficient of the number of juveniles in the control is 91.4 %. The relevant ISO-guideline 11268-2 requires a number of juveniles of at least 30 in the control and a variation coefficient of the number of juveniles of at maximum 30 %. The other additional reproduction test (Johnson and Cameron, 2000, ARW2000-151) was done with a combination product of beflubutamid (like the test ARW2001-46). Whereas the number of juveniles was sufficient and met the validity criterion, the variation coefficient was 37 % instead of 30 %. This test must therefore be regarded as not valid.

B.9.6.3 Risk assessment for earthworms

Since $logP_{ow}$ is > 2, the toxicity data are divided by the factor of 2 (see EPPO risk assessment scheme for soil organisms).

Table B.9.6-2: TER_a and TER_{lt} for earthworms

Test material	Toxicity data (corrected) (mg beflubut./ kg substrate)	$PEC_{initial}$ (mg beflubut./ kg) *	Time scale	TER	Ref.
Beflubutamid UR 50601	366	0.34	acute	1076	ARW 2000-147
Formulation ASU 95 510 H	> 43	0.34	acute	> 127	ARW 2000-150
Metabolite UR 50604	115	0.066	acute	1742	ARW 2000-148
Formulation ASU 92 530 H	< 0.17	0.34	long-term	< 0.5	ARW 2001-45
Formulation ASU 95 510 H	< 0.17	0.34	long-term	< 0.5	ARW 2001-46
Formulation ASU 95510 H	0.34	0.34	long-term	1	ARW 2001-163

* see chapter B.08.03

The long-term TER for reproduction is first calculated using the results from the dose-response reproduction test (ARW2001-45) with the formulation containing only beflubutamid. The corrected NOEC is < 0.17 mg as/kg. Compared to the PEC of about 0.34 mg/kg the TER is < 0.5. This is below the relevant trigger of 5.

Using the dose-response reproduction test (ARW 2001-163) with an NOEC of 0.34 mg/kg with respect to beflubutamid, the resulting TER is 1, still below the trigger of 5. Looking at the amount of reduction in the tests, the reduction at the relevant rates of 3 l product and 0.255 kg as/ha and at the next following rates amounts to 20 to 30 %, independent of the formulation and the application rate. This is not a severe reduction and it is questionable whether this effect is detectable in the field. Nevertheless products with this active substance have to be evaluated critical concerning the amount of beflubutamid.

Concerning risk of metabolites, the main metabolite UR-50604 was tested and the TER estimation (Table B.9.6-2) showed that no risk from the metabolite is likely to occur.

B.9.7 Effects on other soil non-target macro-organisms (Annex IIIA 10.6.2)

No data on other soil non-target macro-organisms have been submitted as the time for 90 % dissipation was less than one year.

B.9.8 Effects on soil non-target micro-organisms (Annex IIA 8.5; Annex IIIA 10.7)

Laboratory tests were performed to examine the effects of beflubutamid on microbial activities in soil. The tests were carried out with the active substance and the metabolite UR-50604.

B.9.8.1 Nitrogen conversion (Annex IIA 8.5; Annex IIIA 10.7)

Title:	**UR-50601: Effects on soil non-target micro-organisms**	
Author:	Carter, J.N. (1997)	
BBA-Ref.-No.:	BMF2000-117	(1)
Test substance:	technical beflubutamid	
Guideline:	SETAC (N)	
Type of test:	N-mineralisation	
Amendment:	lucerne meal	
valid:	yes	
GLP compliance:	yes	

Title:	**UR-50604: Effects on soil non-target micro-organisms**	
Author:	Carter, J.N. (2000)	
BBA-Ref.-No.:	BMF2000-130	(2)
Test substance:	metabolite UR-50604	
Guideline:	SETAC (N)	
Type of test:	N-mineralisation	
Amendment:	lucerne meal	
valid:	yes	
GLP compliance:	yes	

Findings:

Table B.9.8-1: Effects on nitrogen conversion

type of soil	test substance	application rate [kg /ha]	effect compared to untreated control [%]	test duration [d]	influence tolerable	ref.
loamy sand	beflubutamid	0.6	+ 0.3	28	yes	(1)
loamy sand	metabolite UR-50604	0.34	- 8.7	28	yes	(2)

B.9.8.2 Carbon Conversion (Annex IIA 8.5; Annex IIIA 10.7)

Title: **UR-50601: Effects on soil non-target micro-organisms**
Author: Carter, J.N. (1997)
BBA-Ref.-No.: BMF2000-117 (1)

Test substance: technical beflubutamid

Guideline: SETAC (C)
Type of test: C-mineralisation
Activity: long-term respiration
Amendment: lucerne meal
valid: yes
GLP compliance: yes

Title: **UR-50604: Effects on soil non-target micro-organisms**
Author: Carter, J.N. (2000)
BBA-Ref.-No.: BMF2000-130 (2)

Test substance: metabolite UR-50604

Guideline: SETAC (C)
Type of test: C-mineralisation
Activity: long-term respiration
Amendment: lucerne meal
valid: yes
GLP compliance: yes

Findings:

Table B.9.8-2: Effects on carbon conversion

type of soil	test substance	application rate [kg /ha]	effect compared to untreated control [%]	test duration [d]	influence tolerable	ref.
loamy sand	beflubutamid	0.6	+ 0.55	28	yes	(1)
loamy sand	metabolite UR-50604	0.34	- 16.8	28	yes	(2)

B.9.8.3 Risk assessment

The influence of the active ingredient beflubutamid (0.6 kg as/ha) and the metabolite UR-50604 (0.34 kg as/ha) on carbon- and nitrogen conversion is < 25 % in comparison to the untreated control.
When applying beflubutamid containing plant protection products according to the recommended pattern of use no lasting effects on microbial activities are to be expected.

B.9.9 Effects on other non-target organisms (flora and fauna) believed to be at risk (Annex IIA 8.6)

B.9.9.1 Non-target plants

UR 50601 is a chlorosis inducing herbicide inhibiting the plant enzyme phytoene desaturase (PDS) of the carotinoid biosynthetic pathway.

Screening tests
Herbicidal screening studies were conducted with a 10 % WP formulation of beflubutamid (Takamura and Obata, 2000, PFL 2000-154).

Pre-emergence test:
Weed seeds of two mono- and three dicotyledonous species (*Digitaria anguinalis, Echinochloa crus-galli, Chenopodium album, Amaranthus lividus and Ipomoea purpurea*) were planted and tested at 2 kg/ha (topical application). Three weeks after treatment the degree of growth inhibition was assessed. In all species a high amount of growth inhibition was observed. The test was conducted twice.

Post-emergence test:
Weed seeds of two mono- and three dicotyledonous species (*Digitaria anguinalis, Echinochloa crus-galli, Chenopodium album, Amaranthus lividus and Ipomoea purpurea*) were planted and tested in the 0.5 to 2 leaf-stage of the weeds with 2 kg/ha (topical application). Three weeks after treatment the degree of growth inhibition was assessed. In all species a high amount of growth inhibition was observed. The test was conducted twice.

Definitive Tests

Pre- and post-emergence definitive tests were done with a 500 g/L SC-formulation (Okada and Funaki, 1999 (PFL 2000-155)). The tests were not done according to a guideline, but took the draft EPA guidelines OPPTS 850.4225 (seedling emergence) and OPPTS 850.4250 (vegetative vigour) and the OECD draft guideline 208 into account. Six plant species were tested (3 mono- and 3 dicotyledonous species).

Table B.9.9-1: Pre-and post-emergence tests for non-target plants with a 500 g/L SC-formulation

Plant species	**Pre-emergence ED_{50} (kg/ha)**	**Pre-emergence NOEC (kg/ha)**	**Post-emergence ED_{50} (kg/ha)**	**Post-emergence NOEC (kg/ha)**
Lactuca sativa	0.145	0.048	0.0148	-
Raphanus sativus	> 0.3	0.12	0.102	-
Trifolium pratense	0.0257	0.008	0.0282	-
Lolium perenne	> 0.3	0.048	>0.3	0.12
Avena sativa	> 0.3	0.12	>0.3	0.12
Oryza sativa	> 0.3	0.12	>0.3	> 0.3

The lowest ED_{50} was found in *Lactuca sativa* with 14.8 g/ha in the post-emergence test.

Risk assessment:

The risk assessment is based on the ED_{50} of *Lactuca sativa* from the post-emergence test. The highest recommended field rate of Herbaflex (beflubutamid 85 g/L, isoproturon 500 g/L) will be 3 L/ha or 255 g as/ha beflubutamid (Table B.9.9-2).

Table B.9.9-2: Risk assessment of a 500 g/L SC-formulation of beflubutamid

Distance from treated area	% Drift	Amount of drift * [g as/ha]	ED_{50} *Lactuca sativa* [g as/ha]	TER
1 m	4	5.1	14.8	2.9
5 m	0.5	0.64	14.8	23

* taking into account 50 % interception

These data indicate a possible risk to terrestrial non-target plants.

B.9.9.2 Pesticidal activity

Phenoxybutyric acid (UR-50604)

Phenoxybutyric acid (UR-50604) is a main metabolite of beflubutamid (UR-50601) in soil. UR-50601 is applied with a maximum application rate of 255 g as/ha. The metabolite UR-50604 is formed to max. 26.1 % in the soil after 7 days.

For testing the herbicidal activity of the metabolite a bioassay was carried out, using ten weeds and wheat as test plants and the parent compound as a standard.

Report: E. Funaki, T. Okada (1999); Herbicidal activity of the metabolite UR-50604; UBE Industries, Ltd.; 17.09.1999; dates of experimental work: 07.04.1999 to 21.05.1999.
supplemented: 28.02.2001 and 10.04.2001

Guidelines: In house method UBE, not further specified;
internal laboratory standard, comparable to OECD 208.

GLP: No

Materials and Methods: Test material: UR-50604 (metabolite); Batch 980928; 10% WP = 10.3%.
Parent compound: UR-50601; Batch 980928; 10% WP = 10.5%.

Plant material: wheat and ten different weeds species (grass weeds and dicotyledonous weeds). Test plants were seeded in pots, exposed to the test material and placed in greenhouses.
Application: pre-emergence and post-emergence application. UR-50601 was applied at rates of 340, 255, 170 and 85 g as/ha, the metabolite UR-50604 was applied at rates of 255, 191, 127 and 64 g metabolite/ha.

Assessments: The herbicidal activity was assessed visually compared to controls three weeks after treatment.

Statistics: 3 replication of each treatment, mean values, no ANOVA or other test.

Findings: The parent UR-50601 showed strong herbicidal activity to a wide range of grass and broad-leaved weeds after pre-emergence application (Table 1). After post-emergence application strong herbicidal activity to broad-leaved weeds was shown (Table 2). The metabolite UR-50604 did not show any herbicidal activity at equivalent rate after both pre-emergence or post-emergence application, but showed small suppression to *Stellaria media* in contrast to the parent.

Table B.9.9-3: Herbicidal activity of UR-50601 and UR-50604 treated weeds with pre-emergence application

	UR-50604 (g metabolite/ha)				**UR-50601 (g as/ha)**			
Crop/weed	**255**	**191**	**127**	**64**	**340**	**255**	**170**	**85**
Wheat	0	0	0	0	0	0	0	0
Alopecurus myos.	0	0	0	0	90c	80c	80c	0
Poa annua	0	0	0	0	100c	100c	100c	55c
Setaria viridis	0	0	0	0	100c	100c	100c	95c
Veronica persica	0	0	0	0	100c	100c	100c	100c
Lamium amplexicaule	0	0	0	0	100	100c	100c	100c
Stellaria media	10s	0	0	0	95c	85c	50c	10c
Galium aparine	40s	0	0	0	100c	100c	95c	30c
Viola tricolor	0	0	0	0	100c	100c	100c	90c
Papaver rhoeas	0	0	0	0	100c	100c	100c	100c
Chenopodium album	0	0	0	0	100c	100c	100c	100c

0: normal growth – 100: completely killed; c: chlorosis; s: growth suppression

Table B.9.9-4: Herbicidal activity of UR-50601 and UR-50604 treated weeds with post-emergence application

	UR-50604 (g metabolite/ha)				UR-50601 (g as/ha)			
Crop/weed	**255**	**191**	**127**	**64**	**340**	**255**	**170**	**85**
Wheat	0	0	0	0	3c	3c	0	0
Alopecurus myos.	0	0	0	0	5c	5c	0	0
Poa annua	0	0	0	0	70c	10c	3c	0
Lamium amplexicaule	0	0	0	0	100c	100c	100c	100c
Stellaria media	40s	20s	20s	0	20c	20c	0	10c
Galium aparine	0	0	0	0	100c	95c	90c	85c
Viola tricolor	0	0	0	0	100c	100c	100c	100c
Papaver rhoeas	0	0	0	0	100c	100c	100c	100c
Capsella bursa-pastoris	0	0	0	0	100c	100c	100c	100c

0: normal growth – 100: completely killed; c: chlorosis; s: growth suppression

Comment:

The study is acceptable.
A pre-emergence application of the metabolite UR-50604 with a dose of 255 g metabolite/ha (equivalent to a transformation rate of 100 % of the parent compound) showed growth suppressions on *Stellaria media* and *Galium aparine* with more than 5 % of the untreated control. The post-emergence application showed effects on *Stellaria media* with application rates of the metabolite with 255, 191 and 127 g metabolite/ha. According to the first step for the evaluation of the pesticidal activity of metabolites of the "Draft Guidance Document on Relevant Metabolites" the metabolite UR-50604 is to be classified herbicidal active. The second step of the decision scheme takes into account the measured maximum transformation rate of the active substance, which is 26.1 %. Based on the application rate of 255 g as/ha of the parent compound UR-50601, this value corresponds to 66,6 g metabolite/ha. With a dose of 66,6 g metabolite/ha of UR-50604 (in the study 64 g metabolite/ha) no effect of the metabolite on *Stellaria media* or the other tested plant species was observed.

Conclusion:

Based on the above mentioned evaluation concept the metabolite UR-50604 showed not herbicidal activity in the experiment.

This conclusion is supported by an research paper of Prof. Böger (not published) from February 2001. He used a cell-free phytonene desaturase assay for testing the activity of UR-50601 and UR-50604. UR-50601 has been reported as a phytoene desaturase inhibitor. In this assay only the parent compound showed an activity, while the metabolite had no bleaching activity.

B.9.10 Effects on biological methods of sewage treatment (Annex IIA 8.7)

Data from activated sludge respiration inhibition test show no unacceptable risk to sewage treatment plants (EC_{50} >100 mg/L).

B.9.11 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	Johnson, A.J., Cameron, D.M. and Dawe, I.S.	1997	UR-50601: Acute toxicity (LD50) to the bobwhite quail. UBE 48/971672 GLP, unpublished AVS2000-117	Y	UBE
AIIA-8.1.2	Rodgers, M.H., Cameron, D.M. and Dawe, I.S.	1997	UR-50601: Dietary LC50 to the bobwhite quail. UBE 49/971079 GLP, unpublished AVS2000-118	Y	UBE
AIIA-8.1.3	Johnson, A.J. and Cameron, D.M.	1998	UR-50601: Effects on reproduction in bobwhite quail. UBE 50/972155 GLP, unpublished AVS2000-119	Y	UBE
AIIA-8.2.1	Jenkins, C.A.	1999	UR-50604: Acute toxicity to Fish (Rainbow trout). UBE094/992813 GLP, unpublished WAT2000-577	Y	UBE
AIIA-8.2.2.1	Bell, G. and Hargreaves, T.L.	2000	UR-50601:Fish Early Life Stage Toxicity Test for Fathead minnow (Pimephales promelas). UBE 098/994315 GLP, unpublished WAT2000-578	Y	UBE
AIIA-8.2.3	Corden, M.T.	1999	UR-50601: Bioconcentration in Rainbow trout. UBE 085/992393 GLP, unpublished WAT2000-579	Y	UBE
AIIA-8.2.4	Jenkins, C.A.	1999	UR-50604 Acute toxicity to Daphnia magna. UBE096/992814 GLP, unpublished WAT2000-581	Y	UBE
AIIA-8.2.4	Jenkins, C.A.	1999	UR-50601: Acute toxicity to Daphnia magna Determination of 48-hour EC50 under static conditions. UBE62/973063 GLP, unpublished WAT2000-580	Y	UBE

[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-8.2.4	Jenkins, W.R.	1999	ASU 95 510 H (UBH-820-IPU Formulation) Acute toxicity to Daphnia magna. STJ016/994270 GLP, unpublished WAT2000-589	Y	ASU UBE
AIIA-8.2.5	Jenkins, C.A.	1999	UR-50601: Daphnia magna Reproduction Test. UBE063/98388 GLP, unpublished WAT2000-582	Y	UBE
AIIA-8.2.6	Jenkins, C.A.	1999	UR-50604 Algal growth inhibition assay. UBE095/992458 GLP, unpublished WAT2000-585	Y	UBE
AIIA-8.2.6	Jenkins, C.A.	1999	UR-50601: Determination of 120-hour EC50 to Anabaena. UBE74/982576 GLP, unpublished WAT2000-584	Y	UBE
AIIA-8.2.6	Jenkins, C.A.	1999	UR-50601: Determination of 72-hour EC50 to Selenastrum capricornutum. UBE64/973064 GLP, unpublished WAT2000-583	Y	UBE
AIIA-8.2.6	Jenkins, W.R.	1999	ASU 95 510 H (UBH-820-IPU Formulation) Algal growth inhibition assay (Selenastrum capricornutum). STJ014/994268 GLP, unpublished WAT2000-590	Y	ASU UBE
AIIA-8.2.7	Bell, G.	2000	UR-50601 To assess the toxicity to the sediment dwelling phase of the midge Chironomus riparius. UBE 097/993026 GLP, unpublished WAT2000-586	Y	UBE
AIIA-8.2.8	Kelly, C.	1998	UR-50601 Higher Plant (LEMNA) Growth inhibition Test. UBE 075/982375 GLP, unpublished WAT2000-587	Y	UBE

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	Gray, A.P.	1999	UR-50601: Acute toxicity to honey bees (Apis mellifera). UBE 59/972121 GLP, unpublished BIE2000-45	Y	UBE
AIIA-8.3.2	Halsall, N.	1999	UR-50601 Evaluation of the effects of pesticides on the carabid beetle Poecilus cupreus in the laboratory. UBE 092/992727 GLP, unpublished ANA2000-924	Y	UBE
AIIA-8.3.2	Halsall, N.	1999	UR-50601 Evaluation of the effects of pesticides on the green lacewing Chrysoperla carnea in the laboratory. UBE 091/994106 GLP, unpublished ANA2000-923	Y	UBE
AIIA-8.3.2	Halsall, N.	1999	UR-50601 Evaluation of the effects of pesticides on the predacious mite Typhlodromus pyri in the laboratory using the Louis & Ufer method. UBE 089/992726 GLP, unpublished ANA2000-922	Y	UBE
AIIA-8.3.2	Halsall, N.	1999	UR-50601 Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid Aphidius rhopalosiphi in the laboratory. UBE 090/994053 GLP, unpublished ANA2000-921	Y	UBE
AIIA-8.4.1	Johnson, A. J. and Cameron, D. M.	1997	UR-50601 Acute toxicity to the earthworm. UBE 51/971234 GLP, unpublished ARW2000-147	Y	UBE
AIIA-8.4.1	Rodgers, M. H. and Cameron, D. M.	2000	UR-50604 Acute toxicity (LC50) to the earthworm (Eisenia foetida). UBE 107/994388 GLP, unpublished ARW2000-148	Y	UBE
AIIA-8.5	Carter, J.N.	2000	UR-50604: Effects on soil non-target micro-organisms. UBE 105/994202 GLP, unpublished BMF2000-130	Y	UBE

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	Funaki, E. and Okada, T.	2001	Herbicidal activity of the metabolite UR-50604 by pre-emergence treatment. Ube Research Laboratory not GLP, unpublished PFL2001-36	Y	ASU
AIIA-8.6; AIIIA-10.8	Funaki, E. and Okada, T.	2001	Herbicidal activity of the metabolite UR-50604 by post-emergence treatment. Ube Research Laboratory not GLP, unpublished PFL2001-35	Y	ASU
AIIA-8.6; AIIIA-10.8	Funaki, E. and Okada,T.	1999	Herbicidal activity of the metabolite of UR-50604. UBE Industries, Ltd. not GLP, unpublished PFL2000-156	Y	UBE
AIIA-8.6; AIIIA-10.8	Okada, T. and Funaki, E.	1999	The terrestrial plant toxicity study of UR-50601. UBE Industries, Ltd. not GLP, unpublished PFL2000-155	Y	UBE
AIIA-8.6; AIIIA-10.8	Takamura, S. and Obata, T.	1999	The pesticidal evaluation study of UR-50601 -The result of first screening test-. UBE Industries, Ltd. not GLP, unpublished PFL2000-154	Y	UBE
AIIA-8.7	Jenkins, W.R.	1998	UR-50601 Activated sludge - Respiration inhibition test. UBE065/970432 GLP, unpublished WAT2000-588	Y	UBE
AIIIA-10.2.1	Jenkins, C.A.	1999	UR-50601: Acute toxicity to Rainbow trout Determination of 96-hour LC50. UBE60/982140 GLP, unpublished WAT2000-575	Y	UBE
AIIIA-10.2.1	Jenkins, C.A.	1999	UR-50601: Acute toxicity to Bluegill sunfish Determination of 96-hour LC50. UBE61/973904 GLP, unpublished WAT2000-576	Y	UBE
AIIIA-10.2.1	Jenkins, C.A.	1999	ASU 95 510 H (UBH-820-IPU Formulation) Acute Toxicity to Fish (Rainbow trout). STJ015/994269 GLP, unpublished WAT2000-574	Y	ASU UBE

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	Halsall,N.	1999	ASU 95 510 H: Acute toxicity to honey bees (Apis mellifera). STJ002/984619 GLP, unpublished BIE2000-44	Y	ASU
AIIIA-10.5.1	Halsall, N.	1999	ASU 95 510 H Evaluation of the effects of pesticides on the carabid beetle Poecilus cupreus in the laboratory. STJ 007/985091 GLP, unpublished ANA2000-920	Y	ASU
AIIIA-10.5.1	Halsall, N.	1999	ASU 95 510 H Evaluation of the effects of pesticides on the green lacewing Chrysoperla carnea in the laboratory. STJ 006/984983 GLP, unpublished ANA2000-919	Y	ASU
AIIIA-10.5.1	Halsall, N.	1999	ASU 95 510 H Evaluation of the effects of pesticides on the predacious mite Typhlodromus pyri in the laboratory using the Louis & Ufer method. STJ 004/992728 GLP, unpublished ANA2000-918	Y	ASU
AIIIA-10.5.1	Halsall, N.	1999	ASU 95 510 H Evaluation of the effects of pesticides on adults of the cereal aphid parasitoid Aphidius rhopalosiphi in the laboratory. STJ 005/993424 GLP, unpublished ANA2000-917	Y	ASU
AIIIA-10.6.1.1	Johnson, A. J. and Cameron, D. M.	1998	ASU 95 510 H Acute toxicity (LC50) to the earthworm (Eisenia foetida). STJ 003/983507 GLP, unpublished ARW2000-150	Y	ASU
AIIIA-10.6.1.2	Dias, N. A.	2001	Stefes Derosal Liquid: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. HLS 122/010062 GLP, unpublished ARW2001-44	Y	ASU

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-10.6.1.2	Noack, M.	2001	Herbaflex: Earthworm (Eisenia fetida), effects on reproduction. Study-No.: RRR79852 GLP, unpublished ARW2001-163	Y	TSU
AIIIA-10.6.1.2	Rodgers, M. H.	2000	ASU 95 510 H: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. STJ 020/003115 GLP, unpublished ARW2001-46	Y	ASU
AIIIA-10.6.1.2	Rodgers, M. H.	2000	UR-50601: To determine the effects on reproduction and growth of the earthworm, Eisenia fetida. UBE 115/003229 GLP, unpublished ARW2001-45	Y	ASU

Codes of owner

ASU: Stähler Agrochemie GmbH & Co.KG
TSU: Task force von Stähler und UBE
UBE: UBE Industries

Appendix 1

Beflubutamid

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	adenosin diphosphate
AE	acid equivalent
AFID	alkali flame-ionization 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 encephalopathie
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	coeficient 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 pot 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 ionization 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 ionization 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	granulosevirus
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 ionization 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 gaschromatography
Hs	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilization concentration
ICM	integrated crop management
ID	ionization 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 fertilization
k	kilo
K	Kelvin or Henry`s Law constant (in athmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsortion coefficient
K_{om}	organis 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 determination
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 concentratin

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 intend 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-detektor
pH	pH-value
PHED	pesticide handler`s exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
PIXE	proton inducted 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 acic
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 procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogene free
spp	subspecies
sq	square
SSD	sulfur 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 estimination)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily tntake
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 ration
TER_I	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration 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 riboncleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainly 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
ACTM	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	Comite 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 Organization
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 Organization 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 Monotoring 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 Commissin of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commissin for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Restistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Orginazation
ISO	International Organization for Standardization
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 Pesticdes (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 Center for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Cooperation 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 Programmme
WCP	Workd Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wide Fund for Nature

Appendix 2

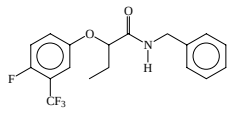
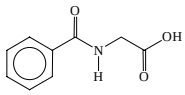
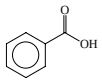
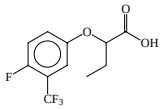
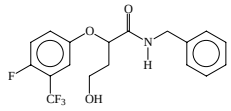
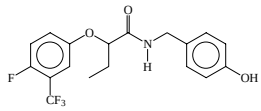
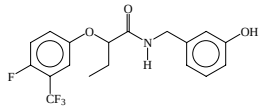
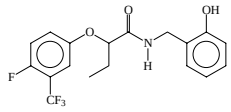
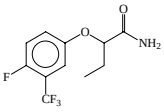
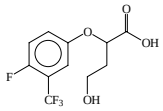
Beflubutamid

Specific Terms and Abbreviations

B.10.2 Appendix II: Specific terms and abbreviations

Abb.	Definition
DAT	Days After Treatment
PAS	Pure Active Substance
RAC	Raw Agricultural Commodity
TAS	Technical Active Substance
TRR	Total Radioactive Residue

List of metabolites of beflubutamid

Code / Name	Chemical Structure	Chemical Name	Found in Matrix
UR-50601 **Beflubutamid**		(*RS*)-N-Benzyl-2-(4-fluoro-3-trifluoromethylphenoxy)-butanamide	Wheat, Soil, Water/ Sediment
Hippuric acid		N-Benzoylglycine	Goat, Rat
UR-50627		Benzoic acid	Wheat straw
UR-50604		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy) butanoic acid	Wheat, Rotat. Crops, Goat, Rat, Soil, Water/ Sediment
UR-50615		(*RS*)-*N*-Benzyl-2-(4-fluoro-3-trifluoromethyl-phenoxy)-4-hydroxybutanamide	Rat
UR-50617		(*RS*)-*N*-(4-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Goat, Rat
UR-50618		(*RS*)-*N*-(3-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Goat, Rat
UR-50619		(*RS*)-*N*-(2-Hydroxybenzyl)-2-(4-fluoro-3-trifluoromethyl-phenoxy)butanamide	Wheat, Rat
UR-50624		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy)butanamide	Wheat, Rotat. Crops, Rat, Soil
UR-50626		(*RS*)-2-(4-Fluoro-3-trifluoro-methylphenoxy)-4-hydroxy butanoic acid	Rat