Addendum

to the Draft Assessment Report

of 02 August 2003

Beflubutamid

(Toxicology)

12 July 2004

Rapporteur Member State: Germany

Introduction and summary

On the ECCO 136 Peer Review meeting on mammalian toxicology (March, 2003, York), it was agreed that the notifier should provide a commentary on the mechanism of tumour induction in the thyroid and the relevance of these tumours to man. Meanwhile, this requirement was fulfilled and a toxicological expert judgement (Funaki, 2003, unpublished) submitted to the RMS. In addition, the long-term study in rats was subject to an internal peer review with special emphasis on possible effects on the thyroid.

The results of this re-evaluation process are the following:

- The RMS considers the increase in thyroid follicular tumours in high dose male rats rather a spontaneously occurring event than a treatment-related effect. Therefore, no mechanism behind could be identified. Accordingly, these tumours are not relevant for human risk assessment and do not warrant classification and labelling of this compound for cancerogenicity.

- The well-known rodent-specific mechanism of tumour induction in the thyroid by an increased acitivity of certain liver enzymes resulting in an extensive metabolism of thyroxine and, as a consequence, in a permanent stimulation of the thyroid by TSH ("phenobarbitone-type mechanism") is very unlikely to be caused by beflubutamid.

Furthermore, few corrections and clarifications with regard to description of the long-term rat study are provided in this addendum which do not alter the general conclusions.

Thyroid tumours and other effects on this organ in the toxicity studies with beflubutamid

In the long-term rat study (Barker and Turner-Cain, 2000, see monograph), an increase in tumours of the thyroid was recorded (Table 1).

Table 1: Total tumour incidence (thyroid only) in the two-year feeding study with beflubutamid in CD rats (excluding interim kill satellite groups)

Sex	**Males**				**Females**			
Dose (ppm)	**0**	**50**	**400**	**3200**	**0**	**50**	**400**	**3200**
Number examined	60	59	60	60	60	40	42	60
Follicular cell adenoma	1	2	1	**5**	0	0	1	0
Follicular cell carcinoma	1	-	2	1	0	0	0	1
Follicular cell tumours (total)	2	2	3	**6**	0	0	1	1
C-cell adenoma	4	3	7	4	3	1	2	1
C-cell carcinoma	4	1	4	1	1	1	1	2
C-cell tumours (total)	8	4	11	5	4	2	3	3

This increase was confined to the frequency of follicular cell adenoma in male animals receiving a high dietary dose of 3200 ppm (equivalent to a mean daily intake of about 150 mg/kg bw). In contrast, no change in the occurrence of follicular cell carcinoma was seen although the total number of male animals bearing follicular cell tumours was higher than in the control or in the low or intermediate dose groups due to the increase in adenoma incidence. The difference gained statistical significance ($p=0.044$) in a test for trend when time-to-tumour methods were applied for statistical analysis. On pair-wise comparison with control males, however, statistical significance was not achieved.
An incidence of 6/60 for this type of tumours (animals with follicular cell tumours/total number of animals in the group) is at the upper edge of the historical control range of the performing laboratory for untreated male rats of this strain. In the background studies, the respective incidence varied between 0/60 and 6/50 (as mentioned in the original study report).

In females, no evidence of any elevation in follicular cell tumours was obtained.
The incidence of C-cell tumours was not affected, neither in males nor in females.

Thus, based solely on the tumour incidence in this study, a final conclusion whether the increase in follicular cell tumours was related to treatment or not, cannot be drawn. Further data must be taken into consideration.

Beflubutamid is devoid of a genotoxic potential. Tumours, if occurring, would be due to an epigenetic mechanism that is usually characterized by preceeding or concomitant non-neoplastic lesions and often also by organ weight changes. Efforts should be taken to clarify that mechanism.

Organ weights and non-neoplastic histological changes in the long-term rat study

There was evidence of a weak increase in thyroid weight in male rats at interim kill that was, however, not confirmed at scheduled termination after 2 years. Since the respective table in the monograph (B.6.5-4) is, unfortunately, not correct (for revised version, see below), the data from the original report have been compiled to allow for a comprehensive overview (Tables 2 - 5).

For better understanding of these tables, the following explanation for using the parameter "adjusted organ weight" instead of the relative organ weight is considered necessary:
Analysis of covariance (ANCOVA) is the preferred method at the performing laboratory Huntingdon Life Science (HLS) to take the differences in bodyweight into consideration when organ weight data are analysed. By this statistical approach, the organ weight group means are adjusted to body weight according to how far the terminal bodyweight in the group of interest departs from the average bodyweight over all groups. This way of adjustment is intended to minimise the impact of interindividual (within-group) variations and is obviously considered by HLS superior to calculation of relative organ weights as it is usually done. Accordingly, relative organ weight data had not been submitted by the notifier.

For some groups, the adjusted thyroid weight was not given. A similar situation was present with another substance (pethoxamid) that is currently subject to the EU evalution process with Germany being the RMS. The notifier is the same and the long-term rat study was also conducted at HLS. On request of the RMS, the following justification for the data gap was submitted by the notifier that is also applicable to the beflubutamid case:
Statistical analysis showed that (in these groups) there was no relationship between thyroid weight and bodyweight. Therefore, it was concluded by HLS that there was actually no need to make an adjustment for bodyweight and that the data should be interpreted on the basis of absolute thyroid weights. According to the original report on the beflubutamid study (Barker and Turner-Cain, 2000), the final body weight is used as a covariate and adjustment is made only when the within-group relationship between organ weight and body weight is significant at the 10% level.

Table 2: Mean thyroid weight (absolute and adjusted for body weight) in male rats at interim kill (week 53)

Dose level	**0 ppm**	**50 ppm**	**400 ppm**	**3200 ppm**
Number examined	20	20	20	20
Absolute thyroid weight (mg)	31.3	33.0	33.5	37.5
Thyroid weight. adjusted for bw (mg)	31.1	32.2	33.6	38.5**

** $p<0.01$ (William´s test)

Table 3: Mean thyroid weight (absolute and adjusted for body weight) in female rats at interim kill (week 53)

Dose level	**0 ppm**	**50 ppm**	**400 ppm**	**3200 ppm**
Number examined	20	20	20	20
Absolute thyroid weight (mg)	27.2	26.2	27.3	25.7
Thyroid weight. adjusted for bw (mg)	26.5	24.8	27.5	27.8

A weak but statistically significant increase in the mean adjusted organ weight was evident in the male rats from the interim kill groups at the highest dose level but not in the females. This increase was mainly due to two high dose males (nos. 304 and 316) with outstanding high individual thyroid weights.
19 males from this satellite group were subjected to histopathological examination. In one animal, minimal follicular cell hyperplasia was seen and in another one minimal focal C-cell hyperplasia. Animals 316 with a high thyroid weight of 59.7 mg was that one showing the minimal follicular cell hyperplasia but animal 304 (thyroid weight 61.4 mg) did not exhibit any pathological change of this organ.
These types of histopathological alteration did not occur in the control group. Unfortunately, the organs and tissues from the low and intermediate dose groups were not examined. One could suspect that these hyperplasias (and the increase in the mean adjusted thyroid weight) were induced by treatment, however, with regard to the extremely low incidence of the lesions, a valid conclusion cannot be drawn. Neoplastic changes of the thyroid were not observed in any of the satellite animals after one year of treatment.

Table 4: Mean thyroid weight (absolute and adjusted for body weight) in male rats at study termination (105 weeks)

Dose level	**0 ppm**	**50 ppm**	**400 ppm**	**3200 ppm**
Number examined	32	30	30	30
Absolute thyroid weight (mg)	43.3	49.4	65.1	45.3
Thyroid weight. adjusted for bw (mg)	-	-	-	-

- analysis not performed (for explanation see above)

Table 5: Mean thyroid weight (absolute and adjusted for body weight) in female rats at study termination (105 weeks)

Dose level	**0 ppm**	**50 ppm**	**400 ppm**	**3200 ppm**
Number examined	24	23	22	29
Absolute thyroid weight (mg)	38.8	38.4	45.6	40.2
Thyroid weight. adjusted for bw (mg)	35.9	36.2	40.9	40.6

At terminal sacrifice, no dose-related and statistically significant increase in thyroid weight was seen neither in male rats nor in females. The remarkably higher mean absolute thyroid weight of 65.1 mg in male rats of the mid dose group (400 ppm) was caused by 3 animals with extremely high individual organ weights. All three male rats were bearing tumours. The details about these animals are as follows:

- Animal no. 185; thyroid weight 304.9 mg; follicular cell carcinoma and cystic hyperplasia
- Animal no. 213; thyroid weight 226.1 mg; follicular cell carcinoma and cystic hyperplasia
- Animal no. 212; thyroid weight 158.7 mg; C-cell carcinoma.

If the apparently tumour-related increase in thyroid weight would be related to the administration of the test substance, one could expect a further elevation at the next dose level that is 8 times higher. This was not the case. The highest individual thyroid weights in the male rats in the three remaining groups were: 81.0 mg (Control), 115.2 mg (50 ppm) and 64.6 mg (3200 ppm). It seems that even the slightly higher incidence of follicular cell adenoma in the top dose group does not have an impact on mean thyroid weight. Extreme increases in organ weight were, at least in this study, confined to carcinoma either of follicular or C-cell origin.

A summary of the non-neoplastic findings of follicular cell origin is given below (Table 6).

Table 6: Non-neoplastic histological thyroid findings in the two-year feeding study with beflubutamid in CD rats (excluding interim kill satellite groups)

Sex	**Males**				**Females**			
Dose (ppm)	**0**	**50**	**400**	**3200**	**0**	**50**	**400**	**3200**
Number examined	60	59	60	60	60	40	42	60
Follicular cell hyper-trophy	0	0	0	0	0	1	0	0
Follicular cell hyper-plasia	0	0	0	1	0	0	0	1
Follicular cell cystic hyperpla-sia	2	2	1	3	1	0	0	2
Follicular cysts	0	1	2	1	0	0	1	2

These data do not provide convincing evidence of a non-neoplastic toxic effect of beflubutamid on the follicular cells neither in males nor in females.When the degree of the few observed alterations (not shown in the table) is additionally taken into consideration, there is also no indication of a treatment-related effect. Furthermore, no dose-related change in the frequency or degree of non-neoplastic C-cell lesions was apparent.

Conclusion:
The lack of a consistent organ weight increase and of concomitant non-neoplastic histological findings suggests that there is no chronic adverse impact of beflutamid on the thyroid that eventually could progress to tumours. Taking into account the historical control data, the observed sligth increase in follicular cell adenoma in high dose males is considered to have occurred by chance and not as a result from treatment.

Efforts to identify a possible oncogenic mechanism

Funaki (2003) re-evaluated the available data from chronic and subchronic studies in rats to investigate whether they support the hypothesis that thyroid disruption was the mode af action responsible for the slightly higher incidence of thyroid follicular adenomas at 3200 ppm in male rats and whether these tumours were of relevance to humans.

The author came to the conclusion that, at least, beflubutamid does probably not induce the well-known rodent-specific mechanism of the so-called "phenobarbitone-type". Substances acting in that way induce micromsomal liver enzymes, in particular UDP glucuronyl transferase, leading to a reduction in circulating thyroxine. As a consequence, the thyroid is permanently stimulated via a hormonal feedback mechanism by TSH from the pituitary to increase hormone production to compensate for the thyroxine losses. The excess production of thyroidal hormones may result in hypertrophy and hyperplasia of the follicular cells and may progress to neoplasia. It has been shown that the rat because of certain biochemical differences is much more vulnerable to this proliferative process than the man.

The main argument against a "phenobarbitone-like" mode of action of beflubutamid is that, although there was an increase in liver weight and limited evidence of hepatotoxicity (centrilobular hepatocyte hypertrophy) at higher dose levels, concomitant consistent increases in thyroid weight and non-neoplastic lesions in this organ were lacking. However, hormone measurements were not done and activity of microsomal liver enzymes was not investigated.

Since no other mode of action could be posutulated else, the author considers the higher tumour incidence in high dose male rats a spontaneous event of no or little if any relevance to humans.

Opinion of the Rapporteur:
The slight increase in the incidence of follicular cell adenoma at the top dose level of 3200 ppm is not considered treatment-related. Therefore further efforts to investigate the mechanism behind will probably fail.

Corrections and clarification of the description of the chronic rat study

When the long-term rat study was re-evaluated for purposes of this addendum, it became apparent, that the original table B.6.5-4 in the draft assessment report (monograph) has been erroneously replaced by a wrong one when the final draft was produced. The origin of this wrong table could not be identified.

Now, we provide here the correct table that is in agreement with the the data from the original study report and that was found in a previous version of the monograph.

Table B.6.5-4 (revised): Body weights and 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
Final body wt (g)								
Week 53	736	758	725	689	385	398	372	339
Week 105	708	772	766	703	486	494	492	433
Unadjusted means: Thyroids (mg)								
Week 53	31.3	33.0	33.5	37.5	27.2	26.2	27.3	25.7
Week 105	43.3	49.4	65.1	45.3	38.8	38.4	45.6	40.2
Adjusted means: Thyroids (mg)								
Week 53	31.1	32.2	33.6	38.5**	26.5	24.8	27.5	27.8
Week 105	-	-	-	-	35.9	36.2	40.9	40.6
Unadjusted means: Liver (g)								
Week 53	26.8	26.7	25.9	30.1	14.9	13.9	13.6	15.5
Week 105	25.8	25.2	26.3	27.6	18.4	17.8	18.5	18.8
Adjusted means: Liver (g)								
Week 53	26.5	25.6	26.0	31.6**	14.5	12.9	13.7	17.0**
Week 105	25.6	24.3	25.5	28.0*	18.0	17.2	17.9	20.1**
Unadjusted means: Kidneys (g)								
Week 53	4.63	4.65	4.65	5.08	2.92	2.75	2.82	3.09
Week 105	5.44	5.35	5.51	5.81	3.37	3.35	3.44	3.75
Adjusted means: Kidneys (g)								
Week 53	4.60	4.51	4.66	5.26**	2.86	2.62	2.83	3.28**
Week 105	5.44	5.23	5.33	5.80	3.34	3.30	3.39	3.85**

Statistical significance: *p<0.05; **p<0.01 (William's test)
- not calculated

On request of the ECCO 136 meeting, the outstanding mean value of 1043 mg/dl protein content in the urine of male control rats in this study (Table B.6.5-3) was checked once more and could be confirmed. It is due to the following three individual values:

- male no. 7: 3842 mg/dl
- male no. 28: 1812 mg/dl
- male no. 29: 1343 mg/dl.

On request of the ECCO 136 meeting the number of thyroids examined at terminal sacrifice from the low and mid dose females should be clarified (see Table 6: 40 and 42 thyroids respectively were examined). This is in accordance with the information given in the original dossier. In the study design on page 24 (Materials and methods) it is written: In addition the thyroid gland of all males were examined to investigate an apparent increase in the number of thyroid-follicular tumors in high dose males. In the low and intermediate female groups only the thyroids from the surviving females and organs with macroscopic changes were examined. Therefore, the number comprised 40 and 42 females, respectively.

References (not cited in the monograph)

Funaki, E (2003): Mechanistical explanation for the occurrence of thyroid gland follicular tumours of combined chronic toxicity/carciongenicity study in rats and their relevance to man. Mode of Action Analysis -UR 50601. Ube Research Laboratory, Ube Industries, Ltd., Japan on behalf of Stähler International GmbH Co. KG, Stade, Germany.

Addendum 2

to the Draft Assessment Report

of 02 August 2002

(relating to Volume 4, Annex C)

Beflubutamid

Confidential

6 June 2006

Rapporteur Member State: Germany

Confidential information available at RMS

Addendum 3

to the Draft Assessment Report

of 2 August 2002

Beflubutamid

Vol. 1 Level 2 + 3

Vol. 3 B.1 (Identity)

B.5 (Methods of analysis)

B.8 (Environmental fate and behaviour)

B.9 (Ecotoxicology)

6 June 2006

Rapporteur Member State: Germany

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Level 2 Overall conclusions

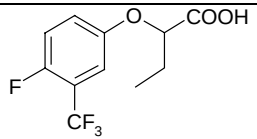
2 Reasoned statement of the overall conclusions

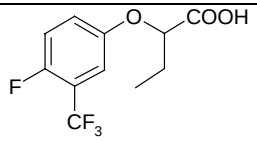
2.5 Fate and behaviour in the environment

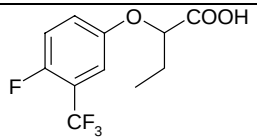
2.5.1 Definition of the residues relevant to the environment

The residue can be defined as beflubutamid and its major metabolite phenoxybutyric acid UR-50604 (soil (aerobic, anaerobic), water/sediment) (see Table 2.5.1). Concerning the herbicidal activity the metabolite UR-50604 is regarded as non-relevant, however, it is considered ecotoxicologically relevant in terrestrial ecosystems. The metabolite UR-50604 has no potential for accumulation in soil.

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
Phenoxy-butyric 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
Phenoxy-butyric acid (UR-50604)		< 0,1µg/L	Not relevant	Not relevant	Not relevant

Code	Active substance		
UR-50601	beflubutamid		
Metabolites		Occurrence **Water/sediment**	Assessment of the relevance with regard to
Code	Structural formula		Aquatic Ecotoxicology
Phenoxy-butyric 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 – 99 days and DT_{90lab} values of 17 days - 328.0 days. 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. DT_{50} values of 1- 18 days were calculated. 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 496 – 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 winter and spring cereals resulting in max. concentrations of 0.005 and 0.017 µg/L for the scenarios “Hamburg” and “Piacenza”, respectively. Therefore, groundwater contamination of the major metabolite UR-50604 > 0,1 µg/L can be excluded. There are only limited data available adressing the stereo-selective degradation of beflubutamid. Based on these data a difference in fate profile of the 2 isomers for parent (beflubutamid) and metabolite (UR-50604) could not be definitely clarified. However, considering the results of the ground water modelling for beflubutamid which are

based on worst case scenarios resulting concentrations of < 0.001 µg/L in groundwater it is extremly unlikely that the variation between isomers alters this assessment. The risk assessment for aquatic organism is based on PECinitial values. Therefore stereo-selective degradation of beflubutamid has no influence on the assessment.

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 UR-50604 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 UR-50604 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.
The applicant has submitted FOCUS PEC_{SW} and PEC_{SED} calculations. However, the input data of these calculation do not reflect worst case conditions for the metabolite UR-50604 (see 2.6.1). The re-calculation of PEC_{SW} and PEC_{SED} as presented in Table B.8.6-4 and B.8.6-7 are therefore based on 100 % conversion of the parent to the metabolite as a worst case assumption.
Notwithstanding, the results of the water/sediment-study were re-analysed regarding the concentration of beflubutamid and its metabolite UR-50604 in water phase and the sediment. The residue dynamics of the metabolite UR-50604 in the water phase and the sediment seems to reflect the slow degradation of the parent compound rather than a potential for accumulation of the metabolite. The proportion of the metabolite in the water and the sediment at the end of the study might indicate that the metabolite formed in the sediment is even transferred back to the water phase.

The ecotoxicological data set of the metabolite UR-50604 comprises toxicity data for the aquatic organisms (fish, daphnia and algae). These toxicity data show that the metabolite is significantly less toxic than the parent compound and therefore not relevant for the risk assessment.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

The toxicity of beflubutamid to 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 birds:	LD_{50} >2000 mg/kg bw
Dietary toxicity to birds:	LC_{50} >970 mg/kg bw/s
Reproductive toxicity to birds:	NOEL 88 mg/kg bw/d

The risk to birds resulting from secondary poisoning through accumulation of beflubutamid in possible prey items can be demonstrated as acceptable with toxicity-exposure-ratios well above the Annex-VI-triggers.

The acute risk assessment for mammals produces TER values that exceed the Annex VI trigger of 10 indicating an acceptable acute risk to wild mammals following application according to label recommendation for winter cereals. The resulting TER of the long-term risk assessment is below the Annex VI trigger of 5 indicating that beflubutamid poses a long-term risk to wild mammals. The refined long-term risk assessment for herbivorous mammals feeding on short grass and cereals shoots result in TERs that exceed the Annex VI trigger of 5, indicating that beflubutamid poses a low long-term risk to these mammals. The risk assessment of the parent compound covers the risk assessment for the metabolite.

Acute toxicity to mammals:	LD_{50} >5000 mg/kg bw
Long-term toxicity to mammals:	NOAEL approx. 17 mg/kg bw/d (reproductive NOAEL from rat multi-gen study)

The risk to mammals resulting from secondary poisoning through accumulation of beflubutamid in possible prey items can be demonstrated as acceptable with toxicity-exposure-ratios well above the Annex-VI-triggers.

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 consequential 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 0.00455 mg/L for *S. capricornutum* should be used for the risk assessment.

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. Considering the maximum application rate of 170 g as/ha the risk is acceptable in a distance of 5 m.

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 0.170 mg/kg the TER is < 1.0. 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 2, still below the trigger of 5. A field study (ARW2005-260) to evaluate the effects of Herbaflex on earthworms was assesed. The results of soil residues showed that both beflubutamid and its metabolite UR-50604 occurred in the soil after treatment with Herbaflex, so that the study reflects the effects of beflubutamid as well as of its metabolite UR-50604 on earthworms. From the results of the study it can be concluded that no statistically significant effects on the development of earthworm populations will arise from the use of Herbaflex at the use rate of 3.0 L/ha applied once compared to an untreated control area. The recommended dose rate for Herbaflex is 2 L/ha. Therefore Herbaflex poses no long-term risk to earthworm populations following applications in accordance to the recommended use.

In the study (ARW2005-258) -assessing the effects of metabolite UR-50604 on reproduction- a NOEC of 3.8 mg/kg was determined. The resulting long-term value exceeds the relevant Annex VI trigger of 5, indicating that the metabolite UR-50604 poses an acceptable long-term risk to earthworms.

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 502 g/L isoproturon and 85 g/L beflubutamid)

Reproductive toxicity to earthworms:	NOEC 6 L/ha (formulation ASU 95 510 H containing 502 g/L isoproturon and 85 g/L beflubutamid)
	NOEC 3.8 mg/kg (Metabolite UR-50604)

A study dealing with the effects on reproduction of Collembola (*Folsomia candida*) (ARW2004-20) caused by Herbaflex was assessed. The study demonstrated that Herbaflex caused no dose related effect on the survival of *Folsomia candida* up to and including the concentration of 320 mg/kg. Therefore, the NOEC for mortality was determined at 320 mg/kg artificial soil. Comparing with the value of the NOEC of 320 mg/kg for mortality and for reproduction Herbaflex poses no risk to collembola following applications in accordance to the recommended use.

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 resulting in a lowest ED_{50} of 14.8 g as/ha for *Lactuca sativa* in the post-emergence test.
The effects of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon) on terrestrial plants at pre- and post emergence application was assessed for two monocotyledons (oat and spring barley) and five dicotyledons (rape, sugar beet, mustard, sunflower and pea).
The lowest ER_{50} value of 0.06 L/ha was seen in sugar beet (*Beta vulgaris*) at post-emergence application of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon). At pre-emergence application of Herbaflex the lowest ER_{50} value of 0.22 L/ha was determined for rape (*Brassica napus*).

The risk assessment for non-target plants resulted in TER values below the relevant Annex VI trigger of 5, indicating a possible risk to terrestrial non-target plants.
TER values greater than 5 could be demonstrated for Herbaflex by a buffer distance of 10 m (without spray reducing nozzles). Using spray reducing nozzles resulting in 90 % drift reduction, no buffer distance needs to be applied. For an acceptabel risk following the ED_{50} of 14.8 g as/ha of *Lactuca sativa* in the post-emergence test with beflubutamid a buffer distance of 5 m has to be applied.
With use of the risk mitigation options, beflubutamid and Herbaflex poses acceptable risk to non-target terrestrial 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.

Level 3 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

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 and the major metabolite.

The metabolite UR-50604 is non-relevant regarding its herbicidal activity, however, it is ecotoxicologically relevant because of its acute and long-term effects on earthworms. There is no potential for accumulation of the metabolite UR-50604 in soil.

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 biological methods of sewage treatment are acceptable.

Due to the effects on aquatic plants an unrestricted use of beflubutamid cannot be considered. Adequate risk mitigation measures are to be set at Member State level.

A risk for terrestrial non-target plants can not be excluded. Adequate risk mitigation measures are to be set at Member State level.

3.2 Proposed decision concerning inclusion in Annex I

It is proposed that beflubutamid can be included in Annex I of Directive 91/414/EEC.

3.3 Rationale 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

Adequate risk mitigation measures for the protection of terrestrial non-target plants and aquatic plants are to be set at Member State level.

To Volume 3

B.1 Identity

B.1.1 Identity of isomers

A study was submitted dealing with the herbicidal activity of the two beflubutamid isomers against target weed species in European cereal fields.
Three test compounds (S-isomer, R-isomer and the racemate) have been tested for their herbicidal activity against the test plants listed below:

Test Plants	
Crop:	Wheat (variety Kobushi)
Grass weeds:	*Alopecurus myosuroides*
	Poa annua
Broadleaf weeds:	*Stellaria media*
	Cerastium glomeratum
	Matricaria inodora L.
	Lamium amplexicaule
	Veronica persica
	Papaver rhoeas L.
	Galium aparine L.
	Viola tricolor

The test plants were grown in plastic pots and treated at early growth stage in different concentrations via spray application. After 26 days an assessment of the growth mass was conducted. The results are listed in the table below.
The different activity of the optical isomers could be shown. S-beflubutamid showed post-emergence activity to a wide range of broadleaved weeds, but R-beflubutamid showed no activities by treatment. Furthermore racemate-beflubutamid showed about half activity of S-isomer which reflected isomer ratio 1:1.

Table B.1.1-1: Mass growth inhibition of beflubutamid isomers compared to the racemate

	S-beflubutamid					R-beflubutamid					Racemate-beflubutamid				
	250	125	62.5	31.3	15.6	250	125	62.5	31.3	15.6	250	125	62.5	31.3	15.6
Phytotoxicity (%)															
Wheat	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Weed control (%)															
Alopecurus myosuroides	10	5	0	0	0	0	0	0	0	0	5	0	0	0	0
Poa annua	93	80	30	10	0	0	0	0	0	0	80	30	10	5	0
Stellaria media	55	28	5	0	0	0	0	0	0	0	35	5	0	0	0
Cerastium glomeratum	65	25	10	5	0	0	0	0	0	0	40	10	0	0	0
Matricaria inodora L.	75	40	25	5	0	0	0	0	0	0	25	25	5	1	0
Lamium amplexicaule	98	98	85	70	10	0	0	0	0	0	98	98	65	20	0
Veronica persica	90	78	65	45	10	0	0	0	0	0	90	75	60	10	0
Papaver rhoeas L.	95	99	90	25	0	0	0	0	0	0	85	85	15	0	0
Galium aparine L.	95	95	55	15	0	0	0	0	0	0	85	65	30	5	0
Viola tricolor	95	95	90	65	30	0	0	0	0	0	95	95	90	40	5
BLWs average	84	70	53	29	6	0	0	0	0	0	69	57	33	10	1

B.1.2 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
AIIA-1.9, 1.10	Funaki, E.; Okada, T.	2003	Herbicidal activity of Beflubutamid isomers 15.10.2003 not GLP, unpublished CHE2004-162	Y	TSU

Codes of company

TSU: Task force Stähler International GmbH & Co. KG / UBE Industries

B.2 Physical and chemical 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.2.2.7.3 (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~~ suspensibility) are negligible.	Acceptable.	Flack, I. (1999) PHY2000-573, Frauen, M.; Stähler, O. (2001) PHY2001-257
...					
...					

B.5 Methods of analysis

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

Report: Stähler, O.; Frauen, M.; Stähler, R.: Validation of the Analytical Method for the Determination of Beflubutamid (UBH-820) in Cereals (Green Plant, Grain and Straw) according to Method L 00.00-34 "*Amtliche Sammlung von Untersuchungsverfahren nach § 35 LMBG* "; Analytical Method No.: AM-RU-1203, Study-No.: RU0303, Protocol No.: 95510-GM-002D; December 4th, 2003 (MET2004-86)

GLP: yes

Acceptability: The study is considered partially acceptable

Material and Methods:
Test material:
Dry crops (grain, straw), commodities with high water content (green plant)

Fortified analyte: beflubutamid

Principle of method: Standard multiresidue method S19: Residues of beflubutamid (UBH-820) are extracted from cereal matrices by water/acetone (1/2, v/v). Sodium chloride and ethyl acetate/cyclohexane (1/1, v/v) are added to achieve a homogeneous partition of the analyte into the organic phase. An aliquot of the organic extract is cleaned-up by gel permeation chromatography (GPC) followed by further fractionation on silica gel. The determination of the beflubutamid is achieved by gas chromatography (GC) with a nitrogen-phosphorus detector (PND).

Findings:
The calibration curve was linear in the range of 0.1 µg/ml to 7.5 µg/ml with a correlation coefficient r= 0.9960. Validation was done by one point calibration with standard solutions analysed before and after samples. No blank values were observed.
At the fortification level of 2 mg/kg some of the recoveries exceeded the highest value (7.5 µg/ml) of the calibration curve and were therefore not in the calibrated range.
For dry matrices (grain and straw) the recovery data at almost all fortification levels were significantly higher than 110% and for grain the RSD was greater than 20% at the lowest fortification level.

Conclusion:
The multiresidue method L 00.00-34 was successfully validated for the determination of residues of beflubutamid in green plant with a limit of quantification of 0.05 mg/kg.
The determination of residues in grain and straw especially at low concentrations lead to unacceptable results. This may be due to the fact that only solvent based standards were used and not matrix based standards.

Table B.5.2-1: Validation data for determination of beflubutamid in cereal matrices

Reference	Sample material	Fortification level [mg/kg]	Average recovery [%]	RSD [%]	Number
Stähler, O., Frauen, M., Stähler, R.: AM-RU-1203; 2003 (MET2004-86)	Green plant	*2.00*	*126.4*	*14.4*	*5*
		0.50	110.0	8.6	5
		0.05*	100.9	5.1	5
	Grain	*2.00*	*126.1*	*9.8*	*5*
		0.50	131.9	9.1	5
		0.05	198.5	47.3	5
	Straw	*2.00*	*121.4*	*9.8*	*5*
		0.50	109.6	7.6	5
		0.05	137.0	14.9	5

* limit of quantification

Report: Rogge, K., Siebers, J. 2002, residue analytical laboratory, BBA (Federal Biological Research Centre) Braunschweig

Finding:
The multiresidue method S19 (principle see above) was tested for determination of beflubutamid in wheat grain in the residue analytical laboratory of the BBA. Beflubutamid was quantified against known amounts of external matrix-matched standards. Acceptable recoveries (recoveries within 70 - 110 %, RSD < 20%) for beflubutamid were obtained for fortification levels of 0.01 mg/kg, 0.05 mg/kg and 0.1 mg/kg. In table B.5.2.-2 only those results are presented that are published on the homepage of the BVL (Federal Office of Consumer Protection and Food Safety). (www.bvl.bund.de/dbanalytik).

Conclusion:
The multiresidue method S19 was successfully validated for the determination of beflubutamid in grain.

Table B.5.2-2: Validation data for determiation of beflubutamid in grain

Matrix	Fortification level [mg/kg]	Average recovery [%]	V [%]	n	Extraction	GPC [mL]	Silica gel	Detection
Wheat grain	0.01	89	11.1	7	E1	80 - 180	Eluate 2 and 3	PND

Remark by RMS
It can be concluded that it is possible to determine beflubutamid with the multiresidue method S19. However, the study of Stähler, O.; Frauen, M.; Stähler, R. (MET2004-86) seems to be not appropriately performed and therefore lead to unacceptable results. Additional data should be requested on Member State level if esteemed necessary.

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

Report: Groß, G; (2004); Development of a method for the determination of Fluoromethylphenoxybutyric acid (UR50604) in soil; BioChem project No.: 04 10 35 2002, (MET2004-288)

GLP: yes

Acceptability: The study is considered acceptable

Materials and methods
Test material: sandy loam (2.3 LUFA Speyer)

Fortified analyte: Metabolite fluoromethylphenoxybutyric acid (UR50604)

Principle of method: The metabolite UR50604 is extracted with acetone. After evaporation of the acetone the residue is re-dissolved with a mixture of acetonitrile and ammonium acetate and cleaned up via SPE cartridge. The analyte is determined by HPLC-UV at 220 nm using a RP18 reversed phase column.

Findings
The method has been validated with a limit of quantification of 0.05 mg/kg. Blank values were not observed. An appropriate calibration curve is presented. The scale of the chromatograms is too high so that the analyte can not sufficiently be identified on the submitted copies. Individual recovery data are presented but additional data of a second extract from the SPE cartridge were added and are included in the recovery results. These additions are in the range of 0 – 1.5 % of the recovery results and have no impact on the validity of the method.

Conclusion
The method is successfully validated and acceptable for the determination of the metabolite UR50604 in soil.

Table B.5.3-1: Validation data for determination of metabolite UR50604 in soil

Reference	Analyte	Detection Method	Fortification level (mg/kg)	Average recovery (%)	RSD (%)	n
Groß, G; (2004) (MET2004-288)	UR50604	HPLC-UV	0.05*	82.7	7.7	5
			0.5	77.6	11.7	5

* limit of quantification

Report: Groß, G.; (2005) Determination of the residues of the active substance beflubutamid and ist metabolite UR50604 in soils from an earthworm field study; BioChem project No.: 0410352012, (MET2005-776)

GLP: yes

Acceptability: The study is considered acceptable

Materials and methods
Test material: soil from earthworm test

Analyte determined: Beflubutamid and fluoromethylphenoxybutyric acid (UR50604)

Principle of method: The soil is extracted with a mixture of acetone and water. After evaporation the residue is re-dissolved with a mixture of acetonitrile and ammonium acetate and cleaned up via Waters OASISHLB 3cc cartridge. The analytes are determined by LC-MS in the Single Ion Monitoring (SIM) mode (beflubutamid: m/z= 414.15, UR50604: m/z = 265.0) using a RP18 column for separation.

Findings
The method is successfully validated for beflubutamid and metabolite UR50604 with a limit of quantification of 0.005 mg/kg. Blank values are not observed. Acceptable chromatograms from samples and blank materials and individual recovery data are presented. Calibrations are performed for two concentration ranges and appropriate calibration curves are given.
The recovery data of the 1. extract and the 2. extract were added up to the recovery result. The values of the 2. extract were up to 10 % of the individual recovery data. Therefore the results of the 1. extract were calculated by RMS from the individual recovery data and are also shown in table 5.3.2.

Conclusion
The method is successfully validated and acceptable for the determination of beflubutamid and the metabolite UR50604 in soil.

Table B.5.3-2: Validation data for the determination of beflubutamid and metabolite UR50604 in soil

Reference	Detection Method	Analyte	Fortification level (mg/kg)	Average recovery (%) RSD (%)		n
				1. extract	1 + 2. extract	
Groß, G.; (2005), MET2005-776	LC-MS	Beflubutamid	0.005*	95.9 6.3	101.7 5.7	5
			0.01	91.3 4.2	94.7 5.2	5
			0.05	90.2 3.8	91.3 3.5	5
			0.5	88.9 3.8	89.5 3.3	5
		UR50604	0.005*	92.9 3.2	92.9 3.2	5
			0.01	91.4 4.8	91.4 4.8	5
			0.05	99.0 2.8	99,0 2.8	5
			0.5	94.4 3.7	94.8 3.7	5

* limit of quantification

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
AIIA-4.2.1	Stähler, O.; Frauen, M.; Stähler, R.	2003	Validation of the Analytical Method for the Determination of Beflubutamid (UBH-820) in Cereals (Green Plant, Grain and Straw) according to Method L 00.00-34 "Amtliche Sammlung von Untersuchungsverfahren nach § 35 LMBG " Analytical Method No.: AM-RU-1203, Study-No.: RU0303, Protocol No.: 95510-GM-002D; GLP, unpublished MET2004-86	Y	TSU
AIIA-4.2.1	Rogge, K., Siebers, J.	2002	Residue analytical laboratory, BBA (Federal Biological Research Centre) Braunschweig published (www. bvl.bund.de/dbanalytik)	N	
AIIA-4.2.2	Groß, G.	2004	Development of a method for the determination of Fluoromethylphenoxybutyric acid (UR50604) in soil; BioChem project No.: 04 10 35 2002, GLP, unpublished MET2004-288	Y	TSU
AIIA-4.2.2	Groß, G.	2005	Determination of the residues of the active substance beflubutamid and ist metabolite UR50604 in soils from an earthworm field study; BioChem project No.: 0410352012, GLP, unpublished MET2005-776	Y	TSU

Codes of company

TSU: Task force Stähler International GmbH & Co. KG / UBE Industries

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

To Evaluation Table 1-1 of 29.09.2004 – open point 2.2:
"RMS is to consider whether all the environmental fate issues associated with the parent and the major metabolite UR-50604, each having 2 isomers have been addressed. (Particular attention to be paid to areas of the assessment where results are borderline and the role of the isomers may make a difference). If necessary, RMS is to discuss further with the applicant, giving consideration to using existing information if possible and requesting additional data only where critical. (IIA 7, IIIA 9)."

Studies which are related to stereo-selective degradation are listed in Table B.8.1-1 (see Funaki, E; 2003 (BOD2004-62).

Table B.8.1-1: Studies related to stereo-selective degradation of beflubutamid

Annex Point	Study to	Author, Report-No.	Outcome
IIA, 7.2.1.3.2	aerobic aquatic degradation	Elsom, Kaur, Kirkpatrick (1998 b), UBE 069/983037 WAS2000-255	This study gave clear differences in partitioning of the isomers of metabolite UR-50604 (ratio of S:R of 26:74 at 14 days, 83:17 at 100 days).
IIA, 7.1.1.1.1	Aerobic soil metabolism	Dean, Goslan, Mayo (1999), UBE 67/983000 BOD2000-1132	This study gave some indication of stereo-selective degradation. This was very marginal for UR-50601 (ratio of S:R of 55:45 at 7 days) but more pronounced for metabolite UR-50604 (ratio of S :R of 40:60 at 7 days, 28:72 at 60 days plus).
IIA, 7.1.1.1.2/01	Anaerobic soil metabolism	Dean, Batt, Mayo (1998), UBE 076/982926 BOD2000-1133	This study gave some indication of stereo-selective degradation. This was very marginal for UR-50601 (ratio of S:R of 55:45 at 7 days).
IIA, 7.1.1.2.1/02	Rate of degradation in three soils	Dean, Mayo (1999), UBE 071/982852 BOD2000-1135	In this study no measurement of the separate isomers was made. Results are expressed as total for the racemate
IIA, 7.1.1.2.2/01	Field dissipation	Wilson (2000), UBE 099/002143 BOD2000-1136	In this study no measurement of the separate isomers was made. Results are expressed as total for the racemate

Only three studies give some indications of stereoselective degradation. The results of this studies regarding the ratio of isomers are summarised in Table B.8.1-2.

Table B.8.1-2: Overview about the concentration (related to 100 % beflubutamid) and isomer ratio for beflubutamid and its isomer UR-50604 as a function of time related to biodegradation studies

		S : R (%)						
		0 day	**7 day**	**14 day**	**30 day**	**60 day**	**90 day**	**100 day**
Aerobic Aquatic (Water/Sediment) aqueous phase								
UR-50604	S+R (%) S:R	0.4	1.3	9.4 26:74	36.8 54:46	31.6 64:36		35.2 83:17
Aerobic soil								
beflubutamid	S+R (%) S:R	96.9 50 : 50	49.5 55 : 45	30.4	21.3	19.9		
UR-50604	S+R (%) S:R	0.3	26.1 40:60	19.8	23.6 29:71	18.9 28:72	24.3 28:72	
Anaerobic soil								
beflubutamid	S+R (%) S:R	91.9 50 : 50	86.9 55 : 45	85.6	79.1	70.7		

At zero time the ratio of S- and R-isomer in soil extracts treated with radio labelled beflubutamid was ca. 1:1, and after 7 days this changed to a ratio of ca 55:45 (S:R) in the aerobic and the anaerobic soil metabolism study. The data indicate a delayed primary degradation of the S-isomer. However the estimated DT_{50} value for the S-isomer would be in this case 2 days longer than for the racemat.
The ratio of optical isomers of the major degradate UR-50604 showed that the relative proportion of S-isomer increased with time from ca. 26 % at day 14 to 83 % at day 100 in results of the water/sediment-study (aerobic aquatic). However, in the aerobic soil metabolism study the relative proportion of S-isomer of UR-50604 decreased from 40 % at day 7 to 29 % at day 30, and this level continued until day 90.

Conclusions
There are only limited data available adressing the stereo-selective degradation of beflubutamid. Based on these data a difference in fate profile of the 2 isomers for parent (beflubutamid) and metabolite (UR-50604) could not be definitely clarified. However, considering the results of the ground water modelling for beflubutamid which are based on worst case scenarios resulting concentrations of < 0.001 µg/L in groundwater it is extremly unlikely that the variation between isomers alters this assessment. The risk assesssment for aquatic organism is based on $PEC_{initial}$ values. Therefore stereo-selective degradation of beflubutamid has no influence on the assessment.

B.8.1.2 Rate of degradation

B.8.1.2.1 Laboratory studies

The degradation rates for beflubutamid and UR-50604 given in monograph (volume 3, table B.8.1-3) were recalculated based on a first order non linear approach using modelling software (Modelmaker version 4.0). The degradation rates are given in table Table B.8.1-3.

Table B.8.1-3: Kinetic 1st order degradation rates of Beflubutamid and its metabolite UR-50604 in aerobic soils calculated by Modelmaker

substance			**beflubutamid**		**UR-50604**		
calculation method			1st order kinetic		1st order kinetic		
soil	temp. (°C)	MWHC (%)	DT_{50} (days)	DT_{90} (days)	DT_{50} (days)	DT_{90} (days)	calculation period (days)
Arrow	20	40	15.8	52.5	18.0	59.8	0 - 120
Wick	20	40	5.3	17.4	0.9	3.2	0 – 120
Speyer 2.2[A]	20	40	98.7	328.0	7.7	25.6	0 – 120
Evesham	20	40	8.7	29.1	3.1	10.3	0 – 120
Speyer 2.2[B]	20	40	20.6	68.4	3.6	12.0	0 – 120

B.8.3 Predicted environmental concentrations in soil (PEC_S) (Annex IIIA 9.1.3)

B.8.3.1 Calculation of PEC_{soil} for beflubutamid and its metabolite UR-50604

To Evaluation Table 1-1 of 29.09.2004 – data requirement 2.2:
"Applicant is to submit new PECsoil calculations using the revised application rate of 170 g as/ha."

Annex Point: IIIA- 9.1 – 9.2
Author: Heimann-Detlefsen, D.
Title: Predicted environmental concentration in soil and water
Date: 12.12.2003
Doc ID: report No. UBE-2003-01; BOD2004-63 + BOD2005-954
Guidelines: not relevant
GLP: not relevant
Validity: not relevant

PEC calculations had to be updated for beflubutamid and its main metabolite due to the change of the intended application rate (now: 170 g as/ha). The PEC for beflubutamid is calculated for a single application at a rate of 170 g as/ha. Since the product is intended for the use in cereals at BBCH 11 – 29, it is assumed that maximal 75 % of the applied dose will reach the soil (corresponding to 25 % interception by plants).
Maximum occurrence of UR-50604 of 30 % compared to beflubutamid was taken into account. This value corresponds very well with the maximum occurrence of UR-50604 of 26.1 % in Southern field studies (see monograph, volume 3, chapter B.8.1.2.2) and with the average as achieved in the earthworm field study (see this addendum, chapter B.9.6.3).

The PEC_{soil} calculation as presented in Table B.8.3-1 is based on recalculated laboratory degradation data for Speyer 2.2^{A} (see B.8.1.1.1).

Beflubutamid: 98.7 d (worst case)
UR-50604: 7.7 d

Table B.8.3-1: Predicted Environmental Concentrations of beflubutamid and the metabolite UR-50604 in soil (PEC_{soil}) following a single application on cereals at a rate of 170 g as/ha

Days after application	Beflubutamid		UR-50604	
	Actual concentration PEC_{soil}	Time weighted average conc. $PEC_{soil,twa}$	Actual concentration PEC_{soil}	Time weighted average conc. $PEC_{soil,twa}$
	[mg/kg soil]			
0 (initial)	0.170	0.170	0.038	0.038
1	0.169	0.169	0.035	0.037
2	0.168	0.169	0.032	0.035
4	0.165	0.168	0.027	0.032
7	0.162	0.166	0.020	0.028
28	0.140	0.154	0.003	0.014
50	0.120	0.143	0.000	0.008
100	0.084	0.122	0.000	0.004

General assumptions: plant interception 25 %, bulk density of soil: 1.5 g/cm^3; soil layer: 5 cm

Conclusions
The PEC_{soil} values for beflubutamid are acceptable. For the metabolite UR-50604 the worst case degradation half-life is 18.0 d (see table Table B.8.3-1). Therefore the PEC_{Soil} values for the metabolite UR-50604 as given in Table B.8.3-1 are slightly underestimated. However, since the risk assessment is based on the initial PEC_{soil} values, no further calculations are needed.

The initial values of PEC_{soil} to be used for the risk assessment are as follows:

Beflubutamid: 0.170 mg/kg dw soil
UR-50604: 0.038 mg/kg dw soil

B.8.4 Fate and behaviour in water (Annex IIA 7.2.1; Annex IIIA 9.2.1, 9.2.3)

B.8.4.3 Biological degradation

B.8.4.3.2 Water/sediment study

To Evaluation Table 1-1 of 29.09.2004 – data requirement 2.3:
"RMS is to discuss with applicant whether any further information is available on the behaviour, stability and potential for accumulation of the metabolite UR-50604 in water-sediment systems." (IIA 7.2.1.3.2).

The applicant has submitted FOCUS PEC_{SW} and PEC_{SED} calculations. However, the input data of these calculations do not reflect worst case conditions for the metabolite UR-50604 (see B.8.6.1). The re-calculations of PEC_{SW} and PEC_{SED} as presented in Table B.8.6–4 and Table B.8.6–7 are therefore based on 100 % conversion of the parent to the metabolite as a worst case assumption.
Notwithstanding, the results of the water/sediment-study were re-analysed regarding the concentration of beflubutamid and its metabolite UR-50604 in water phase and the sediment. The residue dynamics of the metabolite UR-50604 in the water phase and the sediment seems to reflect the slow degradation of the parent compound rather than a potential for accumulation of the metabolite. The proportion of the metabolite in the water and the sediment at the end of the study might indicate that the metabolite formed in the sediment is even transferred back to the water phase.
The ecotoxicological data set of the metabolite UR-50604 comprises toxicity data for the water phase organisms (fish, daphnia and algae). These toxicity data show that the metabolite is significantly less toxic than the parent compound and therefore not relevant for the risk assessment.

B.8.6 Predicted environmental concentrations in surface water and in ground water (PEC_{SW}, PEC_{GW}) (Annex IIIA 9.2.1, 9.2.3)

B.8.6.1 Predicted environmental concentrations in surface water (PEC_{sw})

To Evaluation Table 1-1 of 29.09.2004 – data requirement 2.4:
“Applicant is to submit new PECsurface water calculations using the revised application rate of 170 g a.s./ha”

Annex Point:	IIIA- 9.1 – 9.2
Author:	Heimann-Detlefsen, D.
Title:	Predicted environmental concentration in soil and water
Date:	12.12.2003
Doc ID:	report No. UBE-2003-01 BOD2004-63 + BOD2005-954
Guidelines:	not relevant
GLP:	not relevant
Validity:	not relevant

PEC calculations were updated for beflubutamid and its main metabolite UR-50604 due to change of the indented application rate (now 170 g as/ha). The applicant has submitted FOCUS calculations which for reasons of transparency are documented below. The input data for the FOCUS calculations are presented in Table B.8.6-1:

Table B.8.6-1: Input data for PEC_{sw} and PEC_{sed} calculation by applicant

	Beflubutamid	**Metabolite UR-50604**	**Comment**
$DT_{50\ Soil}$	98.7 d	7.7 d	Worst case scenario soil Speyer 2.2 used for beflubutamid. This value is also near the worst case in field trials (DT_{50} = 103 days).
Absorption parameter	Koc = 1260 1/n = 0.91	KOC = 9 1/n = 0.81	Combination of worst case values used. Although worst case Koc were 852 (1/n=0.86) and 6 (1/n=0.57) for active ingredient and metabolite, respectively, it has to be noted, that the exponent 1/n is more critical than Koc when modelling
$DT_{50\ surface\ water}$	20 d	20 d	UR-50604: In the absence of suitable values for the metabolite, same value was chosen as for Beflubutamid.
$DT_{50\ Sediment}$	65 d	7.7 d	Beflubutamid: Although DT_{50} = 65 days represent the DT_{50} for the whole system, this value was used only for sediment for the calculation of PEC_{SW} and PEC_{SED}. UR-50604: In the absence of suitable values for the metabolite, same worst case value as for soil was chosen.

PEC_{sw} and PEC_{sed} have been calculated using the German EXPOSIT 1.1 as well as the FOCUS approach of STEP 1-2 (Fraunhofer Institute) and STEP 3 (SWASH).

EXPOSIT 1.1 is used for evaluation of the risk assessment for surface water and groundwater in Germany. The program was run independently for beflubutamid and UR-50604, because the calculation of a metabolite is not intended by the program. A 100 % conversion of the metabolite was taken into account, considering only the molecular mass of the substances.
For FOCUS calculation the program was run for beflubutamid and UR-50604 at the same time. In contrast to the modelling by EXPOSIT 1.1, the maximum amount (55 %) of UR-50604 observed in the water/sediment study was taken into account.
The input parameter are given in Table B.8.6-2. The calculated PECini values are presented in Table B.8.6-3.

Table B.8.6-2: Input parameter for PEC_{SW} and PEC_{SED} calculation by EXPOSIT 1.1 and FOCUS (Step 2 and 3)

	Input parameter	**Beflubutamid**	**UR-50604**
General	Molecular mass	355.00 g/mol	266.00 g/mol
	water solubility	3.29 mg/L	1580 mg/L
	Vapour pressure	1.1 x 10^{-6} Pa	1.1 x 10^{-7} Pa
	Application rate	170 g/ha	EXPOSIT: 127.50 g/ha (100 % conversion) STEP 2: 55 % max. observed in water/sediment studies
	crop interception	minimal crop cover (25 %)	
	Application / crop type	winter cereals	
	number of application	1	
EXPOSIT 1.1	Risk group	Group I	Group II
	application time	autumn/early spring	
	Drift percentage at distance to water body	default: 1 m: 2.77 %; 5 m: 0.57 %; 10 m: 0.29 %	
	Runoff & drainage (% of application):	default: 5 %	
	Reduction effect of buffer zone	default: 5 m: 50 %, 10 m: 90 %, 20 m: 97.5 %	
	All other parameter	default	
FOCUS STEP 2: **scenario data used in the calculation**	region and season of application	North & South Europe: Oct. - Feb.	
	Distance to the water body	1 m	
	Spraydrift (% of application):	2.7590 %	
	Runoff + drainage	5.00 % (North E.), 4.00 % (South E)	
	Ratio of field to water body:	10.00	
	Water depth	30.00 cm	
	Sediment depth	5.00 cm	
	Effective sediment depth for sorption	1.00 cm	
	Sediment OC	5.00 %	
	Sediment bulk density	0.80 kg/L	
FOCUS STEP 3	all other parameter	default	

Table B.8.6-3: Initial PEC_{sw} and PEC_{sed} of beflubutamid

Calculation Method	Water body	Region / Scenario		Beflubutamid		UR-50604	
				PEC_{sw} [µg/L]	PEC_{sed} [µg/kg]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg]
EXPOSIT 1.1	Ditch	Germany, Drift, 1 m		1.57	not calculated	1.18	not calculated
		Germany, Run-off		2.40	not calculated	1.40	not calculated
		Germany, Drainage		0.06	not calculated	0.67	not calculated
FOCUS (STEP 2)	Ditch	North Europe		8.374	102.866	3.410	0.288
		South Europe		6.832	83.528	2.830	0.237
FOCUS (STEP 3)	Stream	D1	Lanna	0.953	5.629	--	--
		D2	Brimstone	1.014	2.811	--	--
		D4	Skousbo	0.931	0.366	0.337	0.132
		D5	La Jailliere	1.005	0.263	--	--
		R1	Weiherbach	1.034	0.742	0.086	0.009
		R3	Bologna	1.304	32.129	0.110	0.015
		R4	Roujan	1.414	0.876	0.076	0.009
	Ditch	D1	Lanna	1.104	9.656	1.629	0.685
		D2	Brimstone	1.226	4.178	--	--
		D3	Vredepeel	1.073	0.461	--	--
		D6	Thiva	1.085	1.579	0.399	0.094
	Pond	D4	Skousbo	0.088	0.694	0.254	0.185
		D5	La Jailliere	0.037	0.273	--	--
		R1	Weiherbach	0.129	0.748	0.002	0.002

-- Values not recorded, because the metabolite run is done with the pesticide properties of the parent.

Conclusions

The input parameters as given in Table B.8.6-1 are not fully acceptable for the following reasons:

$DT_{50\ surface\ water}$: There is no differentiation between biological degradation or dissipation of beflubutamid. However, for FOCUS Step 2 and 3 calculations only DT_{50} values based on biological degradation must be used. It is not acceptable to assume that metabolite has the same dissipation time than the parent compound.

$DT_{50\ sediment}$: The use of the DT_{50} whole system for PECsed calculations is acceptable. The geometric mean of both DT_{50} values for the whole system would have been applicable. It is not reasonable to assume that biological degradation in soil and in sediment are the same.

$DT_{50\ soil}$: The degradation rate in soil of 7.7 d for the metabolite is not a worst case value (see Table B.8.1-3).

However, the risk assessment for aquatic organisms is still based on $PEC_{initial}$ values from spray drift according to Ganzelmeier which are presented in Table B.8.6-4 whereby 100 % conversion of the parent to the metabolite UR-50604 is assumed (see monograph, volume 3, chapter B.8.6.1). For reasons of completeness beside $PEC_{initial}$ values also PEC_{twa} values over various time-frames between 1 and 42 d after the last application are also presented for beflubutamid (see Table B.8.6-5).

Table B.8.6-4: Initial PEC_{sw} based on spray drift for beflubutamid and its metabolite UR-50604 following a single application on cereals at a rate of 170 g as/ha

Distance [m]	Drift [%]	beflubutamid initial PEC_{sw} [µg/L]	UR-50604* initial PEC_{sw} [µg/L]
0	100	56.667	42.456
1	2.77	1.570	1.176
5	0.57	0.323	0.242
10	0.29	0.164	0.123

* 100 % conversion to metabolite UR-50604

Table B.8.6-5: PEC_{sw} based on spray drift for beflubutamid

PEC_{sw} [µg/L]	beflubutamid cereals 1 x 170 g as/ha (90^{th} percentile)			
	0 m	1 m	5 m	10 m
initial = actual	56.667	1.570	0.323	0.164
twa short term				
24 h	55.696	1.543	0.3175	0.1615
2 d	54.747	1.517	0.312	0.159
4 d	52.914	1.466	0.302	0.155
twa long term				
7d	50.317	1.394	0.287	0.146
14d	44.897	1.244	0.256	0.130
21d	40.256	1.115	0.230	0.117
28d	36.267	1.005	0.207	0.105
42d	29.849	0.827	0.170	0.087

B.8.6.2 Predicted environmental concentrations in sediment (PEC_{sed})

To Evaluation Table 1-1 of 29.09.2004 – data requirement 2.5:
"Applicant is to submit new PECsediment calculations using the revised application rate of 170 g a.s./ha."

Annex Point:	IIIA- 9.1 – 9.2
Author:	Heimann-Detlefsen, D.
Title:	Predicted environmental concentration in soil and water
Date:	12.12.2003
Doc ID:	report No. UBE-2003-01; BOD2004-63 + BOD2005-954
Guidelines:	not relevant
GLP:	not relevant
Validity:	not relevant

The applicant has submitted FOCUS calculation for PEC_{sed} which for reasons of transparency are documented in chapter B.8.6.1.

RMS has recalculated initial maximum PEC_{sed} values for beflubutamid and its metabolite UR-50604 in sediment arising from drift for the revised application rate of 170 g as/ha. 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 Ganzelmeier drift values of 2.77, 0.57 and 0.29 % respectively, selected as a worst-case (90^{th} percentile) for application to field crops
- Sediment depth of 5 cm.
- Sediment bulk density of 1.5 g/cm^3.
- Maximum use rate of 0.170 kg as/ha.
- 100 % conversion of the parent compound to the metabolite
- One application per year.

The maximum accumulation of beflubutamid in sediment at any interval during aerobic aquatic degradation studies with two water/sediment systems and two radiolabelled forms of beflubutamid was 57.5% and 52.2% of applied radioactivity, respectively (see monograph volume 3, chapter B.8.4.3.2). The higher of these values was used to calculate the loading of beflubutamid to the sediment. The results are given in Table B.8.6-6.

Table B.8.6-6: Initial PEC_{sed} for beflubutamid following a single application on cereals at a rate of 170 g as/ha

Distance (m)	Drift (%)	Resulting loading to ditch (mg/m^2)	Resulting loading to sediment (mg/m^2)	Initial PEC_{sed} (mg/kg)
1	2.77	0.47	0.27	0.0036
5	0.57	0.10	0.06	0.0007
10	0.29	0.05	0.03	0.0004

The calculation of the initial PEC_{sed} value of the metabolite UR-50604 as presented in Table B.8.6-7 was based on the 100 % conversion of the parent compound to the metabolite as a worst case assumption. Taking the molecular weights of beflubutamid (355.3 g/mol) and UR-50604 (266.2 g/mol) into account, that results in an initial concentration of 0.127 kg/ha for the metabolite UR-50604. In comparison to the worst case assumption 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 (see monograph volume 3, chapter B.8.4.3.2).

Table B.8.6-7: Initial PEC_{sed} for metabolite UR-50604 following a single application of beflubutamid on cereals at a rate of 170 g as/ha

Distance (m)	Drift (%)	Resulting loading to ditch (mg/m^2)	Resulting loading to sediment (mg/m^2)	Initial PEC_{sed} (mg/kg)
1	2.77	0.35	0.14	0.0019
5	0.57	0.07	0.03	0.0004
10	0.29	0.04	0.01	0.0002

B.8.6.3 Predicted environmental concentrations in groundwater (PEC_{gw})

To Evaluation Table 1-1 of 29.09.2004 – data requirement 2.6, 2.7, 2.1, open point 2.1
"Applicant is to submit new PECgroundwater calculations using the revised application rate of 170 g a.s./ha in FOCUS modelling. RMS is to discuss with the applicant choice of appropriate degradation parameters to be input to the FOCUS model and recalculation of PECgw for parent and UR-50604 using all of the relevant FOCUS scenarios.
RMS is to decide on appropriate sorption parameters, (either average or median of the 3 Koc values), to be input to the FOCUS groundwater model for the new PECgw calculations, in discussion with applicant.
Applicant must demonstrate that the metabolite UR-50604 will not reach groundwater in concentrations exceeding 0.1 µg/l, through FOCUS modelling or further studies e.g. lysimeter or field leaching studies, or must address the relevance of UR-50604."

Annex Point: IIIA- 9.1 – 9.2
Author: Heimann-Detlefsen, D.
Title: Predicted environmental concentration in soil and water
Date: 12.12.2003
Doc ID: report No. UBE-2003-01; BOD2004-63 + BOD2005-954
Guidelines: not relevant
GLP: not relevant
Validity: not relevant

The applicant has submitted new $PEC_{groundwater}$ calculations, some calculations have been performed with FOCUS-PELMO (vers. 3.3.2) using the worst case scenario of Piacenza by varying the DT_{50} (inclusion of worst case soil data of Speyer 2.2 and not normalised values), application amount (127.5 g/ha with and 170 g/ha without interception), and absorption values (median and mean data). In any case, concentrations of beflubutamid and the

metabolite UR-50406 in groundwater remained < 0.1 µg/L. However, the input parameter of the calculations do not completely follow the FOCUS recommendations. Therefore the RMS has performed new FOCUS-PELMO 3.3.2 simulations, which are presented below in detail.

Considering an application rate of 170 g as/ha for beflubutamid, a new FOCUS-PELMO 3.3.2 simulation has been performed by the RMS. Since the Arrow soil has to be included for the normalisation of laboratory values to pF2 conditions, the derivation of the mean DT_{50} value for beflubutamid and its metabolite UR-50604 was recalculated and is given in Table B.8.6-8 (see also Table B.8.1-3). For the normalisation procedure the FOCUS recommendations (Generic Guidance for FOCUS Groundwater Scenarios, version 1.1, April 2002) have been applied.

Table B.8.6-8: Normalisation of Beflubutamid and UR-50604 laboratory DT_{50} values for use in FOCUS-PELMO to 20 °C and pF2 conditions

Soil	Soil type	Beflubutamid		UR-50604	
		DT_{50} (days) 40 % MWHC	**DT_{50} (days) 100 % FC**	**DT_{50} (days) 40 % MWHC**	**DT_{50} (days) 100 % FC**
Arrow	sandy loam	15.8	10.6	18.0	12.1
Wick	sandy loam	5.3	3.6	0.9	0.6
Speyer 2.2 (1^{st} soil)	loamy sand	98.7	75.8	7.7	5.9
Speyer 2.2 (2^{nd} soil)	loamy sand	20.6	15.8	3.6	2.8
Evesham 3	Sandy clay loam*	8.7	5.4	3.1	1.9
Geom. mean			**12.0**		**3.0**

* indicated as “clay loam” in the DAR

For the simulation of groundwater contamination nine scenarios for winter cereals and six for spring cereals are appropriate in order to calculate the concentrations in groundwater both for beflubutamid and UR-50604. Again the “Generic Guidance for FOCUS Groundwater Scenarios” has been used to determine the respective input parameters which are presented in Table B.8.6-9. For the sorption parameter of the metabolite UR-50604 the arithmetic mean K_{OC} value of 12.3 based on three K_{OC} values as well as 1/n of 0.87 were retained. The following degradation scheme has been used:

Beflubutamid → UR-50604→ CO_2/bound residues

The results of the FOCUS-PELMO simulation are given in Table B.8.6-10.

Table B.8.6-9: Input data for beflubutamid and UR-50604 to FOCUS-PELMO simulation

Crop	Crop specific values (emergence etc.)	Winter and spring cereals default
Application	Rate Time Interception	0.170 kg as /ha 7 days after emergence, spring: BBCH : 13-29 autumn: BBCH: 11-29 25 %
Active substance	**Beflubutamid**	
	Molecular mass	355.3 g/mol
Volatilization		Not considered
	vapour pressure	1.1 x 10^{-5} Pa
	water solubility	3.290 mg/L
	plant uptake factor	0.5 (default)
Sorption parameter	average K_{oc}	1260
	Freundlich exponent 1/n	0.92
Transformation to UR-50604	normalised DT_{50} (20 °C, pF2)	12.0 days (geometric mean, n=5)
	Temp. correction factor (Q10)	2.2
	Walker exponent for moisture correction	0.7
Metabolite	**UR-50604**	
		100 % conversion of parent
	Molecular mass	266.2
	plant uptake factor	0.5 (systemic herbicide)
Sorption parameter	K_{oc} (arithm. mean, n = 3)	12.3
	Freundlich exponent 1/n	0.87
Transformation to CO_2	normalized DT_{50} (20 °C, pF2)	3.0 days (geometric mean, n=5)
	Temp. corr. factor (Q10)	2.2
	Walker exponent for moisture correction	0.7

Table B.8.6-10: Results of FOCUS-PELMO 3.3.2 simulation for beflubutamid and UR-50604

Crop	**Winter cereal**		**Spring cereal**	
Substance	**Beflubutamid**	**UR-50604**	**Beflubutamid**	**UR-50604**
Weather/soil scenario:	Concentration in groundwater (µg/L) (80^{th} percentile value in the percolate at 1 m soil depth)			
Chateaudun	< 0.001	< 0.001	< 0.001	< 0.001
Hamburg	< 0.001	**0.005**	< 0.001	< 0.001
Jokioinen	< 0.001	< 0.001	< 0.001	< 0.001
Kremsmunster	< 0.001	< 0.001	< 0.001	< 0.001
Okehampton	< 0.001	**0.002**	< 0.001	< 0.001
Piacenza	< 0.001	**0.017**	---	---
Porto	< 0.001	< 0.001	< 0.001	< 0.001
Sevilla	< 0.001	< 0.001	---	---
Thiva	< 0.001	< 0.001	---	---

Conclusion
The calculation shows that the use of beflubutamid in spring and winter cereals results in concentrations in groundwater below 0.1 µg/L for the parent compound and the metabolite UR-50604.

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** **BVL registration number**	**Data protection claimed** **Y/N**	**Owner**
AIIA-7.1.1.1.1; AIIA-7.1.1.1.2; AIIA-7.1.1.2.1	Funaki, E.	2003	Beflubutamid (UR-50601), Environmental fate issues associated with the isomers of parent UR-50601 and metabolite UR-50604, UBE Industries, 28.11.2003 not GLP, unpublished BOD2004-62	Y	TSU
AIIA-7.1.1.2.1; AIIA-7.1.2; AIIIA-9.1.1.1; AIIIA-9.1.2.1; AIIIA-9.1.3	Heimann-Detlefsen, D.	2003	Predicted environmental concentration in soil and water UBE-2003-01, 12.12.2003 not GLP, unpublished BOD2004-63	Y	TSU
AIIIA-9.1.3	Heimann-Detlefsen, D.	2005	Predicted environmental concentration in soil and water - Amendment 1. UBE-2003-01, Amendment 1, 11.07.2005 not GLP, unpublished BOD2005-954	Y	TSU

Codes of company

TSU: Task force Stähler International GmbH & Co. KG / UBE Industries

B.9 Ecotoxicology

B.9.1 Effects on birds (Annex IIA 8.1; Annex IIIA 10.1)

B.9.1.5 Risk assessment for birds

To Evaluation Table 1-1 of 29.09.2004 – open point 3.3:
"To refine risk assessment for new GAP"

The risk assessment was updated for the revised application rate of 170 g as/ha.

Toxicity:
Details of avian toxicity studies with beflubutamid are provided in the monograph, volume 3, chapter B.9.1. These data are summarised in Table B.9.1-1.

Table B.9.1-1: Summary of avian toxicity data (see monograph, volume 3, chapter B.9.1)

Test material	Species	Test	Study endpoint
Beflubutamid	Bobwhite quail	Acute	LC_{50} > 2000 mg/kg bw
Beflubutamid	Bobwhite quail	5-day-dietary	LC_{50} > 5200 mg/kg diet = > 970 mg/kg bw/d
Beflubutamid	Bobwhite quail	Reproduction	NOEL 1000 mg/kg diet = 88 mg/kg bw/d

Exposure:
The herbicide Herbaflex (ASU 95 510 H) is a suspension concentrate containing 85 g/L beflubutamid and 500 g/L isoproturon. Herbaflex is intended for single application in autuum or spring by foliar spray at a maximum rate of 170 g as/ha for the control of annual weed species after germination of the weeds (up to BBCH growth stage 11-29) occurring in winter cereals (up to BBCH growth stage 11-29).
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 Estimated Theoretical Exposure (ETE) values to beflubutamid for appropriate scenarios were estimated according to the EU Guidance Document on Risk Assessment for Birds and Mammals (SANCO/4145/2000), based on the maximum use rate of 170 g as/ha. As beflubutamid is predominantly sprayed on weeds early after emergence of winter cereal in autumn or in spring, ETE values were calculated for the following scenarios: cereals, early (grasses, cereal shoots) and large herbivorous bird and insectivorous bird.
Maximum ETE values were estimated for use in acute and short-term risk assessments while time-weighted average ETE values were calculated for use in assessing long-term risks. ETE values were calculated using the following equation:

$$\text{ETE (mg as/kg bw/day)} = \frac{\text{FIR}}{\text{bw}} \times \text{RUD} \times \text{Application rate} \times f_{TWA} \text{ x PT x PD x AV}$$

where:
- FIR Food Intake Rate (g fresh weight per day)
- bw Body weight (g)
- RUD Residue per unit dose (mg/kg fresh weight)
- f_{TWA} Time-weighted average factor (only used for calculating long-term ETE)
- PT Proportion of diet obtained in treated area
- PD Proportion of food-type in diet
- AV Avoidance factor (no avoidance =1)

As recommended by the EU Expert Group on Higher Tier Risk Assessment for Birds and Mammals, the 90th percentile residues on food items were used for the acute risk assessment, and the 50th percentiles for the short and long-term risk assessments. The f_{TWA} was calculated from the following equation:

$$f_{TWA} = (1-e^{-kt})/kt$$

where: $k = \ln 2/DT_{50}$
t = averaging time

Initial ETE values were estimated assuming that PT, PD and AV were equivalent to 1. The resulting values are shown in Table B.9.1-2, Table B.9.1-3 and Table B.9.1-4.

Table B.9.1-2: Estimates of acute exposure to beflubutamid

Avian guild	Species	Food type	FIR/bw	RUD 90th percentile	Application rate (kg/ha)	Acute ETE (mg/kg bw/day)
Large herbivore	Goose (3000 g)	grasses, cereal shoots	0.44	142	0.170	10.62
Insectivore	Wren (10 g)	Small insects	1.04	52	0.170	9.19

Table B.9.1-3: Estimates of short-term exposure to beflubutamid

Avian guild	Species	Food type	FIR/bw	RUD mean	Application rate (kg/ha)	Short-term ETE (mg/kg bw/day)
Large herbivore	Goose (3000 g)	grasses, cereal shoots	0.44	76	0.170	5.69
Insectivore	Wren (10 g)	Small insects	1.04	29	0.170	5.13

Table B.9.1-4: Estimates of long-term exposure to beflubutamid

Avian guild	Species	Food type	FIR/bw	RUD mean	Ftwa	Application rate (kg/ha)	Long-term ETE (mg/kg bw/day)
Large herbivore	Goose (3000 g)	grasses, cereal shoots	0.44	76	0.53	0.170	3.01
Insectivore	Wren (10 g)	Small insects	1.04	29	n.a.	0.170	5.13

n.a. = not applicable

Toxicity-exposure ratios (TERs):

The acute, short-term and long-term risk of beflubutamid to birds was assessed by calculation of toxicity exposure ratios (TER) according to the following equation:

$$TER = \frac{LD_{50}\ (mg/kg\ bw)\ or\ NOEL\ (mg/kg\ bw/\ d)}{ETE\ (mg/kg/d)}$$

The TER values were calculated using the toxicity data given in Table B.9.1-1. The resulting TER values are shown in in Table B.9.1-5, Table B.9.1-6 and Table B.9.1-7.

Table B.9.1-5: Acute risk to birds from exposure to beflubutamid

Avian guild	Species	Food type	Toxicity LD_{50} (mg as/kg bw	Acute ETE (mg/kg bw/day)	TER
Large herbivore	Goose (3000 g)	grasses, cereal shoots	> 2000	10.62	> 188
Insectivore	Wren (10 g)	Small insects	> 2000	9.19	> 218

Table B.9.1-6: Short-term risk to birds from exposure to beflubutamid

Avian guild	Species	Food type	Toxicity LD_{50} (mg as/kg bw/d)	Acute ETE (mg/kg bw/day)	TER
Large herbivore	Goose (3000 g)	grasses, cereal shoots	> 970	5.69	> 170
Insectivore	Wren (10 g)	Small insects	> 970	5.13	> 189

Table B.9.1-7: Long-term risk to birds from exposure to beflubutamid

Avian guild	Species	Food type	Toxicity NOEL (mg as/kg bw/d)	Acute ETE (mg/kg bw/day)	TER
Large herbivore	Goose (3000 g)	grasses, cereal shoots	88	3.01	29
Insectivore	Wren (10 g)	Small insects	88	5.13	17

Conclusion:
The acute, short-term and long-term risk assessment for all scenarios produces TERs that exceed the Annex VI trigger of 10 and 5, respectively, indicating an acceptable risk to herbivorous and insectivorous birds feeding in cereals after application of beflubutamid.

B.9.1.6 Bioaccumulation and food chain behaviour

To Evaluation Table 1-1 of 29.09.2004 – open point 3.2:
"RMS to address risk posed to fish and worm eating birds"

The log P_{OW} of the active substance beflubutamid was determined to be 4.28, hence above 3.0, which triggers an assessment of the potential risk of secondary poisoning.

Details of avian toxicity studies with beflubutamid are provided in volume 3, chapter B.9.1 of the monograph. Regarding the long-term risk the assessment will be based on the NOEL for reproductive effects in bobwhite quail (*Colinus virginianus)* of 1000 ppm (approx. 88 mg/kg bw/d).

The risk assessment for earthworm-eating birds (Table B.9.1-8) and fish-eating birds (Table B.9.1-9) is depicted below in short tabular form.

Table B.9.1-8 Risk to earthworm-eating birds

Parameter	Beflubutamid	Comment
PEC_{soil} (twa, 7 days) [mg/kg soil]	0.166	see [Table B.8.1-3]
K_{OW}	19055	-/-
K_{oc}	699	10th percentile due to variation between 496 and 1793 (n = 4)
f_{oc}	0.02	default
BCF_{worm}	13.7	$BCF_{worm} = (PEC_{worm} / PEC_{soil}) = (0.84 + 0.01 \times K_{OW}) / f_{oc} \times K_{oc}$
PEC_{worm}	2.27	$PEC_{worm} = PEC_{soil} \times BCF$
Daily dose [mg/kg bw]	2.500	$ETE = PEC_{worm} \times 1.1$
NOEDD [mg/kg bw]	88	1000 ppm (= 88 mg/kg bw/d) see monograph Vol 3 chapter B.9.1.3
TER_{lt}	35.2	> 5

Table B.9.1-9 Risk to fish-eating birds

Parameter	Beflubutamid	Comment
PEC_{sw} [mg/L]	0.0016	see [Table B.8.6-4] $PEC_{initial}$ for 1 m distance as worst case
BCF_{fish}	230	see monograph Vol 3 chapter B.9.2.1.9
PEC_{fish}	0.368	$PEC_{fish} = PEC_{water} \times BCF_{fish}$
Daily dose [mg/kg bw]	0.077	$ETE = PEC_{fish} \times 0.21$
NOEDD [mg/kg bw]	88	1000 ppm (= 88 mg/kg bw/d) see monograph Vol 3 chapter B.9.1.3
TER_{lt}	129	> 5

Conclusion:

The risk to birds resulting from secondary poisoning through accumulation of beflubutamid in possible prey items can be considered acceptable.

B.9.3 Effects on other terrestrial vertebrates (Annex IIIA 10.3)

B.9.3.2 Risk assessment for terrestrial vertebrates

To Evaluation Table 1-1 of 29.09.2004 – open point 3.1 and 3.3:
"RMS to carry out long-term risk assessment for mammals using new guidance. This will cover dry weight to wet weight issues as well as daily doses. To refine risk assessment for new GAP."

The risk assessment was updated for the revised application rate of 170 g as/ha.

Toxicity:
Details of mammalian toxicity studies with beflubutamid are provided in volume 3, chapter B.6 of the monograph. 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 the NOAEL for reproductive effects in a multi-generation study with rats of 200 ppm (approx. 17 mg/kg bw/ day).

Exposure:
The herbicide Herbaflex (ASU 95 510 H) is a suspension concentrate containing 85 g/L beflubutamid and 500 g/L isoproturon. Herbaflex is intended for single application in autuum or spring by foliar spray at a maximum rate of 170 g as/ha for control of annual weed species after germination of the weeds (up to BBCH growth stage 11-29) occurring in winter cereals (up to BBCH growth stage 11-29).
Regarding winter cerals, most of beflubutamid is taken up mainly by the seedlings and to a lesser extent by roots and leaves.
The Estimated Theoretical Exposure (ETE) values to beflubutamid for appropriate scenarios were estimated according to EU Guidance Document on Risk Assessment for Birds and Mammals (SANCO/4145/2000), based on the maximum use rate of 170 g as/ha. As beflubutamid is predominantly sprayed on weeds early after emergence of winter cereal in autuum or in spring, ETE values were calculated for the following scenarios: cereals, early (grasses, cereal shoots) and small herbivorous mammal.
Maximum ETE values were estimated for use in acute risk assessments while time-weighted average ETE values were calculated for use in assessing long-term risks. ETE values were calculated using the following equation:

$$\text{ETE (mg as/kg bw/day)} = \frac{\text{FIR}}{\text{bw}} \times \text{RUD} \times \text{Application rate} \times f_{TWA} \text{ x PT x PD x AV}$$

where:

	FIR	Food Intake Rate (g fresh weight per day)
	bw	Body weight (g)
	RUD	Residue per unit dose (mg/kg fresh weight)
	f_{TWA}	Time-weighted average factor (only used for calculating long-term ETE)
	PT	Proportion of diet obtained in treated area
	PD	Proportion of food-type in diet
	AV	Avoidance factor (no avoidance =1)

As recommended by the EU Expert Group on Higher Tier Risk Assessment for Birds and Mammals, the 90th percentile residues on food items were used for the acute risk assessment, and the 50th percentiles for the long-term risk assessments. The f_{TWA} was calculated from the following equation:

$$f_{twa} = (1-e^{-kt})/kt$$

where: $k = \ln 2/DT_{50}$
t = averaging time

Initial ETE values were estimated assuming that PT, PD and AV were equivalent to 1. The resulting values are shown in Table B.9.3-1 and Table B.9.3-2.

Table B.9.3-1: Estimates of acute exposure to beflubutamid

Mammal group	Species	Food type	FIR/bw	RUD 90th percentile	Application rate (kg/ha)	Acute ETE (mg/kg bw/day)
small herbivore	vole (25 g)	Grasses, cereal shoots	1.39	142	0.170	33.56

Table B.9.3-2: Estimates of long-term exposure to beflubutamid

Mammal group	Species	Food type	FIR/bw	RUD mean	f_{TWA}	Application rate (kg/ha)	Long-term ETE (mg /kg bw/day)
small herbivore	vole (25 g)	Grasses, cereal shoots	1.39	76	0.53	0.170	9.52

Toxicity-exposure ratios (TERs)

The acute and long-term risk of beflubutamid to wild mammals was assessed by calculation of toxicity exposure ratios (TER) according to the following equation:

$$\text{TER} = \frac{LD_{50}\ (\text{mg/kg bw}) \text{ or } \text{NOAEL}\ (\text{mg/kg bw/ d})}{\text{ETE}\ (\text{mg/kg/d})}$$

The TER values were calculated using a LD_{50} value of >5000 mg/kg bw and the NOAEL value of 17 mg/kg bw. The resulting TER values are shown in Table B.9.3-3 and Table B.9.3-4.

Table B.9.3-3: Acute risk to mammals from exposure to beflubutamid

Mammal group	Toxicity NOEDD (mg as/kg bw/d)	Species	Food type	ETE (mg/kg/day)	TER
small herbivore	> 5000	vole (25 g)	grasses, cereal shoots	33.56	> 149

Table B.9.3-4: Long-term risk to mammals from exposure to beflubutamid

Mammal group	Toxicity NOEDD (mg as/kg bw/d)	Species	Food type	ETE (mg/kg/day)	TER
small herbivore	17	vole (25 g)	grasses, cereal shoots	9.52	1.8

Conclusion:
The acute risk assessment produces TER values that exceed the Annex VI trigger of 10 indicating an acceptable acute risk to wild mammals following application according to the label recommendation for winter cereals. The resulting TER of the long-term risk assessment is below the Annex VI trigger of 5 indicating that beflubutamid poses a long-term risk to wild mammals. For long-term exposure to beflubutamid, a refinement of the Tier 1 risk assessment is required to reduce further uncertainty which may arise from the TER value found to be < 5 for herbivorous mammals.

B.9.3.3 Risk assessment for metabolites

The only major metabolite of beflubutamid found in soil and groundwater is UR-50604. It was found in the rat metabolism study (see monograph chapter 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. The risk assessment of the parent compound covers the risk assessement for the metabolite.

B.9.3.4 Refined risk assessment

Relevant species

Hare (*Lepus europaeus*)
In the Tier 1 risk assessment the vole is considered as indicator species for cereals fields at early growth stage feeding cereal shoots. However, voles predominately prefer mainly rough, ungrazed grassland including young forestry plantations with thick grass cover as feeding habitat (Gurney et al., 1998 AVS2004-28). In comparison the hare prefers open fields and pastures bordered by hedgerows and woodlots, often around agriculture fields and crops. They live in shallow forms; clumps of grass, weeds, or bush. The hare represents a typical inhabitant of open areas, and thus may be found in cereal fields in the early developmental stages when the crop provides no shelter for small mammals. This might coincide with the application of Herbaflex on weed of winter cereals at early development stages in spring or autumn. The breeding season for *L. europaeus* is between midwinter (January/February) and midsummer. Application time for Herbflex is outside the mating period of the hares.
In the Tier 2 risk assessment a worse case scenario is laid down in assuming a diet of 100 % plant material and it is assumed that 100 % of the the diet consists of grasses and cereal shoots, e.g. preliminary cereals.
The FIR/bw values for cereal shoots or grasses eating hare were calculated according to Crocker et al. (2002,AVS2006-29) based on the standard hare weight of 3000 g.

Table B.9.3-5: Refined long-term risk to mammals from exposure to beflubutamid

Species	Toxicity NOEDD (mg as/kg bw)	Food type	FIR/ bw	RUD mean	Application rate (kg/ha)	f_{TWA}	Long-term ETE (mg/kg bw/day)	TER
Hare (3000 g)	17	Grasses, cereal shoots	0.21	76	0.170	0.53	1.44	11.8

Conclusion:
The refined long-term risk assessment for herbivorous mammals feeding on short grass and cereals shoots produce TERs that exceed the Annex VI trigger of 5, indicating that beflubutamid poses a low long-term risk to these mammals.

B.9.3.5 Bioaccumulation and food chain behaviour

The log P_{OW} of the active substance beflubutamid was determined to be 4.28, hence above 3.0, which triggers an assessment to the potential risk of secondary poisoning.

The risk assessment for earthworm-eating mammals (Table B.9.3-6) and fish-eating mammals (Table B.9.3-7) is depicted below in short tabular form.

Table B.9.3-6: Risk to earthworm-eating mammals

Parameter	Beflubutamid	Comment
PEC_{soil} (twa, 7 days) [mg/kg soil]	0.166	see [Table B.8.-1.3]
K_{OW}	19055	-/-
K_{oc}	699	10th percentile due to variation between 496 and 1793 (n = 4)
f_{oc}	0.02	default
BCF_{worm}	13.7	$BCF_{worm} = (PEC_{worm} / PEC_{soil}) = (0.84 + 0.01 \times K_{OW}) / f_{oc} \times K_{oc}$
PEC_{worm}	2.27	$PEC_{worm} = PEC_{soil} \times BCF$
Daily dose [mg/kg bw]	3.18	$ETE = PEC_{worm} \times 1.4$
NOEDD [mg/kg bw]	17	see monograph Vol 3 chapter B.9.1.3
TER_{lt}	5.3	> 5

Table B.9.3-7: Risk to fish-eating mammals

Parameter	Beflubutamid	Comment
PEC_{sw} (twa, 21 days) [mg/L]	0.0016	see [Table B.8.6-4] $PEC_{initial}$ for 1 m distance as worst case
BCF_{fish}	230	see monograph Vol 3 chapter B.9.2.1.9
PEC_{fish}	0.368	$PEC_{fish} = PEC_{water} \times BCF_{fish}$
Daily dose [mg/kg bw]	0.048	$ETE = PEC_{fish} \times 0.13$
NOEDD [mg/kg bw]	17	see monograph Vol 3 chapter B.9.1.3
TER_{lt}	105	> 5

Conclusion:

The risk to mammals resulting from secondary poisoning through accumulation of beflubutamid in possible prey items can be considered acceptable.

B.9.6 Effects on earthworms (Annex IIA 8.4; Annex IIIA 10.6.1)

B.9.6.2 Sublethal effects

METABOLITES

To Evaluation Table 1-1 of 29.09.2004 – data requirement 3.1:
"The applicant to address the long-term risk to earthworms from the a.s. and the risk for metabolites."

Annex Point:	IIA-8.4.2
Author:	Müther-Paul, J.
Title:	Sublethal toxicity of UR-50604 on earthworms, *Eisenia fetida* using an artificial soil test
Date:	05.08.2005
Doc ID:	report-No. 20041457/01-Nref; ARW2005-258
Guidelines:	ISO 11268-2 (1998), OECD 222 (2004)
GLP:	yes
Validity:	yes

Materials and methods
Test substance: UR-50604, batch no. 040407, purity (analysed) 99.9 wt%.
Adult earthworms (*Eisenia fetida)* were exposed for 56 days to UR-50604 at concentrations of 0 (control), 0.038, 0.19, 0.38, 3.80, 38.0 mg as/kg soil (dry weight), in artificial soil.
Each batch of moistured artificial soil (724 g) was mixed with the corresponding amount of the test item solution (50 g). Earthworms were then placed on the soil surface of the test vessels. The test incorporated four replicate vessels of 10 worms for each exposure concentration and for the untreated control. Assessments of mortality and the body weight change were made after 28 days, assessment of reproduction after 56 days.

Findings
Temperature was maintained at 17 – 22.5 °C. The study was conducted twice. The first performance was not valid because of the control replicates received 20 adult earthworms instead of 10 at test start. Effects of UR-50604 on mortality and body weight change and reproduction data in the second test performance are presented in Table B.9.6-1.

Table B.9.6-1: Effect of UR-50604 on Eisenia fetida mortality, bodyweight change and reproduction (2. performance of study)

	Treatment rate [mg/kg soil dry weight]					
	control	0.038	0.19	0.38	3.80	38.0
corrected mortality [%]	2.5	-2.6	-2.6	-2.6	-2.6	-2.6
mean weight change [%]	16.2	23.7	22.2	19.9	26.9	38.2*
mean number of juveniles per replicate	227.3	193.5	192.8	203.5	197.5	169.0
deviation from control for reproduction [%]	--	-14.9	-15.9	-10.5	-13.1	-25.6

* = statistically significantly different compared to the control ($P \leq 0.05$)

Conclusion:
Mortality in the control group was 2.5 % in the second performance. No mortality was observed in the test item treatment groups. The NOEC was determined to be 3.8 mg/kg dry weight due to the increase of weight of adult earthworms.

B.9.6.3 Field study

To Evaluation Table 1-1 of 29.09.2004 – data requirement 3.1:
"The applicant to address the long-term risk to earthworms from the a.s. and the risk for metabolites."

Annex Point:	IIIA-10.6.1.3.
Author:	Strömel, C.; Teresiak, H.
Title:	Field study to evaluate the effects of Herbaflex on earthworms
Date:	05.10.2005
Doc ID:	report-No. AC/STA/04/01; ARW2005-260
Guidelines:	ISO 11268-3 (1999)
GLP:	yes
Validity:	yes

Materials and methods
Test item: Herbaflex (code ASU 95510 H), batch no. 9218, containing as isoproturon: 509 g/L (nominal: 500 g/L) and beflubutamid: 87.5 g/L (nominal: 85 g/L)
The trial was conducted as a field study on a permanent meadow already existing for about 10 years in the north of Germany and used as extensive grassland. The area selected did not receive an application of any pesticde for the least ten years. The study site was not tilled and received no plant protection products or fertiliser beside 428 kg/ha lime to improve the pH of the test site. Groundcover at application was between 85 % and 95 % with a crop height of approximately 3 to 7 cm. With in the duration of the study the meadow was irrigated 5 times with well water. The soil of the site was silty sand (pH 4.9, TOC: 1.20 %, max. WHC: 39.5 %; microbial biomass: 19 mg C/100 g dry weight). The trial consisted of three variants with four replicates each: untreated control, Herbaflex (1 x 3 L/ha) and as toxic standard DuPontBenomyl as (1 x 15 L/ha). Herbaflex and DuPontBenomyl were applied in late April, after application water was applied to wash the test item and the reference substance into the soil.
Within the course of the study four samplings were carried out: two days prior treatment, 1, 6 and 12 months after application. The earthworm sampling was performed by using hand sorting in combination with formalin extraction.
In addition samples of vegetation and soil were taken in the course of the study to determine the starting exposure of the earthworm population as well as to show the dissipation of the active substance and its metabolite UR-50604 at the application rate of 3 L Herbaflex/ha (255 g beflubutamid/ha). The concentrations of beflubutamid and UR-50604 were analysed in the 0 – 5 cm and the 0 – 30 cm soil layer in regular intervals (0, 2, 7, 14, 28 … 383 days) as required also for field degradation studies.

Findings
The maximum occurrence of beflubutamid was reached at DAT (day after treatment) 2 (126.9 µg/kg dry matter, mean of two data points) and for UR-50604 at DAT 7 (18.30 µg/kg dry matter, single data point) (Tab. 3). These data correspond to data of beflubutamid achieved in field degradation studies after application of 255 g as/ha before. The maximum of

beflubutamid was 140 µg/kg and the maximum of UR-50604 was 16 µg/kg, both data derived from field study in Spain (spring application) (see monograph, volume 3 chapter B.8.1.2.2).
The maximum occurrence of the metabolite as percentage of the active substance ranged between 0 and 38.7 % at DAT 28. Average occurrence of the metabolite as percentage of the active substance between DAT 14 and 116 was 28.8 % (mean) or 26.7 % (median) which is in the magnitude as achieved in field studies in Spain before (26.1 %).
Earthworm population of the test site were represented by endogeic species *Aporrectodea caliginosa*, *Aporrectodea rosea* an anecic species *Lumbricus terrestris*. Efficiency rates of earthworm extraction, using the combined hand sorting/Formalin method, were between averaged 88 and 100 %. Earthworm population at the beginning of the study (13th April 2004) was around 380 individuals per m² and thus above the required level which is determined in the ISO 11268-3 with a minimum of 100 individuals per m² in grassland and at least two species (*Aporrectodea caliginosa, Lurnbricus terrestris*). Statistical analysis of data showed an even allocation within the whole trial area.
It turned out that treatment of Herbaflex at 3.0 L/ha does not affect the total earthworm population during the year after application. Compared to the control the population of Herbaflex plots ranged between + 8 % and -3 %. The population treated with the toxic standard DuPont Benomyl was reduced by 88 % directly after treatment and still showed a 77 % reduction one year after the treatment.
A. caliginosa was the eudominant species on the trial site and population density varied between 184 and 265 individuals/m² in the untreated control. No negative impact could be found for this species following the application of 3 L Herbaflex/ha whereas DuPont Benomyl caused a significant reduction of the population lasting one year at least.
A. rosea could not be statistically evaluated on species level because mainly found in one replicate. According to the testing unit the insular occurrence of this species is not unusual for the test site area.
L. terrestris was the second dominant species with a population size ranging from 7.3 to 19.1 ind./m² in untreated control. The earthworm field study showed some slight significant effects on juvenile population of *Lumbricus terrestris* one month after the treatment of 3 L Herbaflex/ha. Since one year after the treatment a high population density was observed among the juveniles, it is concluded that any effect of beflubutamid/Herbaflex is not long lasting.

Conclusions
Although the earthworm population was dominated by *Aporrectodea caliginosa* the study is acceptable. The finding of the relatively low population density of *Lumbricus terrestris* can be traced back to the fact that only the soil up to 50 cm depth was sampled. However *Lumbricus terrestris* as an anecic earthworm constructs burrows up to 2.5 m deep and could therefore retrive into deeper soil layers.
The results of soil residues showed that both beflubutamid and its metabolite UR-50604 occurred in the soil after treatment with Herbaflex, so that the study reflects the effects of beflubutamid as well as of its metabolite UR-50604 on earthworms.
From the results of the study it can be concluded that no statistically significant effects on the development of earthworm populations will arise from a single application of Herbaflex at the use rate of 3.0 L/ha compared to the untreated control area.

B.9.6.4 Summary of toxicity data on earthworms

Beflubutamid and its metabolite UR-50604 were tested for acute effects on earthworms. Detailed descriptions of these studies are provided in the monograph volume 3 chapter B.9.6.1. The long term toxicity data for beflubutamid are also described in the monograph volume 3 chapter B.9.6.2
The long term toxicity data the metabolite UR-50604 and the formulation Herbaflex are summarised in table Table B.9.6-2.

Table B.9.6-2: Summary of the long term earthworm toxicity data

Test substance	Test	Endpoint	Value	Reference
Metabolite UR-50604	reproduction	NOEC	3.8 mg/kg	Müther-Paul, 2005 (20041457/01-NRef) IIA-8.4.2, ARW2005-258
Herbaflex (ASU 95510 H: beflubutamid 85 g/L, isoproturon 500 g/L)	field study	NOEC	3.0 L/ha	Strömel et.al, 2005 (AC/STA/04/01) IIIA-10.6.1.3, ARW2005-260

B.9.6.5 Risk assessment

METABOLITE

The long-term TER value for the metabolite UR-50604 was calculated using the NOEC of 3.8 mg/kg and the maximum initial PEC_{soil} of 0.038 mg/kg (see chapter B.8.3). The resulting value exceeds the relevant Annex VI trigger of 5, indicating that the metabolite UR-50604 poses a low long-term risk to earthworms.

$$TER_{lt} = \frac{NOEC\,(mg/kg)}{PEC_{soil}\,(mg/kg)} = \frac{3.8}{0.038} = 100$$

ACTIVE SUBSTANCE and FORMULATION

The risk assessment regarding the long term effects of beflubutamid on earthworms resulted in a long-term TER far below the trigger of 5 (see Monograph Volume 3 chapter B.9.6.3).
However, in the earthworm field study with 3 L Herbaflex/ha no effects were observed on total earthworm population and on the species *Aporrectodea caliginosa* and *A. rosea*. There were some slight significant effects on the juvenile population of *Lumbricus terrestris* one month after treatment with 3 L/ha. Since one year after treatment a high population density was observed among the juveniles, it is concluded that any effect of beflubutamid/Herbaflex is not long lasting and recovery is obtained within the vegetation period after spring treatment.
The results of soil residues showed that both beflubutamid and its metabolite UR-50604 occurred in the soil after tretament with Herbaflex, so that the study reflects the effects of beflubutamid as well as of its metabolite UR-50604 on earthworms.

The recommended dose rate for Herbaflex is 2 L/ha. Therefore Herbaflex poses no long-term risk to earthworm populations following applications accordance to recommended use.

B.9.7 Effects on other soil non-target macro-organisms (Annex IIIA 10.6.2)

B.9.7.1 Laboratory testing

To Evaluation Table 1-1 of 29.09.2004 – data requirement 3.2:
"Data are required to address the risk to soil macro-organisms (e.g. study on collembola)"

Annex Point: IIIA-10.6.2
Author: Bruhnke, C.
Title: Inhibition of Reproduction of Collembola (*Folsomia candida*)
Date: 28.11.2003
Doc ID: report-No. ICR92952; ARW2004-20
Guidelines: ISO 11267 (1999)
GLP: yes
Validity: yes

Materials and methods
The effects of Herbaflex (Batch: 8325) on the reproduction of *Folsomia candida* in artificial soil by dermal and alimentary uptake were examined in a laboratory study. The test item Herbaflex was incorporated once into artificial soll with the test item concentration levels of 10, 32, 100, 320 and 1000 mg/kg dry weight. Control was artificial soil with demineralised water without test or reference item.
Test organism was *Folsomia candida* WILLEM. At the beginning of the test the collembola were juvenile springtails (11-12 days old). *Folsomia candida* (80 springtails per control and 50 per each test and reference item concentration) were exposed in glass beakers with a volume of 100 mL (inner diameter 4.3 cm) filled with artificial soil. E605 FORTE was tested as toxic reference treatment from February 03 to March 03, 2003 (LC_{50} 0.14 mg/kg for corrected adult mortality and EC_{50} 0.11 mg/kg for reproduction). During exposure springtails were fed with granulated dry yeast. Mortality was determined after 28 days. For reproduction the number of juveniles was determined after 30 days.

Findings
Mortality and reproduction data are presented in Table B.9.7-1.

Table B.9.7-1: Effects of Herbaflex on collembola (*Folsomia candida*)

	Test item concentration [mg/kg soil dry weight]					
	control	10	32	100	320	1000
corrected mortality [%]	-	0	0	0	0	33.7*
mean number of juveniles per surviving females	71,5	81,0	79,1	74,4	63,0	40,6*
deviation from control for reproduction** [%]	-	13	11	4	-12	-43

* statistically significantly different compared to the control ($P \leq 0.05$)
** negative values = reduction of reproduction

Conclusion:
Herbaflex caused no dose related effect on the survival of *Folsomia candida* up to and including the test item concentration of 320 mg/kg artificial soil. Therefore, the NOEC for mortality was determined at 320 mg/kg artificial soil.
The NOEC value for the reproduction was determined at 320 mg/kg artificial soil.

B.9.7.2 Risk assessment

The recommended dose rate for Herbaflex is 2 L/ha which results in a PECsoil of 2.933 mg Herbaflex /kg soil based on a soil depth of 5 cm and a soil density of 1.5 g/cm³. Compared with the NOEC value of 320 mg/kg for mortality and for reproduction Herbaflex poses no risk to collembola following applications accordance to recommendad use.

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 Toxicity to plants

To Evaluation Table 3.3 of 29.09.2004 – data requirement 3.2:
"Applicant to submit study on non-target fauna and flora."

Annex Point:	IIIA-10.8
Author:	Fiebig, S.
Title:	Terrestrial Plants Toxicity, Seedling Emergence, Tier II. Stähler Agrochemie GmbH & Co. KG Project No. 010130SS, Study No. TNK77872
Date:	28.09.2001
Doc ID:	PFL2001-122
Guidelines:	OECD 208 Draft (July 2000)
GLP:	Yes
Validity:	Yes

Materials and Methods
The phytotoxicity of the test item Herbaflex (batch number 0029) with 490 g/L isoproturon and 81 g/L beflubutamid to six terrestrial plant species was determined over a period of 21 days (2001-05-29 to 2001-06-19 and 2001-07-12 to 2001-08-02, respectively.
The test was conducted with the nominal concentrations 3.0 - 1.5 - 0.75 - 0.375 - 0.188 L/ha (factor 2.0) (oats, onion, carrot) and 3.0 - 0.75 - 0.188 - 0.047 - 0.012 L/ha (factor 4) (sugar beet, rape, soybean) selected on the basis of a preliminary phytotoxicity test.
Test plants were two monocotyledons (oat, *Avena sativa*; onion, *Allium cepa*) and four dicotyledons (sugar beet, *Beta vulgaris*; rape, *Brassica napus*; carrot, *Daucus carota*; soybean, *Glycine max*.). The test item was applied on the soil surface after the seeds were sown. The test containers were bottom watered with nutrient solution as needed.
The toxic effects of the test item were determined on day 7, 14, and 21 by visual observations (number of emerged seedlings, number of dead plants and phytotoxicity rates) and on day 21 by shoot height and fresh weight determination. Shoot height, fresh weight and number of dead plants were checked for significant differences.

Findings

The NOEC, the EC_{25}- and EC_{50}-values with the confidence ranges calculated from percentage inhibition of the plant growth are summarized in the following tables.

Table B.9.9-1 Shoot height: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	3.0	> 3.0	-	> 3.0	-
onion	0.188	0.32	0.25 - 0.41	0.64	0.49 - 0.83
sugar beet	0.750	1.06	0.76 - 1.47	2.17	1.56 - > 3.0
rape	0.188	0.29	0.22 - 0.40	0.57	0.42 – 0.77
carrot	0.188	0.31	0.26 - 0.36	> 3.0	-
soybean	3.0	> 3.0	-	> 3.0	-

- not determinable

Table B.9.9-2: Fresh weight: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	3.0	> 3.0	-	> 3.0	-
onion	0.188	< 0.188	-	0.64	0.23 - 0.33
sugar beet	0.750	0.41	0.32 - 0.51	2.17	0.60 - 0.95
rape	0.188	0.07	0.05 - 0.11	0.57	0.15 - 0.34
carrot	0.188	0.26	0.23 - 0.30	> 3.0	-
soybean	3.0	> 3.0	-	> 3.0	-

- not determinable

Table B.9.9-3: Number of emerged seedlings: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	3.0	> 3.0	-	> 3.0	-
onion	3.0	> 3.0	-	> 3.0	-
sugar beet	3.0	> 3.0	-	> 3.0	-
rape	3.0	> 3.0	-	> 3.0	-
carrot	3.0	> 3.0	-	> 3.0	-
soybean	3.0	> 3.0	-	> 3.0	-

- not determinable

Table B.9.9-4: Dead plants: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	3.0	> 3.0	-	> 3.0	-
onion	0.375	0.43	0.38 - 0.49	0.56	0.50 - 0.63
sugar beet	0.188	0.53	0.39 - 0.72	1.21	0.88 - 1.64
rape	0.188	0.54	0.49 - 0.60	0.69	0.62 - 0.76
carrot	3.0	> 3.0	-	> 3.0	-
soybean	3.0	> 3.0	-	> 3.0	-

- not determinable

Table B.9.9-5: Phytotoxicity rates after 21 days

concentration [L/ha]	phytotoxicity rate [%]						
	oats	onion	carrot	concentration [L/ha]	sugar beet	rape	soybean
control	0	13	0	control	0	0	0
0.188	0	11	0	0.012	< 10	0	0
0.375	0	16	< 10	0.047	< 10	< 10	0
0.75	< 10	83	< 10	0.188	0	14	0
1.5	< 10	83	0	0.75	50	71	0
3.0	< 10	90	10	3.0	85	53	< 10

Conclusion
The lowest ER_{50} of 0.22 L/ha was determined for rape (*Brassica napus)*.

Annex Point: IIIA-10.8
Author: Fiebig, S.
Title: Terrestrial Plants Toxicity, Vegetative Vigour, Tier II.
Stähler Agrochemie GmbH & Co. KG
Project No. 010130SS, Study No. TNK77872
Date: 28.09.2001
Doc ID: PFL2004-25
Guidelines: OECD 208 Draft (July 2000)
GLP: yes
Validity: yes

Materials and methods
The phytotoxicity of the test item Herbaflex (batch number 0029) with 490 g/L isoproturon and 81 g/L beflubutamid to six terrestrial plant species was determined over a period of 21 days (2001-05-04 to 2001-05-25 (oat, onion, sugar beet, soybean) and 2001-05-15 to 2001-06-05 (rape, carrot).
Test plants were two monocotyledons (oat, *Avena sativa*; onion, *Allium cepa*) and four dicotyledons (sugar beet, *Beta vulgaris*; rape, *Brassica napus*; carrot, *Daucus carota*; soybean, *Glycine max*.). The test item was once applied onto the foliage of the plants that reached the 2-4 leaf stage. The plants were watered from the bottom and fertilised during the test with nutrient solution as needed.
The test was conducted with the nominal concentrations 0.037 – 0.11 – 0.33 – 1.0 – 3.0 L/ha (factor 3) selected on the basis of a preliminary test.
The toxic effects of the test item were determined on day 7, 14, and 21 by visual observations and on day 21 by shoot height and fresh weight determination. Shoot height, fresh weight and number of dead plants were checked for significant differences.

Findings
The NOEC, the EC_{25}- and EC_{50}-values with the confidence ranges calculated from percentage inhibition of the plant growth are summarized in the following tables.

Table B.9.9-6: Shoot height: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	0.11	0.41	0.25 - 0.69	1.61	0.97 - 2.68
onion	0.33	0.81	0.46 - 1.40	> 3.0	-
sugar beet	< 0.037	0.07	0.05 - 0.10	0.16	0.12 - 0.22
rape	0.11	0.52	0.26 - 1.05	> 3.0	-
carrot	1.00	2.66	1.94 - > 3.0	> 3.0	-
soybean	0.11	0.45	0.28 - 0.71	1.54	0.97 - 2.45

- not determinable

Table B.9.9-7: Fresh weight: NOEC, EC_{25} and EC_{50} values with confidence range (p)

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	0.11	0.30	0.25 - 0.36	0.48	0.40 – 0.57
onion	0.33	0.19	0.11 – 0.34	0.88	0.50 - 1.55
sugar beet	< 0.037	0.04	< 0.037 - 0.05	0.06	0.05 - 0.07
rape	0.11	0.12	0.09 – 0.18	0.33	0.23 - 0.48
carrot	1.00	1.57	1.22 - 2.01	2.71	2.11 - > 3.0
soybean	< 0.037	0.05	0.03 - 0.10	0.38	0.97 - 2.45

- not determinable

Table B.9.9-8: Phytotoxic effect: dead plant (NOEC, EC_{25} and EC_{50} values with confidence range (p))

Species	NOEC [L/ha]	EC_{25} [L/ha]	p = 95 % [L/ha]	EC_{50} [L/ha]	p = 95 % [L/ha]
oats	0.33	0.75	0.58 - 0.99	1.56	1.19 - 2.05
onion	0.33	2.22	0.80 > 3.0	> 3.0	-
sugar beet	0.037	0.13	0.12 - 0.15	0.18	0.16 - 0.20
rape	0.33	0.59	0.49 - 0.71	0.89	0.74 - 1.07
carrot	n.o.	n.o.	-	n.o.	-
soybean	0.33	1.06	0.95 - 1.17	1.40	1.26 - 1.55

n.o. = not observed (effects < 10 % were not considered)
- not determinable

Conclusion

The lowest ER_{50} of 0.06 L/ha was determined for sugar beet (*Beta vulgaris*).

Annex Point:	IIA-8.6
Author:	Fiebig, S.
Title:	Standardized Bioassay for determination of ED_{10}- (NEL) and ED_{50}-values for herbicides and selected following crops in soil UBE Industries, Project No. 010111SS, Study No. TPB77893
Date:	08.08.2001
Doc ID:	PFL2004-27
Guidelines:	BBA
GLP:	Yes
Validity:	Yes

Materials and methods

The effects on the biomass (fresh weight) of the test item ASU 92530 H (Beflubutamid 515 g/L SC, batch number 0014) on seven terrestrial plant species were determined over a period of 14 days. Two independent test series were conducted with the nominal concentrations 0.5 – 0.25 – 0.125 – 0.0625 – 0.0313 – 0.0157 mg/kg dw soil (dilution factor 2, 1st test series) and 3.0 – 1.0 - 0.33 – 0.11 – 0.037 – 0.012 mg/kg dw soil (dilution factor 3, 2nd test series).

All concentrations were related to the dry weight (dw) of the soil. Test plants were two monocotyledons (oat and spring barley) and five dicotyledons (rape, sugar beet, mustard, sunflower and pea). The test item was uniformly incorporated into the soil at various concentrations. The soil was stored overnight to reach sorption equilibrium and then the plants were transplanted into the soil. At the end of the test the fresh weight of the shoots was determined.

Findings

The ED_{10} (NOEL) and the ED_{50}-values with confidence ranges calculated from percentage inhibition of plant growth (fresh weight) for both test series are summarized in the following tables.

Table B.9.9-9: Fresh weight: ED_{10} (NOEL) and the ED_{50}-values with confidence ranges (p) (1st test series)

Species	ED_{10} (NOEL) [mg/kg dw soil]	ED_{50} (NOEL) [mg/kg dw soil]	p = 95 % [mg/kg dw soil]
oats	> 0.5	> 0.5	-
spring barley	> 0.5	> 0.5	-
sugar beet	0.30	> 0.5	-
rape	> 0.5	> 0.5	-
mustard	0.23	> 0.5	
sunflower	> 0.5	> 0.5	-
pea	> 0.5	> 0.5	-

- not determinable

Table B.9.9-10: Fresh weight: ED_{10} (NOEL) and the ED_{50}-values with confidence ranges (p) (2^{nd} test series)

Species	ED_{10} (NOEL) [mg/kg dw soil]	ED_{50} (NOEL) [mg/kg dw soil]	p = 95 % [mg/kg dw soil]
oats	0.48	> 3.00	-
spring barley	2.31	> 3.00	-
sugar beet	0.44	1.85	1.33 - 2.56
rape	0.58	1.35	1.12 - 1.64
mustard	0.02	0.25	0.18 - 0.36
sunflower	> 3.00	> 3.00	-
pea	> 3.00	> 3.00	-

- not determinable

Conclusion
The lowest ED_{50} of 0.25 mg/kg dw soil was determined for mustard (*Sinapis alba*).
Although the study is valid, it cannot be used for the risk assessment for terrestrial plants. The active substance beflubutamid is taken up mainly by the seedlings and to a lesser extent by roots and leaves. The formulated product is intended for post emergence use in winter cereals. In this study the plants were not exposed according to the effects of beflubutamid. The plants were transplanted in the exposed soil. Neither seedlings nor leaves were exposed to beflubutamid.

Annex Point: IIA-8.6
Author: Fiebig, S.
Title: Standardized Bioassay for determination of ED_{10} – (NEL) and ED_{50} – values for herbicides and selected following crops in soil
Stähler Agrochemie GmbH & Co KG
Project –No. 010111SS, Study. No. TPB77871
Date: 24.08.2001
Doc ID: PFL2004-26
Guidelines: BBA
GLP: Yes
Validity: Yes

Materials and methods
The effects on the biomass (fresh weight) of the test item Herbaflex (490 g/L Isoproturon 81 g/L Beflubutamid, batch number 0029) on seven terrestrial plant species were determined over a period of 14 days. The test was conducted with the nominal concentrations 2 – 0.667 – 0.222 – 0.074 – 0.025 – 0.0083 mg/kg dw (soil dry weight) selected on the basis of a preliminary phytotoxicity test.
Test plants were two monocotyledons (oat and spring barley) and five dicotyledons (rape, sugar beet, mustard, sunflower and pea). The test item was uniformly incorporated into the soil at various concentrations. The soil was stored overnight to reach sorption equilibrium and then the plants were transplanted into the soil. At the end of the test the fresh weight of the shoots was determined.

Findings
The ED_{10} (NOEL) and the ED_{50}-values with confidence ranges calculated from percentage inhibition of plant growth (fresh weight) for both test series are summarized in the following table.

Table B.9.9-11: Fresh weight: ED_{10} (NOEL) and the ED_{50}-values with confidence ranges (p) (1st test series)

Species	ED_{10} (NOEL) [mg/kg dw soil]	ED_{50} (NOEL) [mg/kg dw soil]	p = 95 % [mg/kg dw soil]
Oats	0.0923	0.4387	0.3250 - 0.5921
spring barley	0.7751	1.5698	1.3265 - 1.8578
sugar beet	0.5289	0.8854	0.8018 - 0.9777
Rape	0.4322	0.6136	0.5649 - 0.6664
mustard	0.4028	0.8040	0.7039 - 0.9185
sunflower	0.0946	0.3443	0.2685 - 0.4415
Pea	1.1867	> 2.000	-

- not determinable

Conclusion
The lowest ED_{50} of 0.3443 mg/kg dw soil was determined for sunflower (*Helianthus annuus*). Although the study is valid, it cannot be used for the risk assessment for terrestrial plants. The active substance beflubutamid is taken up mainly by the seedlings and to a lesser extent by roots and leaves. The formulated product is intended for post emergence use in winter cereals. In this study the plants were not exposed according to the effects of beflubutamid. The plants were transplanted in the exposed soil. Neither seedlings nor leaves were exposed by beflubutamid.

B.9.9.2 Summary of results and risk assessment

Beflubutamid:
The risk assessment for effects of beflubutamid on terrestrial plants is outlined in the monograph volume 3 chapter B.9.9.

Herbaflex:
The effects of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon) on terrestrial plants at pre- and post emergence application is summarised in the following table.

Table B.9.9-12: Effects of Herbaflex on terrestrial plants

Plant species		**ER_{50} [L/ha]**	
		seedling emergence	vegetative vigour
Oat	*Avena sativa*	>3.0	0.48
onion	*Allium cepa*	0.28	0.88
sugar beet	*Beta vulgaris*	0.75	**0.06**
rape	*Brassica napus*	**0.22**	0.33
carrot	*Daucus carota*	>3.0	2.71
soybean	*Glycine max*	>3.0	0.38

The lowest ER_{50} value of 0.06 L/ha was seen in sugar beet (*Beta vulgaris*) at post-emergence application of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon). At pre-emergence application of Herbaflex the lowest ER_{50} value of 0.22 L/ha was determined for rape (*Brassica napus*).

The risk assessment (TER values) for non-target plants performed below, is using the PEC drift values by Rautmann et al. given in the EU Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002), the maximum application rate for Herbaflex of 3.0 L/ha and the lowest ER_{50} value (see Table B.9.9-13 and Table B.9.9-14).

TER calculation based on the most sensitive species:

Table B.9.9-13: Seedling emergence and seedling growth test: *Brassica napus*

			TER values based on ER_{50} 220 mL/ha	
Distance m	drift rate %	PEC mL/ha	conventional	drift reduction 50 %
0	100	3000	0.07	--
1	2.77	83.1	2.65	**5.3**
5	0.57	17.1	**12.87**	**25.74**
10	0.29	8.7	**25.30**	**50.60**

Table B.9.9-14: Vegetative vigour test: *Beta vulgaris*

			TER values based on ER_{50} 60 mL/ha			
Distance m	drift rate %	PEC mL/ha	conventional	drift reduction		
				50 %	75 %	90%
0	100	3000	0.02	--	--	--
1	2.77	83.1	0.72	1.4	2.9	**7.2**
5	0.57	17.1	3.5	**7.0**	**14.0**	**35.1**
10	0.29	8.7	**6.90**			

Under conditions of the post-emergence application at 3 L Herbaflex/ha and an ER_{50} of 0.06 L/ha, TER values are greater than 5 for a buffer distance of 10 m (without spray reducing nozzles). Using spray reducing nozzles resulting in 90 % drift reduction, no buffer distance needs to be applied.

Conclusion

With use of the mitigation options presented below, Herbaflex poses acceptable risk to non-target terrestrial plants.

Table B.9.9-15: Recommended mitigation measures

Mitigation option	**No-spray buffer zone**	**Drift reduction**
1	10 m	0 %
2	5 m	50 %
3	0 m	90 %

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** **BVL registration number**	**Data protection claimed** **Y/N**	**Owner**
AIIA-8.4.2	Müther-Paul, J.	2005	Sublethal toxicity of UR_50604 on earthworms, Eisenia fetida using an artificial soil test. 20041457/01-NREf GLP, unpublished ARW2005-258	Y	TSU
AIIIA-10.1	Gurney, J.E.; Perrett, J.; Crocker,D.R.; Pasqual, J.A.	1998	Mammal Bible -Mammals and farming: Information for risk assessment. MAFF, CSL Milestone Report AVS2004-28	N	-
AIIIA-10.1	Crocker, D.R. et al.	2002	Methods for estimating daily food intake of wild birds and mammals. CSL, Final Report AVS2006-29	N	-
AIIIA-10.1	Anonymous	2003	Risk Assessment for Birds. 2003 not GLP, unpublished AVS2004-43	Y	TSU
AIIIA-10.2	Anonymous	2003	Effects on Aquatic organism. 2003 not GLP, unpublished WAT2004-77	Y	TSU
AIIIA-10.6	Noack, U.	2003	Herbaflex (Beflubutamid) Assessment of Effects on Earthworm. 2003 not GLP, unpublished ARW2004-23	Y	TSU
AIIIA-10.6.1.3	Strömel, C.; Teresiak, H.	2005	Field study to evaluate the effects of Herba-flex on earthworms. AC/STA/04/01 GLP, unpublished ARW2005-260	Y	TSU
AIIIA-10.6.1.3	Groß, G.	2005	Determination of the residues of the active substance Beflubutamid and its metabolite UR-50604 in soils from an earthworm field study. 0410352012 GLP, unpublished ARW2005-261	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** **BVL registration number**	**Data protection claimed** **Y/N**	**Owner**
AIIIA-10.6.1	Heimann-Detlefsen, D.	2005	Effects on Earthworm Population, Risk Assessment with Respect to the Long-Term Effects of Herbaflex (Beflubutamid/Isoproturon), Beflubutamid (UR-50601), and Metabolite (UR-50604). UBE-2005-01 not GLP, unpublished ARW2005-259	Y	TSU
AIIIA-10.6.2	Bruhnke, C.	2003	Herbaflex - Inhibition of reproduction of collembola (folsomia candida). 030708SS ! ICR92952 GLP, unpublished ARW2004-20	Y	TSU
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Terrestrial plants toxicity, seedling emergence, tier II. TNK77872 GLP, unpublished PFL2001-122	Y	TSU
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Terrestrial plants toxicity, vegetative vigour, tier II. TNW7787 GLP, unpublished PFL2004-25	Y	TSU
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Standardized bioassay for the determination of ED10 - (NOEL) and ED50 - values for herbicides and selected following crops in soil. TPB77871 GLP, unpublished PFL2004-26	Y	TSU
AIIIA-10.8	Fiebig, S.	2001	ASU92530 H: Standardized bioassay for the determination of ED10 - (NOEL) and ED50 - values for herbicides and selected following crops in soil. TPB77893 GLP, unpublished PFL2004-27	Y	TSU

Codes of company

TSU: Task force Stähler International GmbH & Co. KG / UBE Industries

Addendum 4

to the Draft Assessment Report

of 2 August 2002

Beflubutamid

Vol. 3 B.9 (Ecotoxicology)

31 October 2006

Rapporteur Member State: Germany

Contents

B.9 Ecotoxicology

B.9.9 Effects on other non-target organisms (flora and fauna) believed to be at risk (Annex IIA 8.6)

B.9.9.2 Summary of results and risk assessment

Herbaflex:
In Addendum 3 (6 June 2006) the risk assessment for the formulated product Herbaflex has erroneously been conducted with an application rate of 3.0 L/ha. The correct application rate however is 2.0 L/ha (= 170 g as/ha).

The effects of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon) on terrestrial plants at pre- and post emergence application is summarised in the following table.

Table B.9.9-12: Effects of Herbaflex on terrestrial plants

Plant species		**ER_{50} [L/ha]**	
		seedling emergence	vegetative vigour
Oat	*Avena sativa*	>3.0	0.48
onion	*Allium cepa*	0.28	0.88
sugar beet	*Beta vulgaris*	0.75	**0.06**
rape	*Brassica napus*	**0.22**	0.33
carrot	*Daucus carota*	>3.0	2.71
soybean	*Glycine max*	>3.0	0.38

The lowest ER_{50} value of 0.06 L/ha was seen in sugar beet (*Beta vulgaris*) Beta vulgaris at post-emergence application of Herbaflex (85 g/L beflubutamid and 500 g/L isoproturon). At pre-emergence application of Herbaflex the lowest ER_{50} value of 0.22 L/ha was determined for rape (*Brassica napus*).

The risk assessment (TER values) for non-target plants performed below, is using the PEC drift values by Rautmann et al. given in the EU Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002), the maximum application rate for Herbaflex of 2.0 L/ha and the lowest ER_{50} value (see Tables B.9.9-13 and B.9.9-14).

TER calculation based on the most sensitive species:

Table B.9.9-13: Seedling emergence and seedling growth test: *Brassica napus*

			TER values based on ER_{50} 220 mL/ha	
Distance	drift rate	PEC		drift reduction
m	%	mL/ha	conventional	50 %
0	100	2000	0.11	--
1	2.77	55.4	3.97	**7.9**
5	0.57	11.4	**19.3**	**38.6**
10	0.29	5.8	**37.93**	**75.9**

Table B.9.9-14: Vegetative vigour test: *Beta vulgaris*

			TER values based on ER_{50} 60 mL/ha			
Distance	drift rate	PEC		drift reduction		
m	%	mL/ha	conventional	50 %	75 %	90%
0	100	2000	0.03	--	--	--
1	2.77	55,4	1.08	2.2	4.3	**10.8**
5	0.57	11.4	**5.3**	**10.5**	**21.1**	**52.6**
10	0.29	5.8	**10.3**			

Under conditions of the post-emergence application at 2.0 L Herbaflex/ha and an ER_{50} of 0.06 L/ha, TER values are greater than 5 for a buffer distance of 5 m (without spray reducing nozzles). Using spray reducing nozzles resulting in 90 % drift reduction, no buffer distance needs to be applied.

Conclusion
With use of the mitigation options presented below, Herbaflex poses an acceptable risk to non-target terrestrial plants.

Table B.9.9-15: Recommended mitigation measures

Mitigation option	**No-spray buffer zone**	**Drift reduction**
1	5 m	0 %
2	5 m	50 %
3	0 m	90 %

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** **BVL registration number**	**Data protection claimed** **Y/N**	**Owner**
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Terrestrial plants toxicity, seedling emergence, tier II. TNK77872 GLP, unpublished PFL2001-122	Y	SIT
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Terrestrial plants toxicity, vegetative vigour, tier II. TNW7787 GLP, unpublished PFL2004-25	Y	SIT
AIIIA-10.8	Fiebig, S.	2001	Herbaflex: Standardized bioassay for the determination of ED10 - (NOEL) and ED50 - values for herbicides and selected following crops in soil. TPB77871 GLP, unpublished PFL2004-26	Y	SIT

Annex point/ reference number	**Author(s)**	**Year**	**Title** **source (where different from company)** **report no.** **GLP or GEP status (where relevant), published or not** **BVL registration number**	**Data protection claimed** **Y/N**	**Owner**
AIIIA-10.8	Fiebig, S.	2001	ASU92530 H: Standardized bioassay for the determination of ED10 - (NOEL) and ED50 - values for herbicides and selected following crops in soil. TPB77893 GLP, unpublished PFL2004-27	Y	SIT

Codes of company

SIT: Stähler International GmbH & Co. KG