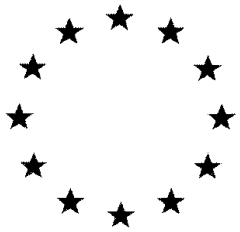
European Commission

Peer Review Programme



ECCO Peer Review Meetings

Full Report on Beflubutamid

- Reports of the meetings
- Comments on the draft assessment report
- Other documents considered at the meetings

ECCO-Team, at: Pesticides Safety Directorate (PSD), York

17.10.2003

ECCO PEER REVIEW PROGRAMME

FULL REPORT ON **BEFLUBUTAMID**

CONTENTS

PART 1: REPORTS

PART 2: COMMENTS AND OTHER DOCUMENTS

DOCUMENTS ON BEFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Physical Chemical Properties (ECCO 135)

1. List of end points (not included in Full Report)

Date	Supplier	File name
20 January 2003	Belgium	Beflubutamid 135 2endpoints

2. Comments

Date	Supplier	File name
8 January 2003	United Kingdom	beflubutamid 135 com01 UK
3 February 2003	Belgium	beflubutamid 135 com02 BE

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting

Date	Supplier	Content	File name

5. Addenda (not included in Full Report)

Date	Supplier	File name

6. Other Documents (not included in Full Report)

Date	Supplier	File name

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool, 3 Peasholme Green, York YO1 7PX
Website: www.pesticides.gov.uk
Switchboard: 01904 640500 GTN: 5138 5840
Direct Dial: 01904 455840 Fax: 01904 455722
International: (+44) 1904 455897 International Fax: (+44) 1904 455722
Email: adrian.parr@psd.defra.gsi.gov.uk

Herbert Köpp
Federal Office for Consumer Protection
and Food Safety (*BVL*)
Brunswick
Germany **by email**

Our ref : ASY 255

Date : 8 January 2003

Dear Herbert

UK COMMENTS ECCO FOR ROUND 14

EC NEW ACTIVE SUBSTANCE : BEFLUBUTAMID
RAPPORTEUR:- GERMANY

ECCO 135 - MEETING TO DISCUSS PHYSICAL AND CHEMICAL PROPERTIES

On behalf of the Pesticides Safety Directorate of the United Kingdom Department for Environment, Food and Rural Affairs, please find attached our comments on the monograph for beflubutamid. We are submitting these comments for your information as rapporteur and for any discussion at ECCO 135 on 11 - 14 February 2003.

Yours sincerely

Adrian Parr

Adrian Parr
Approvals Committee Branch

cc: ECCO Team – PSD

The Pesticides Safety Directorate is making no comments other than in those areas outlined below:

Phys/chem properties and methods

C.1.2.1.1

Are there any data on the relative biological activity of the isomers?

C.1.2.1.3

The level of the impurities in the technical specification seem high when considered against the batch analysis data. Consideration should be given to requesting a revised technical specification.

Beflubutamid : Comments from Belgium on the Draft Assessment Report (RMS : Germany)
Sections : Identity, Physical and chemical properties, Methods of analysis (ECCO 135)
Date : 3 February 2003
Contact : Dr. ir. Annick De Meester (Tel. : (+32) (0)2 210 51 05 / e-mail : Annick.De.Meester@cmlag.fgov.be)

DAR point (Annex point)	**Comment**
Identity	
Volume 4, C.1.2.1.3 and C.1.2.2 (IIA 1.10 and 1.11)	Although it is not explicitly mentioned, we presume the 5-batch analytical profile for each of the 3 manufacturing sites refers to pilot scale production. Batch analysis data for full-scale production batches will thus have to be submitted for each plant once commercial production methods have stabilised. At that time, a revision of the certified max. impurity contents may also be in order, as for some impurities the current values appear quite high compared to the actual batch results.
Physical and chemical properties	
Volume 3, B.2.1.6 (IIA 2.6)	Could the RMS clarify which method (flask method or column elution) was used for determination of solubility in water?
Volume 3, B.2.1.8 (IIA 2.8)	It is stated that log P_{ow} was determined using the flask method. However, the resulting log P_{ow} value of 4.28 lies just outside the applicability range of this method (-2 to 4).
Volume 3, B.2.2.2.2 (IIIA 2.2)	RMS states that no method is available for the determination of oxidising properties of liquids. Although we agree that in this case (aqueous SC) oxidising properties of the formulation are unlikely considering the properties of its components, we would like to note that FIFRA Guideline 63-14 (i.e. testing of reactivity towards reducing agents e.g. zinc) provides a suitable alternative to EEC A17 for liquids.
Volume 3, B.2.2.5.3 (IIIA 2.5)	Could the RMS clarify at what temperature and concentration surface tension was determined?
Volume 3, B.2.2.7.1 (IIIA 2.7)	Accelerated storage stability was determined after 12 weeks at 35°C instead of after 14 days at 54°C. Did the notifier provide a justification for this?
Volume 3, B.2.2.7.3 (IIIA 2.7)	Could the RMS clarify which physical properties were determined after 2 years storage (we presume emulsion stability is a copy/paste error).
Methods of analysis	
Volume 1, Endpoints	With respect to the residue methods, we propose to add which analyte(s) is (are) being determined by each method.
Volume 4, C.1.2.4 (IIA 4.1.2)	LOQ of impurity methods is apparently not reported.
Volume 3, B.5.3.2 and B.5.3.3 (IIA 4.2.3)	Proposed residue method for water apparently only determines parent compound. If other ECCO meetings conclude that metabolite UR-50604 is relevant, a validated method for its determination in water will be required.

DOCUMENTS ON BETFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Mammalian Toxicology (ECCO 136)

1. List of end points (not included in Full Report)

Date	Supplier	File name

2. Comments

Date	Supplier	File name
17 February 2003	United Kingdom	beflubutamid 136 com01 UK
25 February 2003	Belgium	beflubutamid 136 com02 BE
4 March 2003	The Netherlands	beflubutamid 136 com03 NL

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting

Date	Supplier	Content	File name

5. Addenda (not included in Full Report)

Date	Supplier	File name

6. Other Documents (not included in Full Report)

Date	Supplier	File name

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool, 3 Peasholme Green, York YO1 7PX
Website: www.pesticides.gov.uk
Switchboard: 01904 640500 GTN: 5138 5840
Direct Dial: 01904 455840 Fax: 01904 455722
International: (+44) 1904 455897 International Fax: (+44) 1904 455722
Email: adrian.parr@psd.defra.gsi.gov.uk

Herbert Köpp
Federal Office for Consumer Protection
and Food Safety (*BVL*)
Brunswick
Germany **by email**

Our ref : ASY 407

Date : 17 February 2003

Dear Herbert

UK COMMENTS ECCO FOR ROUND 14

EC NEW ACTIVE SUBSTANCE : BEFLUBUTAMID
RAPPORTEUR:- GERMANY

ECCO 136 - MEETING TO DISCUSS MAMMALIAN TOXICOLOGY

On behalf of the Pesticides Safety Directorate of the United Kingdom Department for Environment, Food and Rural Affairs, please find attached our comments on the monograph for beflubutamid. We are submitting these comments for your information as rapporteur and for any discussion at ECCO 136 on 10 - 14 March 2003.

Yours sincerely

Adrian Parr
Approvals Committee Branch

cc: ECCO Team – PSD

The Pesticides Safety Directorate is making no comments other than in those areas outlined below:

Beflubutamid: General comments

When indicating compliance with an OECD test method it is helpful to also indicate the date of the guideline (as some guidelines have been updated).

The UK agrees with the proposed ADI and dermal absorption values but has the following comments on the toxicology evaluation.

B.6.3.3.2 12-month dog study

Although not statistically significant, there was a slight increase in APTT (by up to 8-10%) in both males and females at 60 mg/kg bw/day. It may be questionable to rely on statistical analysis when there are only 4/sex/dose level. However in the absence of good evidence of other direct effects on the liver at this dose in this study, it would seem reasonable to regard this as a non-adverse effect. The proposed NOAEL of the RMS is therefore accepted. However we think the DAR could have included a comment on the slight increase in APTT at 60 mg/kg bw/day, especially as it is an effect consistent with other studies.

B.6.4.1.3 *In vitro* mammalian cell gene mutation

In Table B.6.4-5 does the mean mutation frequency refer to the mean mutation frequency per viable cell?

The statistically significant increase in the second assay in the absence of S9 (with no such increase in the first assay) indicates an equivocal rather than a negative result. However based on the results for all genotoxicity studies it is agreed that it can be concluded that the active substance is not genotoxic.

B.6.5 Carcinogenicity

The DAR states that the increased incidence of thyroid follicular tumours in male rats are treatment-related but without relevance to humans. No reasoning for considering the tumours to be without relevance to humans is provided in the DAR.

The UK notes that in this case the oncogenic potency is low (T25 > 100 mg/kg bw/day). Humans are also considerably less sensitive than rodents to perturbation of thyroid hormone homeostasis by non-genotoxic xenobiotics and the consequent induction of thyroid tumours. However, in order to conclude the tumours are not relevant to humans there would need to be more mechanistic evidence for beflubutamid, eg evidence of induction of UDPGT and enhanced thyroid hormone clearance.

B.6.8.1 Toxic effects of other metabolites

Further evidence that the toxicity of UR-50604 can be evaluated based on the toxicity results with the parent compound is that (according to B.6.1.1) it was the major metabolite of the parent compound in rat plasma.

B.6.10.12 Acceptable Operator Exposure Level

The NOAEL for thyroid tumours in the rat carcinogenicity study of 400 ppm (17.7 mg/kg bw/day) is only 59 times above the proposed AOEL of 0.3 mg/kg bw/day. We do not consider this an adequate safety margin for tumours which currently have to be considered as potentially relevant for humans.

Hence it is proposed to use an assessment factor of 300 to achieve an **AOEL of 0.1 mg/kg bw/day**. This results in a margin of 177 on the NOAEL for thyroid tumours. This is considered to be a sufficient margin because:

- there was a wide margin between the NOAEL (17.7 mg/kg bw/day) and the LOAEL (150 mg/kg bw/day) for these tumours

- there was only a slight, non-statistically significant increase in the tumours at 150 mg/kg bw/day which was at the upper end of the historical control range.

B.6.10.13 Acute reference dose

The UK considers that n acute reference dose of 1 mg/kg bw/day should be proposed, based on the developmental toxicity seen at 100 mg/kg bw/day in the rat developmental toxicity study. We note that the latest JMPR guidance (2002) considers that an acute reference dose should always be set if justified by the toxicity data.

B.6.11.7 Supplementary studies for combinations of plant protection products

The product Herbaflex contains two active substances, beflubutamid and isoproturon. The RMS addresses the possible toxic effects from the presence of two active substances by reference to the studies (acute, irritancy and sensitisation) with the preparation. The UK considers that some further reasoning is required to address whether there are possible additive and/or synergistic effects. The UK notes that both substances affect the liver (isoproturon is reported to cause hepatocyte degeneration).

Batches tested

The RMS should confirm that the technical specification of the four batches of beflubutamid used in the toxicity studies are comparable with the technical specification for which authorisation is sought.

SCIENTIFIC INSTITUTE OF PUBLIC HEALTH
-Louis Pasteur-

Division Toxicology

phone : +32 2 642 5351
telefax : +32 2 642 5224
contact person : Ph. Castelain
e-mail : ph.castelain@iph.fgov.be

your letter dated
your references :

our references: Phc-ecco136-beflubutamid
date 25.02.2003

annex(es)

e-mail
RMS: h.koepp@bba.de
ecco@bba.de
p.s.d.ecco@psd.defra.gsi.gov.uk

Ecco 136 – mammalian toxicology
CONCERNS Belgian comments on draft : BEFLUBUTAMID

P91
Based upon the data available in this 90d mouse study, it is questionable whether the effects on the liver at the lowest dose should be considered as really adverse. While it is observed that no clinico-chemical data and minimal haematology endpoints were measured, it is the opinion of BE that 400ppm could be regarded as the NOAEL (61 mg/kg bw/d).

P114
B.6.5. Rat carcinogenicity
BE is in favour of setting the NOAEL=2.2 mg/kg bw/d. The effects observed at 17.7 mg/kg bw/d are a.o. adaptive responses, but other adverse effects (prolonged clotting time, proteinuria) are also observed.

P146
B.6.10
BE is in favour of the establishment of the ADI based on the 2 yr rat carcinogenicity study, i.e. 2.2 mg/kg bw/d / 100 = 0.022 mg/kg bw/d. The AOEL is based upon the 90d rat study, i.e. 29 mg/kg bw/d / 100 = 0.3 mg/kg bw/d.
The establishment of an ARfD is not deemed necessary in the absence of seriously adverse effects after unique exposure.

Yours sincerely,

Ph. Castelain

Federal Ministry of Social Affairs,
Public Health
and Environment

Address : Juliette Wytsman 16
B-1050 BRUSSELS
Phone. : +32 2 642 5111
Telefax : + 32 2 642 5001
http://www.iph.fgov.be

To: ECCO-Team PSD
Cc: ECCO-Team BVL
From: CTB
Date: 3 March 2003

Subject: Comments of **the Netherlands** on EU-monograph **beflubutamid**

Mammalian toxicology, metabolism and classification and labelling

General remark
Changes introduced in the endpointlist by The Netherlands are made by a strike through the old text and new text written as highlighted text.

Volume 1, level 1 – 4

Adjustments should be made according to the comments on the summaries in Volume 3, Annex B.

Appendix 3 Listing of endpoints

Rapporteur Member State	Month and year	Active substance
Germany	**August 2002**	**Beflubutamid**

Chapter 2.3 – Impact on Human and Animal Health

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

Rate and extent of absorption:	Nearly completely absorbed based on excretion via bile and urine. After single dose, concentration in blood higher in males than in females.
Distribution:	Widely distributed, highest concentrations in liver, kidneys and plasma. Some indication of selective uptake into blood cells.
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Completely excreted within 120 hours mainly via bile (66% (f)-85% (m) in 48 hours after low dose and 47% (f) – 42% (m) after high dose). Urinary excretion higher in females than in males, excretion in faeces higher in males than in females.
Metabolism in animals	Extensively metabolised by hydroxylation, cleavage of the amide bond and conjugation as glucuronides (major metabolites: phenoxybutyric acid, hippuric acid)
Toxicologically significant compounds (animals, plants and environment)	Parent compound and major metabolites

Acute toxicity (Annex IIA, point 5.2)

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

Short-term toxicity (Annex IIA, point 5.3)

Target / critical effect	Decreased bw; decreased relative weights of liver (rat,mouse,dog), kidney + thyroid gland (rat), liver centrilobular hypertrophy, kidney dilatation renal pelvis. Reproductive organs of male dogs: at and above 300 mg/kg bw/day acinar hypertrophy (prostate), spermatozoa absent and round spermatids and spermatocytes in ductules (epididymides) and degenerative spermatids and spermatocytes (testes).
Lowest relevant oral NOAEL / NOEL	90-d oral, rat: 400 ppm (30 mg/kg bw/d)
Lowest relevant dermal NOAEL / NOEL	No data - Not required
Lowest relevant inhalation NOAEL / NOEL	No data - Not required

Genotoxicity (Annex IIA, point 5.4)	No evidence of genotoxic potential. Precipitation was apparent in the in vitro tests at and above 500 µg. The precipitate appeared to have an effect on the bioavailabilty of the test material to the cells.

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

Target/critical effect	Liver, kidney + thyroid gland (rat)
Lowest relevant NOAEL / NOEL	104-wk oral, rat: 50 ppm (2.2 mg/kg bw/d)
Carcinogenicity	~~No carcinogenic potential with relevance to humans.~~ ~~No carcinogenic potential with relevance to humans.~~ Conclusions from rat study is that the observed increased incidence of thyroid follicular tumours are treatment related. Therefor, beflubutamid is considered to have carcinogenic potential (cat.3).

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	Impairment of body weight development during lactation, delay in age for vaginal opening (F1-females) at parental toxic doses doses; offspring kidney changes at 3200 ppm. Reproductive organs of male dogs: at and above 300 mg/kg bw/day acinar hypertrophy (prostate), spermatozoa absent and round spermatids and spermatocytes in ductules (epididymides) and degenerative round spermatids and spermatocytes (testes).
Lowest relevant reproductive NOAEL / NOEL	2-gen. rat: 200 ppm (approx. 17 mg/kg bw/d)
Developmental target / critical effect	Developmental effects on the kidney/ureter at maternally toxic doses.
Lowest relevant developmental NOAEL / NOEL	100 mg/kg bw/d (rat, rabbit)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

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

Other toxicological studies (Annex IIA, point 5.8)

No data

Medical data (Annex IIA, point 5.9)

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

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI (Juiste studie?????)	0.022 mg/kg bw	104-wk, oral rat	100
AOEL	0.3 mg/kg bw/d	90-d, rat	100
ARfD (acute reference dose)	~~Not necessary~~ 1.25 mg/kg bw	~~Not allocated~~ micronucleus test	100

Dermal absorption (Annex IIIA, point 7.3)

No studies performed; 100% assumed (worst case)

Acceptable exposure scenarios (including method of calculation)

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

B.4 Proposals for classification and labelling

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

Carcinogenic substance, category 3
Hazard symbol: Xn
Risk phrase: R40 Possible risk of irreverible effects

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

Sensibilisation study is inconclusive.

B.4.3 References relied on

No comments.

B.6 Toxicology and metabolism

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

Some conclusions from the metabolism studies are missing in the List of end points. Please correct this.

- There is indication for selective uptake in blood cells, and the concentration in blood is higher in males than in females.
- Highest concentration of radioactivity after a single dose are found in liver, kidneys and plasma.
- Excretion via bile after a single low dose was higher in males (85%) than in females (66%), whereas no sex-difference was observed after a high dose. Urinary excretion was higher in females than in males, and excretion in the faeces was higher in males than in females.

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

No comments

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

28-day study
The conclusion of the 28-day rat oral toxicity study is not complete. The NOAEL of 400 ppm is based on lower body weight gain, a reduction in adipose tissue in males, decreased WBC and lymphocyte numbers in males, increased total protein and globulin concentrations in females and higher relative kidney weight at the next higher dose of 3200 ppm. Please correct this.

90-day studies
rat
No explanation is given for the observed higher control values of Met-Hb in females compared to males. The higher control value in females may obscure any effect on MetHb in females.
In table B.6.3-3 absolute liver weights in control males are given as 0.3 g. Please correct this.
In the conclusion, it is stated that the NOAEL is based on observed reduction in food consumption. However, food consumption is not presented in the tabel. In addition, the observed changes of organ weights needs to be changed in increased relative organ weights. Please correct this.

Mouse
The study is considered to be acceptable for range-finding study only, since the study was performed for the selection of dose levels for a carcinogenicity study. Consequently, only selected parameters were studied.

The observed decrease in body weight gain in males was considered not toxicologically relevant, since the decrease was inversely dose related. However, decreased body weight gain was also observed in females, and also in other toxicology studies with rat, dog and mouse, and is therefore considered toxicologically relevant.
It was stated that the liver was enlarged in male mice at all treatment levels. However, in the lower dose groups only 1/10 mice showed liver enlargement. Liver enlargement in males was considered relevant only at and above 3200 ppm.
In table B.6.3-5 it is not clear why the observed increase in total centrilobular hepatocyte hypertrophy in males of the lowest dose group is not statistically significant increased, whereas the same increase in females is significantly increased. Please clarify this.
The LOAEL in this range-finding study is 400 ppm, based on increased relative liver weights in females of all dose groups and centrilobular hepatocyte hypertrophy in males in all dose groups. The Netherlands do not agree with the proposed NOAEL in this study which was derived from the carcinogenicity study in mice. The carcinogenicity study was performed with other groups of mice, and only limited data on toxicity are available for 13 weeks exposure in that carcinogenicity study. Therefore, in the present range-finding study, a NOAEL could not be established, and the LOAEL is 400 ppm (61 mg/kg bw/day).

Dog
The RMS stated that the observed lower body weights are not treatment-related. However, in all other toxicology studies with rats, mice and dogs, decreased body weight gain, resulting in decreased final body weights were obseved, and considered toxicologically relevant. In the present study with dogs, the observed lower body weights are considered treatment-related, however, the decrease in body weight is too small for setting a NOAEL only on this effect.
It is not clear why the observed statistically significant decreases in glucose, sodium and calcium (males) and statistically significant increases in globulin, urea and phosphorus in females were not presented and are considered not toxicologically relevant. It has to be noted that also in the one year toxicity study with dogs, statistically significant differences e.g. changes in plasma urea, sodium, calcium and triglycerides were observed, but also not presented and considered toxicologically not relevant. Please give arguments for ignoring the effects on clinical biochemical parameters.
The Netherlands do not agree with the the opinion of the RMS that the observed histopathological changes in the prostate, epididymides and testes of dogs dosed 300 and 1000 mg/kg bw/day are of equivocal toxicological significance. The observed effects on prostate (acinar atrophy), epididymides (absent spermatozoa, round spermatids and spermatocytes in ductules) and testes (degenerate/exfoliate round spermatids and spermatocytes) were dose-related. Since the effects occured at low incidences in the lower dose group, the small groups of test animals may account for the absence of the effect in the 300 mg/kg bw/day group in the 52-week study with dogs. The argument of the RMS that in rat reproductive fertility was not affected is no argument to disregard the effects observed in male dogs, since dogs may be more sensitive for this effect than rats. Therefore, the Netherlands concludes from the effects on male reproductive organs in dogs, that reproductive fertility is affected at and above 300 mg/kg bw/day. Please add in the conclusion of the study, and add in the List of Endpoints.

12-months study
Food consumption was lower in males of the high dose group, and not changed in females. Please correct this. Statistically significant differences in changes in plasma urea in males, sodium, calcium and triglycerides were considered not toxicologically relevant, though effects on these parameters were also observed in the 90-day study with dogs (see remark 90-day study dog). Please give arguments for ignoring the effects on clinical biochemical parameters.
The conclusion of the study suggests that all effects described are observed in both sex. However, the NOAEL is based on lower body weight gain (males), increased APTT (males

and females), increased PT (males, females week 52 only), increased AP (females) and GPT (females), reduction in plasma total protein (males, females), increased liver weight (male, female), liver enlargement (male) and histopathological changes in the liver (male, female at week 52 only) observed in the 300 mg/kg bw/day group. Please correct.

B.6.4 Genotoxicity (Annex IIA 5.4)

In vitro mutagenicity tests:
At and above 625 µg/plate or 500 µg/ml, precipitation was apparent in the cultures. In the mammalian cytogenicity test it is stated, that the precipitations appeared to have an effect on the bioavailibility of the test material to the cells. Please add this remark in the List of Endpoints.

In vivo study in somatic cells:
Clinical signs are indicative for reaching bone marrow, although no effect was observed on the proportion of immature erythrocytes (P:M ratio). Please add this remark in the findings of the study.

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

Rat
Table B.6.5-3: Are the reported control urinary protein values at week 104 correct? Please check these values.
Table B.6.5-4: The reported relative mean thyroid weights at week 105 seem to be not correct. Please check these values.
Table B.6.5-5: Data on neoplastic findings and non-neoplastic findings are not clear. No time of death of the animals is reported; neoplastic findings are reported for all 60 males, whereas data on females are confined to 40 and 42 animals in the mid-dose groups. However, non-neoplastic findings are reported for 60 females and males per dose. Can the RMS explain these differences in reported data of females?
The conclusion on carcinogenicity is lacking. Please add.
From the description of neoplastic findings, the conclusion is that the observed increase in thyroid follicular tumours are considered treatment-related. Consequently, since no data on the mechanism of tumour-induction are provided, the substance has to be considered as carcinogenic cat. 3. Please correct in the conclusion of the study as well as in the List of Endpoints and Proposals for Classification and Labeling (B.4).

Mouse
The conclusion on carcinogenicity is lacking. Please add.

B.6.6 Reproductive toxicity (Annex IIA 5.6)

In general: A remark should be made concerning the observed reproductive toxicity in male dogs in the 90-days toxicity study. In addition, this remark on observed effects on male dog reproductive organs should be added to the List of Endpoint: Reproductive organs of male dogs were affected at and above 300 mg/kg bw/day, showing acinar hypertrophy (prostate), absent spermatozoa and round spermatids in ductules (epididymides) and round spermatids and spermatocytes in testes. Please add this remark.
B.6.6.2.2. Rabbit teratogenicity study: dose selection was based on a pilot study and a preliminary study. However, the selected high dose from this main study (100 mg/kg bw/day) did not result in toxicity in the preliminary and pilot studies, and is therefore not suitable as high dose level for the main study.
In the preliminary study, animals sacrified for human reasons (days 16-21 of pregnancy) showed reduced or no food intake. However, in table B.6.6-11 it is not clear that food consumption was related to surviving animals only. Please correct.

B.6.7 Delayed neurotoxicity (Annex IIA 5.7)
No comments.

B.6.8 Further toxicological studies (Annex IIA 5.8)
No comments.

B.6.9 Medical data and information (Annex IIA 5.9)
B.6.9.5 first aid measures: Since the active substance is not irritating or corrosive, a person should vomit after swallowing the substance.

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and drinking water limit (Annex IIA 5.10)
Summary of mammalian toxicology: See comments in List of Endpoints and sections B6.1-B6.6. Corrections should be made according to the remarks given in these sections.

ARfD: In the micronucleus test, clinical effects (tremors, hunched posture, piloerection, slow respiration, underactive, unstable gait) were observed at and above 250 mg/kg bw, which are considered relevant effects for determination of an ARfD. The RMS is asked to check other toxicity studies for clinical signs relevant for allocating an ARfD, since clinical signs in other toxicity were reported only briefly. Based on the effects observed in the micronucleus test, a NOAEL of 125 mg/kg bw can be derived. Considering a safety factor of 100, the ARfD is 1.25 mg/kg bw.
In B.6.10.13, arguments based on expected exposure to residues are used for not allocating an ARfD. However, an ARfD is based on toxicological effects only. Therefore, the suggested effects on exposure has to be removed.

B.6.11 Acute toxicity including irritancy and skin sensitisation of preparations (Annex IIIA 7.1)
After induction, dermal reactions were observed in both groups, whereas no reaction should be observed in the control animals. The control group is therefore doubtful. An explanation is lacking.
Since the control group showed dermal reactions whithout description of the severity, the reactions in the test group cannot be evaluated. Therefore, the results of the skin sensitisation study are inconclusive.
It is not clear why challenges were also performed 50% diluted with water.

B.6.12 Dermal absorption (Annex IIIA 7.3)
No comments.

B.6.13 Toxicological data on non active substances (Annex IIIA 7.4 and point 4 of the introduction)
No comments.

B.6.14 Exposure data (Annex IIIA 7.2)
No comments

B.6.15 References relied on
No comments

DOCUMENTS ON BEFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Fate & Behaviour (ECCO 137)

1. List of end points (not included in Full Report)

Date	Supplier	File name

2. Comments

Date	Supplier	File name
6 March 2003	Denmark	beflubutamid 137 com01 DK
18 March 2003	United Kingdom	beflubutamid 137 com02 UK

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting

Date	Supplier	Content	File name

5. Addenda (not included in Full Report)

Date	Supplier	File name

6. Other Documents (not included in Full Report)

Date	Supplier	File name

Danish Environmental Protection Agency
Danish Ministry of the Environment

ECCO-Team PSD

cc. RMS Germany

Pesticides
In your reply, please refer to File No.
File no. M: 7042-0288
Ref.: cdh/11
7 March 2003

Re: ECCO 137

Danish comments on the draft assessment report on **beflubutamid** prepared by Germany concerning **fate and behaviour**.

Overall comments

This DAR is very well written and presented and we agree to most of the conclusions. We agree to the conclusion regarding groundwater contamination with the metabolite UR-50604 and support that the notifier has to submit a new simulation, not only with the PELMO-FOCUS model but also using PEARL-FOCUS.

We can therefore not support an inclusion of beflubutamid in annex 1, unless safe use have been shown at an acceptable amount of scenarios – regardless of UR-50604's toxicological properties.

Yours sincerely,

Christian Deibjerg Hansen

Contact point e-mail: stm@mst.dk

Danish Environmental Protection Agency · Strandgade 29 · DK-1401 Copenhagen K
Phone +45 32 66 01 00 · Fax +45 32 66 04 79 · Telex 31 209 miljoe dk · CVR 10 05 86 35 · mst@mst.dk · ww.mst.dk/homepage

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool, 3 Peasholme Green, York YO1 7PX
Website: www.pesticides.gov.uk
Switchboard: 01904 640500 GTN: 5138 5840
Direct Dial: 01904 455840 Fax: 01904 455722
International: (+44) 1904 455897 International Fax: (+44) 1904 455722
Email: adrian.parr@psd.defra.gsi.gov.uk

Herbert Köpp
Federal Office for Consumer Protection
and Food Safety (*BVL*)
Brunswick
Germany **by email**

Our ref : ASY 255

Date : 18 March 2003

Dear Herbert

UK COMMENTS ECCO FOR ROUND 14

EC NEW ACTIVE SUBSTANCE : BEFLUBUTAMID
RAPPORTEUR:- GERMANY

ECCO 137 - MEETING TO DISCUSS ENVIRONMENTAL FATE AND BEHAVIOUR

On behalf of the Pesticides Safety Directorate of the United Kingdom Department for Environment, Food and Rural Affairs, please find attached our comments on the monograph for **beflubutamid.** We are submitting these comments for your information as rapporteur and for any discussion at ECCO 137 on 8 - 11 April 2003.

We have no comments to make on **pethoxamid**.

I apologise for the slight delay in sending these comments, due to circumstances beyond my control.

Yours sincerely

Adrian Parr
Approvals Committee Branch

cc: ECCO Team – PSD

The Pesticides Safety Directorate is making no comments other than in those areas outlined below:

The soil extraction methods are not outlined in the following sections of Volume 3 of the Draft Assessment Report:

- Aerobic degradation (B.1.1.1)
- Anaerobic degradation (B.1.1.2)
- Soil photolysis (not numbered, usually B.8.1.2)
- Water/sediment studies (B.8.4.3.2)

It would be useful for the methods used in these studies to be outlined in the evaluation.

DOCUMENTS ON BEFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Residues (ECCO 138)

1. List of end points (not included in Full Report)

Date	Supplier	File name

2. Comments

Date	Supplier	File name
23 April 2003	The Netherlands	beflubutamid 138 com01 NL

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting

Date	Supplier	Content	File name

5. Addenda (not included in Full Report)

Date	Supplier	File name

6. Other Documents (not included in Full Report)

Date	Supplier	File name

To: ECCO-Team PSD
Cc: ECCO-Team BVL
From: CTB
Date: 3 April 2003

Subject: Comments of **the Netherlands** on EU-monograph **beflubutamid**

Residues

General remark
Changes introduced in the endpointlist by Member State The Netherlands (NL) are made by a strike through the old text and new text written as highlighted text.

Volume 1, level 1 – 4
Adjustments should be made according to the comments on the summaries in Volume 3, Annex B.

NL noticed that in level 2 (paragraph 2.4.1) the RMS defines the residue definition for plants and animal commodities as beflubutamid (no metabolites). But in paragraph 2.4.2 the RMS states “residues of beflubutamid and its metabolite UR-50604 in grain and straw could be relevant for consumers or for feeding of domestic animals concerning residues in animal products following feed intake”. The statement in paragraph 2.4.2 infers that metabolite UR-50604 should be included in the residue definition, but the RMS finally does not conclude that it should be.

Appendix 3 Listing of endpoints

Rapporteur Member State	Month and year	Active substance
Germany	August 2002	Beflubutamid

Chapter 2.2 – Methods of Analysis

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Parent compound. GC-PND, LOQ = 0.05 mg/kg (cereal grain) confirmation by GC-ECD. Insufficiently validated. Applicablitiy of multiresidue method required. Results for at least 2 control samples are required and recoveries for at least 5 samples per concentration level (at LOQ and 10x LOQ) are required. Information on matrix effects (slope with/without matrix) and linearity of the calibration model is lacking, see B.5.2.1 When UR-50604 is included in the residue definition full validation is required for this metabolite as well
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	not relevant or required, residue levels in feed uncertain, see B.5.2.2 and B.7.3
Soil (principle of method and LOQ)	
Water (principle of method and LOQ)	
Air (principle of method and LOQ)	
Body fluids and tissues (principle of method and LOQ)	not required

Chapter 2.4 – Residues

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

Plant groups covered	wheat
Rotational crops	carrot, wheat
Plant residue definition for monitoring	beflubutamid or sum of beflubutamid and metabolite UR-50604, see B.7.3
Plant residue definition for risk assessment	beflubutamid or sum of beflubutamid and metabolite UR-50604, see B.7.3
Conversion factor (monitoring to risk assessment)	none

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

Animals covered	lactating goat
Animal residue definition for monitoring	none or sum of beflubutamid and metabolite UR-50604: residue levels in feed uncertain, see B.7.3
Animal residue definition for risk assessment	none or sum of beflubutamid and metabolite UR-50604: residue levels in feed uncertain, see B.7.3
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	yes

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

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

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

Freezer storage stability of beflubutamid and UR-50604 was proven on wheat grain, straw and forage during the course of the residue trials covering the storage conditions of the samples prior to analysis (200 days for grain, straw, forage).

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

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle	no studies required / conducted		
Liver	possibly needed for ruminants, intake level for livestock uncertain, see B.7.3 and B.7.8.		
Kidney			
Fat			
Milk			
Eggs			

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

Crop	Northern or mediterranean region	Trials results relevant to the critical GAP (a) (mg/kg)	Recommendation /comments	MRL (mg/kg)	STMR (b) (mg/kg)
spring barley	N S	4x <0.05 mg/kg grain 4x <0.05 mg/kg grain		~~0.05 mg/kg~~; insufficient data	0
spring wheat	N S	1x <0.05 mg/kg grain 2x <0.05 mg/kg grain		~~0.05 mg/kg~~; insufficient data	0
durum wheat	N	1x <0.05 mg/kg grain		~~0.05 mg/kg~~; insufficient data	0
winter wheat	N S	~~4x <0.05 mg/kg grain~~ 2x<0.01; 2x <0.05 mg/kg grain 2x <0.05 mg/kg grain		~~0.05 mg/kg~~; insufficient data	0
Group (barley, wheat, oats, rye, triticale)	N S N/S	2x <0.01; 8x <0.05 mg/kg grain 8x <0.05 mg/kg grain 2x 0.01; 16x <0.05 mg/kg grain see B. 7.12	Trials selected at treatment stage BBCH 27-30, dose rate 0.242 –0.271 kg ai/ha and PHI = 66-116 days Within 25% limits of critical GAP	0.05 * mg/kg, provisional based on N/S	$STMR_{RAC}$ 0.05* mg/kg, provisional based on N/S

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

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

ADI	0.022 mg/kg bw/d
TMDI (European Diet) (% ADI)	~~0.001 mg/kg bw (4.7 %)~~; should be recalculated, see B.7.15
NEDI (% ADI)	not calculated
Factors included in NEDI	not applicable
ARfD	not assigned
Acute exposure (% ARfD)	not applicable

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)			
Crop/processed crop	Number of studies	Transfer factor	% Transference *
no data generated; not required			

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

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

~~cereals grain;~~ barley, wheat, oats, rye, triticale	0.05* mg/kg; provisional because analytical methods are insufficiently validated (see B.5.2.1) and discrepancy between metabolism data and residue trials has to be clearified (see B.7.6).
~~other food of plant origin~~	~~0.05 mg/kg~~

Volume 3
The residue related items (Annex B5 and Annex B7) were reviewed.

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.7.10 B.5.2.1 Plant material

- NL considers the method presented in B.5.2 insufficiently validated for the parent compound. The following data are needed for full validation:
  a. Based on the results presented an LOQ of 0.05 mg/kg could be possible for cereals, but the LOQ should be further validated by presenting the results of at least 2 control samples (should be below 0.3x LOQ).
  b. Recovery and precision results are required for at least 5 samples per concentration level (at LOQ and 10x LOQ level).
  c. Information on matrix effects (slope with/without matrix) is needed.
  d. Information on the linearity of the calibration models is needed.
  e. Further implementation in a Multi-Residue Method was not investigated.
  Results from supervised residue trials have to be considered provisional, until the method used in these trials is considered as sufficiently validated.
- Information is only available on dry crops (cereals: green plant, mature grains, straw). No other matrices were investigated. This is acceptable because the intended use is on cereals only.
- At the moment the residue definition for plant products is uncertain (see B.7.3). When metabolite UR-50604 is included in the residue definition, than full validation is required for metabolite UR-50604 as well.

B.7.11 B.5.2.2 Foodstuff of animal origin

At the moment it is uncertain if an enforcement method for animal commodities is needed. Cereals (forage, grain, straw, processed products) are fed to livestock, but residue levels are uncertain (see B.7.3).

B.5.4 Analytical methods (residue) for body fluids and tissues (Annex IIA 4.2.4; Annex IIIA 5.2)

No comments.

B.5.5 Evaluation and assessment

Comments from previous chapters have to be included in this chapter.

B.5.6 References relied on

No comments.

B.7 Residue data

B.7.1 Metabolism, distribution and expression of residues in plants (Annex IIA 6.1 and Annex IIIA 8.1)

Only one crop group (cereals) was investigated. This is acceptable, because beflubutamid is intended for use on cereals only.

B.7.2 Metabolism, distribution and expression of residues in livestock (Annex IIA 6.2 and Annex IIIA 8.1)

No comments

B.7.3 Definition of the residue (Annex IIA 6.7; Annex IIIA 8.6)

NL disagrees with the proposed definition of the residue in plants:
Based on a metabolism study in wheat, the residue definition for plant products for enforcement and for dietary risk assessment should be the sum of beflubutamid and metabolite UR-50604. Although beflubutamid can be assigned as marker molecule for straw, this is not the case for grains and husks. Here metabolite UR-50604 together with an unidentified compound U1 comprises the main part of the residue. Compound U1 is not taken up in the residue definition because it is a polar, water soluble compound, which is not readily hydrolysed by enzymes or degraded by strong acid and base treatments or derivatised to a more mobile residue. In this case an enforcement method for both parent and metabolite UR-50604 in plant products is needed.

NL disagrees with the proposed definition of the residue in animal commodities:
Based on the metabolism study in goat, the residue definition for animal commodities for enforcement and for dietary risk assessment should be the sum of beflubutamid and metabolite UR-50604. Although beflubutamid can be assigned as marker molecule for milk and fat, this is not the case for liver and kidney, where metabolite UR-50604 comprises a major part of the residue. In this case an enforcement method for parent and metabolite UR-50604 in animal commodities is needed.

At the moment it is uncertain if a residue definition for animal commodities is needed:
Cereals (forage, grain, straw, flour, cereal remainders after beer production or grain milling) are fed to livestock, but residue levels are uncertain. Based on trials, residues in grain and straw are <0.05 mg/kg, but residues in forage are much higher. Residue levels in cereal forage are unclear as no PHI is stated in the use pattern (see B.7.4). Cereal forage is fed to livestock, but information on dietary feeding levels is not given in the feeding table in the Lundehn document (appendix G). Although cereal forage is the same crop type as grass, cereal forage intake is much lower than grass intake and feeding levels for grass may not be used for feeding levels of cereal forage. Assuming intake levels as for straws, percentage dry matter as for grass, and a residue level of 0.29 mg/kg (from residue trials at 27-28 days after last application), intake levels are 0.29 mg/kg in dry weight feed for dairy cattle and 0.73 mg/kg in dry weight feed for beef cattle (see table below). These intake levels exceed the trigger values of 0.1 mg/kg in dry weight feed and therefore a residue definition and an enforcement method for animal commodities is needed.

But formally cereal forage is not stated in the European feeding table and therefore forage can be omitted from the intake calculation. In that case no residue definition and no enforcement method is needed, as intake from straw and grains is below the trigger value of 0.1 mg/kg in dry weight feed.

An appeal is made to ECCO to update the feeding table for livestock, as there are more feeding crops that are not addressed in this table (carrots, Jerusalem artichokes, roots from witloof; processed fractions of sugar beets & industrial chicory & cereals, remainders of

mushrooms & potatoes & oilseeds). In ECCO a discussion is needed about dealing with feeds that are not listed in this table.

Maximum dietary burden for livestock

Group	I	Total residue intake	Total residue intake
		mg/kg bw/day	mg/kgdm in feed
Dairy cattle			
Product	cereal forage	-	-
% dry matter of product	20	-	-
% product in dry weight diet	20	-	-
Intake fresh product (kg/animal/day)	20.00	-	-
Residue in fresh product (mg/kg)	0.29	-	-
Residue intake (mg/animal/day)	5.80	0.01	0.29
Beef cattle			
Product	cereal forage	-	-
% dry matter of product	20	-	-
% product in dry weight diet	50	-	-
Intake fresh product (kg/animal/day)	37.50	-	-
Residue in fresh product (mg/kg)	0.29	-	-
Residue intake (mg/animal/day)	10.88	0.03	0.73

B.7.4 Use pattern

To NL it is not clear if cereal forage is excluded from feeding. In the use pattern, no PHI is stated. So if cereal forage is used as feed for livestock, no restrictions for use are given and the possibility exists that cereal forage is taken immediately after application (resulting in very high residues).

B.7.5 Identification of critical GAPs

No comments.

B.7.6 Residues resulting from supervised trials (Annex IIA 6.3; Annex IIIA 8.2)

To NL it is not clear why the parent concentration in straw in the residue trials (<0.05 mg/kg at 62-116 days after treatment) is much lower than the parent concentration in straw in the metabolism study (0.25-0.35 mg/kg at 105 days after treatment). Application time and dose rate seem the same.

- If the growing condition (netted area versus open field) is the only reason for this difference, than the results from residue trials are considered plausible and no further actions have to be undertaken. Growing conditions are only summarized for the pilot metabolism study (netted area outside) but not for the final metabolism study. Residue trials are conducted in the open field.
- If the extraction conditions are the reason for this difference, than the extraction efficiency of the extraction solvent used in the supervised residue trials has to be verified using radiolabeled incurred residues. Extraction solvent for the metabolism study was not summarized, extraction solvent for supervised residue trials was methanol/water (9:1).

Results from supervised residue trials are considered provisional until a plausible explanation is given for the residue difference between metabolism study and supervised residue trials.

B.7.7 Effects of industrial processing and/or household preparation (Annex IIA 6.5; Annex IIIA 8.4)

No comments.

B.7.8 Livestock feeding studies (Annex IIA 6.4; Annex IIIA 8.3)

The necessity for feeding studies awaits the outcome of the discussion on feeds that are not listed in the European feeding table(see B.7.3). When only straw and grains are considered, than no feeding studies are needed. When forage is included in the feed intake calculation, than feeding studies for ruminants are needed.

B.7.9 Residues in succeeding or rotational crops (Annex IIA 6.6; Annex III 8.5)

No comments.

B.7.10 Proposed pre-harvest intervals for envisaged uses, or withholding periods, in the case of post-harvest uses (Annex IIA 6.8; Annex IIIA 8.7)

If cereal forage has to considered (see B.7.3), than a PHI has to be established for cereal forage.

B.7.11 Community MRLs and MRLs in EU Member States (Annex IIIA 12.2)

No comments.

B.7.12 Proposed EU MRLs and justification for the acceptability of those MRLs (Annex IIA 6.7; Annex IIIA 8.6)

The RMS did not underline the selected residue values, but based on the 18 values in the endpointlist NL assumes that alle values for grain have been selected.

RMS derived MRLs for winter wheat, spring wheat, durum wheat, and spring barley. Wheat and barley are major crops in both Northern and Southern Europe. In order to establish MRLs 8 trials have to be available for each of the European regions. As this is not the case for the individual crops, MRLs for individual crops cannot be derived.

In stead NL proposes to derive a group MRL for barley, oats, rye, triticale and wheat from the results of barley and wheat (maize, millet, sorghum, immature wheat, immature spelt and rice are excluded explicitly). Proposed MRLs remain provisional until the methods used in the residue trials are properly validated (see B.5.2.1). Further the discrepancies between the metabolism study and the residue trials have to be clearified (see B.7.6) and a final decision on the residue definition has to be made. The decision on the residue definition does not change the proposed MRL.

B.7.13 Proposed EU Import tolerances and justification for the acceptability of those residues

No comments.

B.7.14 Basis for differences, if any, in conclusions reached having regard to established or proposed CAC MRLs

No comments.

B.7.15 Estimates of potential and actual dietary exposure through diet and other means (Annex IIA 6.9; Annex IIIA 8.8)

RMS estimated the TMDI (European WHO diet) and the NTMDI (German diet for 4-6 year old child) using all possible plant products set at a residue level of 0.05 mg/kg. For risk assessment, only the MRLs derived directly or indirectly (through livestock feed) from the crops intended for use have to be used. The %ADI value will therefore be lower than stated by the RMS.
Further in the German model it seems odd to calculate the intake for wine grapes, tea, hops and coffee for a 36-50 year old woman, where only use on cereals is intended.

NL proposes a group MRL for barley, wheat, oats, rye and triticale. When the MRLs for these products are set at 0.05 mg/kg, than residue intake for the European WHO/FAO diet is 10.1 µg/person/day, corresponding to 0.8% of the ADI.
The German model is not in the possession of NL and could therefore not be evaluated.

The RMS does not give any statement on the acute risk for consumers. A statement has to be given if an Acute Reference Dose is needed, and if so what is the acute risk for the consumer?

B.7.16 Summary and evaluation of residue behaviour (Annex IIA 6.10; Annex IIIA 8.9)
Comments from previous chapters have to be included in this chapter.

B.7.17 References relied on
No comments

DOCUMENTS ON BEFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Ecotoxicology (ECCO 139)

1. List of end points (not included in Full Report)

Date	Supplier	File name

2. Comments

Date	Supplier	File name
23 April 2003	France	beflubutamid 139 com01 FR
6 May 2003	Sweden	beflubutamid 139 com02 SE
6 May 2003	Denmark	beflubutamid 139 com03 DK
28 April 2003	The Netherlands	beflubutamid 139 com04 NL
8 May 2003	United Kingdom	beflubutamid 139 com05 UK
27 May 2003	Belgium	beflubutamid 139 com06 BE

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting

Date	Supplier	Content	File name

5. Addenda (not included in Full Report)

Date	Supplier	File name

6. Other Documents (not included in Full Report)

Date	Supplier	File name

MINISTERE de l'EDUCATION NATIONALE et de la RECHERCHE et de la TECHNOLOGIE
MINISTERE de l'AGRICULTURE et de la PÊCHE

DGAL

S. S. M.
STRUCTURE SCIENTIFIQUE MIXTE

Date: 20/03/03

Competent Authority :
Sylvie Malezieux
Ministère de l'Agriculture et de la Pêche
Direction Générale de l'Alimentation
251, rue de Vaugirard
75732 - PARIS Cedex 15
Tel: 33 1 49 55 81 85 FAX 33 1 49 55 49 59
e.mail : sylvie.malezieux@agriculture.gouv.fr

From
Annick Venant
INRA – GMPV – Route de Saint-Cyr – F 78026
Versailles Cedex
Tel: 33 1 30 83 32 91 FAX 33 1 30 83 31 49
e.mail : venant@versailles.inra.fr

To **Ecco team (BBA)**
e.mail : ecco@bba.de

cc **Rapporteur member state : Germany**
e.mail : h.koepp@bba.de

Objet : comments from France on draft monograph on BEFLUBUTAMIDE

Dear Colleagues,

Please find attached our comments on the " Ecotoxicology " section of the draft Assessment Report for the new active substance BEFLUBUTAMIDE.

Yours sincerely,

Annick Venant
P/L'Ingénieur d'Agronomie
Sylvie Malézieux

EU Review program on active substances in Plant Protection Products

Comments of France on BEFLUBUTAMID draft monograph

Section : Ecotoxicology

The section (volume 3) and the related summary in the volume 1, level 2 is clearly presented. France has no additional comment or request as regards this section.

KEMI
KEMIKALIEINSPEKTIONEN
NATIONAL CHEMICALS INSPECTORATE

Pesticides Division
☎ 08-783 11 00
e-post: kemi@kemi.se

Diarienummer

2003-05-06

F-2043-371-00

RMS: DE, Herbert Köpp, BBA
(h.koepp@bba.de)
cc. ECCO-TEAM (PSD)
(ecco@psd.defra.gsi.gov.uk)

Swedish Comments to ECCO 139 on Ecotoxicology of beflubutamide.

In general, the ecotoxicology section of the monograph was well prepared, and we generally support the conclusions drawn by the rapporteur. However, we have some comments on the assessment of the risk assessment for birds and mammals and for earthworms, and on the assessment of the relevance of a soil metabolite suspected to leach to groundwater.

Birds and mammals
No corrections were made for dry to wet weight of the feed intake ratio. The long term assessment was based on dietary NOEC instead of daily dose, and therefore the different feed intake between laboratory animals and animals in the field is not taken into account (see Guidance document for Birds and Mammals). We also note that one of the representative species reported in Annex B, the herbivorous mammal, is not included in the list of endpoints.

Earthworms
In the long term study on the parent compound, no NOEC could be established since significant effects were seen at the lowest treatment level (0.255 kg as/ha). The long term TER was determined to be <0.5, indicating unacceptable risk. Besides, in the available short term studies, the metabolite UR-50604 was more toxic than the parent compound. We feel that the risk for long term effects to earthworms needs to be further addressed.

Relevance of metabolite suspected to leach to groundwater
Due to the observed higher toxicity of UR-50604 than the parent compound to earthworms, the relevance of this metabolite in groundwater needs to be further addressed.

Postadress *Postal address*	*Besöksadress* *Office address*	*Telefon* *Telephone*	*Telefax*	*Postgiro*
Box 1384 S-171 27 Solna	Sundbybergsvägen 9	Nat 08 783 11 00 Int 468 783 11 00	Nat 08 735 76 98 Int 468 735 76 98	4465054-7

Danish Environmental Protection Agency
Danish Ministry of the Environment

ECCO-Team PSD

cc. RMS

Pesticides
In your reply, please refer to File No.
File no. M: 7042-0288
Ref.: cdh/11
1 May 2003

Re: ECCO 139

Danish comments on the draft assessment report on **beflubuthamid** prepared by Germany concerning **ecotoxicology**.

Overall comments

This DAR is very well written and presented and we agree to most of the conclusions. However we believe that there still are some studies concerning the metabolite UR 50604, which should be submitted.

The water / sediment study showed that the metabolite UR 50604 occur in the water as well in the sediment phase. Since the degradation time in water is aprox. 65 days we believe that a long-term fish and daphnia study should be submitted. Furthermore should a sediment dwelling study, be submitted as well.

We can therefore not support an inclusion of beflubutamid in annex 1, unless these studies have been submitted and evaluated.

Yours sincerely,

Christian Deibjerg Hansen

Contact point e-mail: stm@mst.dk

Danish Environmental Protection Agency · Strandgade 29 · DK-1401 Copenhagen K
Phone +45 32 66 01 00 · Fax +45 32 66 04 79 · Telex 31 209 miljoe dk · CVR 10 05 86 35 · mst@mst.dk · ww.mst.dk/homepage

Board for the authorisation of pesticides, Stadsbrink 5, NL-6707 AA, Wageningen, P.O. Box 217, phone +31 317 471810, Fax +31 317 471899

To: ECCO-Team BBA en RMS DE
From: CTB
Date: 24 april 2003

Subject: Comments of the Netherlands on monograph beflubutamid ecotoxicology

Volume 1, Level 2

2.6.1 Effects on terrestrial vertebrates
Report LC50 and NOEC also as daily dose as this is the end point to be used in the risk assessment.
Since only toxicity results for aquatic organisms are considered here it is better to state that the metabolite UR 50604 is not of ecological relevance with respect to aquatic organisms.

2.6.3.2 Effects on other arthropod species, p.34
Please mention the trigger of 30% in table 2.6-1.
Based on effects >30% higher tier studies are needed for T. pyri (31% on mortality, corrected for control level?) and A. rhopalosiphi (44% on fecundity, corrected for control level?).

2.6.4 Effects on earthworms and other soil macro-organisms, p. 35
The results of the reproducction toxicty tests are not consistent. It might be necessary to perform a new test.

Volume 1, level 3

No comments.

Volume 1, level 4

Ecotoxicology
Based on effects >30% higher tier studies are needed for T. pyri (31% on mortality, corrected for control level?) and A. rhopalosiphi (44% on fecundity, corrected for control level?).
The results of the reproducction toxicty tests with earthworms are not consistent. It might be necessary to perform a new test.

List of end points

Effects on terrestrial vertebrates
LC50 and NOEC for birds should also be reported as daily dose.

Toxicity exposure ratios for terrestrial vertebrates
Risk assessment for birds and mammals should be based on LC50 and NOEC converted to a daily dose.

Toxicity data for aquatic species, p. 83
NOEC of 0,56 mg/L for development of Chironmus riparius is not mentioned.

Bioconcentration, p.83
Based on the study under B.9.2.1.9 a CT50 < 1 day can be concluded.

Volume 3

General
Summaries are very short compared to the fate and behaviour section. It is not possible to judge the studies based on the information given. Presenting some basic data in tables as was done in the fate and behaviour section gives a much better insight in the study.
Summaries are not consistent with regard to reporting the purity of the technical substance.

Board for the authorisation of pesticides, Stadsbrink 5, NL-6707 AA, Wageningen, P.O. Box 217, phone +31 317 471810, Fax +31 317 471899

B.9.1 Effects on birds

B.9.1.2 Dieatary toxicity, p. 283
LC50 should also be calculated and reported as daily dose according to the guidance in SANCO/4145/2000 (Guidance document on risk assessment for birds and mammals).

B.9.1.3 Effects on reproduction, p. 284
NOEC should also be calculated and reported as daily dose according to the guidance in SANCO/4145/2000.

B.9.1.5 Risk assessment for birds, p.285
toelichting op het hanteren van dagelijkse dosis in de risicobeoordeling

B.9.2 Effects on aquatic organisms

B.9.2.1.1 Fish acute toxicity, bluegill sunfish, P.286
The 3 highest concentration levels are above water solubility according to the list of end points (3,2 mg/L). Measured concentrations show that low solubility plays a role and this should be carefully considered. It is not clear from the summary whether homogenity of the test media was proven. If not, the end point should be recalculated with the worst case assumption that exposure can not be higher than water solubility.

B.9.2.1.1 Fish acute toxicity, rainbow trout, p. 286
The highest concentrations are above water solubility according to the list of end points (3,2 mg/L). Measured concentrations show that low solubility of the test substance plays a role in the experiment and this should be carefully considered. It is not clear from the summary if homogenity of the test media was proven. If not, the end point should be recalculated with the worst case assumption that exposure can not be higher than water solubiltity. Water solubility will be even less at the lower temperature used for tests with rainbow trout.

B.9.2.1.3 Invertebrates - acute toxicity, p. 288
The highest concentrations are above water solubility according to the list of end points (3,2 mg/L). Measured concentrations show that low solubility of the test substance plays a role in the experiment and this should be carefully considered. It is not clear from the summary if homogenity of the test media was proven. If not, the end point should be recalculated with the worst case assumption that exposure can not be higher than water solubiltity.

B.9.2.1.5 Sediment dwellers, p. 290
The highest test concentration is above water solubility according to the list of end points (3,2 mg/L). Measured concentrations show that low solubility of the test substance plays a role in the experiment and this should be carefully considered. It is not clear from the summary if homogenity of the test media was proven. If not, the end point should be recalculated with the worst case assumption that exposure can not be higher than water solubiltity.

B.9.2.1.6 Algae, Anabaena flos aquae, p. 291
It is not clear from the summary if homogenity of the test media was proven. If not, the end point should be recalculated with the worst case assumption that exposure can not be higher than water solubiltity.

B.9.2.2 Evaluation of toxicity results and data on bioaccumulation
In this section toxicity results with aquatic organisms are considered. Therefore it is better to state here that the metabolite UR-50604 is not of ecological relevance with respect to aquatic organisms.
It is better to state that the bioaccumulation potential is acceptable based on an assessment in line with the guidance document.

B.9.3 Effects on other terrestrial vertebrates

B.9.3.2 Risk assessment for mammals, p.296
toelichting op het hanteren van dagelijkse dosis in de risicobeoordeling

Board for the authorisation of pesticides, Stadsbrink 5, NL-6707 AA, Wageningen, P.O. Box 217, phone +31 317 471810, Fax +31 317 471899

B.9.4 Effects on bees

B.9.4.1.1 Acute oral and contact toxicity of beflubutamid, p. 297
It is preferable to report the end points as the actual measured dose and not the nominal dose.

B.9.4.1.2 Acute oral and contact toxicity of formulated beflubutamid, p. 297
It is preferable to report the end points as the actual measured dose and not the nominal dose.

B.9.5 Effects on other artropod species, p. 299
Summaries are very short and do not give insight in end points in the control and **reproduceerbaarheid**. It is unclear whether the reported end points are corrected for the control level.

B.9.5.2.2 Risk assessment, p. 305
It would be much more clear if the results are presented as a table as in the list of end points. Based on effects >30% higher tier studies are needed for T. pyri (31% on mortality, corrected for control level?) and A. rhopalosiphi (44% on fecundity, corrected for control level?).

B.9.6 Effects on earthworms

B.9.6.2 Other studies, p. 307
There is no clear dose respons relation in the first reproduction toxicity study and one should ask oneself if the effects can be atributed to the test substance. The same holds true for the second reproduction toxicity study. For the test with the formulation it is unclear how a clear dose respons relation for effects on juvenile numbers does not result in significant effects. If this is the results of high variability in the control it should be discussed whether the test is valid.

B.9.8 Effects on soil micro-organisms

B.9.8.1 Nitrogen conversion, p. 310
Please report the results of the study with the active substance and the metabolite seperately to avoid confusion. It is not clear from the summaries if the tests are valid with regard to the difference between both controls (<15%). Does the effect in table B.9.8-1 refer to absolute levels compared to the control or nitrogen turnover rate compared to the control. In the OECD 216 guideline the latter is the preferred parameter since it is more relevant for the effects on the process.

B.9.8.2 Carbon conversion, p. 311
Please report the results of the study with the active substance and the metabolite seperately to avoid confusion. It is not clear from the summaries if the tests are valid with regard to the difference between both controls (<15%). Does the effect in table B.9.8-2 refer to absolute levels compared to the control or carbon conversion rate compared to the control. In the OECD 216 guideline the latter is the preferred parameter since it is more relevant for the effects on the process.

PESTICIDES SAFETY DIRECTORATE
Mallard House, Kings Pool, 3 Peasholme Green, York YO1 7PX
Website: www.pesticides.gov.uk
Switchboard: 01904 640500 GTN: 5138 5840
Direct Dial: 01904 455840 Fax: 01904 455722
International: (+44) 1904 455897 International Fax: (+44) 1904 455722
Email: adrian.parr@psd.defra.gsi.gov.uk

Herbert Köpp
Federal Office for Consumer Protection
and Food Safety (*BVL*)
Brunswick
Germany **by email**

Our ref : ASY 255

Date : 8 May 2003

Dear Herbert

UK COMMENTS ECCO FOR ROUND 14

EC NEW ACTIVE SUBSTANCE : BEFLUBUTAMID
RAPPORTEUR:- GERMANY

ECCO 139 - MEETING TO DISCUSS ECOTOXICOLOGY

On behalf of the Pesticides Safety Directorate of the United Kingdom Department for Environment, Food and Rural Affairs, please find attached our comments on the monograph for **beflubutamid.** We are submitting these comments for your information as rapporteur and for any discussion at ECCO 139 on 3 – 6 June 2003.

Yours sincerely

Adrian Parr
Approvals Committee Branch

cc: ECCO Team – PSD

The Pesticides Safety Directorate is making no comments other than in those areas outlined below:

Beflubutamid

End point Tables

We consider that a number of amendments are required to the endpoint tables. We also consider that a more detailed explanation is required of the proposed acceptability of risk to non-target arthropods and earthworms. Details are as follows:

Effects on terrestrial vertebrates

In the endpoint table, please amend reference to 'insectivorous mammal' (in relation to acute and long-term risk) to 'herbivorous mammal'. Also in line with values included in Vol. 3, please amend the long-term TER for herbivorous mammals from '114' to '7'.

Effects on aquatic organisms

In the toxicity data endpoint table, we consider that reference under the endpoint column to 'Fronds' should ideally be clarified to 'Fronds EC50' with the toxicity endpoint amended from '0.02' to '0.029' mg a.s./l. We agree given the effects on aquatic algae that a 10 metre buffer zone is required. In the fish bioconcentration endpoint table we recommend that based on details given in Vol. 3, a CT90 value of <1 day should be included. It is noted that although this endpoint table states the level of residues in fish after the 14 day depuration phase as < 5%, no details for this is given in the very brief summary of the bioconcentration study included in Vol. 3.

Effects on bees

In the endpoint table the HQ value is stated as 1.275. Based on details included in Vol3 we consider this should be amended to 2.55.

Effects on other arthropod species

It is noted from the endpoint table and also from details included in Vol. 3, that in a lab test with *T. pyri* a mortality level of 31% was obtained and in a lab test with *Aphidius rhopalosiphi* fecundity was reduced by 44%. Both of these affects are in breach of the Annex VI trigger of 30%. However no explanation has been included as to why this is regarded as acceptable.

Effects on earthworms

Details in Vol. 3 indicate a long-term TERs to earthworms from exposure to the formulation ASU 95510H of <0.5 or 1.0, depending on which of the two conducted studies with this formulation are used. Given that the <0.5

estimate is the worst case we consider that this value should be included in the endpoint table (TER currently stated as 1).

It is noted that the long-term earthworm TER for both the beflubutamid formulations ‘ASU 92 530 H’ and ‘ASU 95 510 H’ are < 0.5 and are therefore in breach of the Annex VI trigger of 5. However it is explained in Vol. 3 that given the relatively low mortality levels of 20-30 % in the lab trials the risk to earthworms will be acceptable. It may be useful to give a fuller explanation as to why higher tier earthworm field trials are not required (as stated in Annex VI) and as to why under field conditions no long-term effects on earthworm populations would be expected. Such an explanation could include consideration of numbers of applications per year and of soil persistence.

From: Hofkens Sofie [Sofie.Hofkens@health.fgov.be]
Sent: 26 May 2003 14:29
To: 'h.koepp@bba.de'; ECCO (PSD) (E.C.C.O. Account); 'ecco@bba.de'
Cc: Fontier Herman; Hucorne Pierre
Subject: beflubutamide

Dear all,

Hereby the Belgian comments on the DAR on beflubuthamid concerning ecotoxicology:

1. Birds

As the log Pow exceeds 3, the risk for birds feeding on contaminated earthworms & fish should be assessed.

2. Mammals

If the long term risk for small herbivorous mammals is recalculated according to the latest guideline on birds and mammals, the risk is not acceptable. Risk refinement seems appropriate.

3. Earthworms

We have still some concerns with regard to the long-term earthworm toxicity. We do agree that effects up to 30 % could be due to biological variation with regard to field tests. In this case we are dealing with standardized laboratory test in which effects around 30 %, in our opinion, could be relevant. If we look at the test with Herbaflex on p 318 of the DAR : 5 dose levels were tested with 4 repetitions each. This is, according to the guideline, the minimum to establish a NOEC. Accordingly this NOEC of 6 L/ha seems the most appropriate to us. The resulting TER equals 1. With TER-values this low it is appropriate to evaluate the product in the field. Certainly because the DT90f is often above 100 days.

As the log Pow > 3, bio-accumulation in earthworms should be discussed.

7. Other soil non-target organisms

As the DT90f exceeds 100 days and effects on reproduction of earthworms are observed : a test on collembola or a litter bag study should be envisaged.

Kind regards,

Sofie Hofkens

ir. S. Hofkens
Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu
DG Dier, Plant en Voeding
Arkadengebouw 5de verdieping
1010 BRUSSEL
Tel 02/210 50 87
Fax 02/210 51 15
www.fytoweb.fgov.be

Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement
DG Animaux, Végétaux et Alimentation
Quartier Arcades - 5ème étage
1010   BRUXELLES
tél 02/210.50.87
fax 02/210.51.15
www.phytoweb.fgov.be

DOCUMENTS ON BEFLUBUTAMID DRAFT ASSESSMENT REPORT

Section: Overview Meeting (PSD 140)

1. List of end points (not included in Full Report)

Date	Supplier	File name
August 2003	RMS/Germany	beflubutamid_140_2endpoints_Aug03

2. Comments

Date	Supplier	File name

3. Comments received but not discussed (because deadline of submission was not met)

Date	Supplier	File name

4. Documents tabled at the meeting (not included in Full Report)

Date	Supplier	Content	File name

5. Addenda and Evaluation Table (not included in Full Report)

Date	Supplier	File name
August 2003	RMS/Germany	beflubutamid_140_3eval_table_0-1_Aug03

ANNEX 2 TO CONCISE OUTLINE REPORT OF ECCO 140 PEER REVIEW MEETING

Specific comments from the **Overview Meeting** on the active substances are listed below. The conclusions of the meeting were as follows:

BEFLUBUTAMID

Rapporteur Member State: Germany

1a. Comments received and discussed:

Date	Supplier	File Name

1b. Comments received but not discussed (because deadline of submission was not met):

Date	Supplier	File Name

1c. Documents tabled at the meeting:

Date	Supplier	Content	File Name

1d. Addenda:

Date	Supplier	File Name

1e. Miscellaneous:

Date	Supplier	Content	File Name

1 Physical and chemical properties, Methods of analysis section

- A revised technical specification will be submitted before the end of 2003. These data are considered essential for Annex I inclusion.

- Concerns were raised over whether it is acceptable for Annex I inclusion to be given to an active substance for which only 50% of the technical material has herbicidal activity. The RMS were asked to consider whether this is acceptable or whether a data requirement should be set for the use of the whole of the active isomer in the technical material.

- The data requirement for the confirmatory method for metabolite UR-50604 was confirmed as still being required. The Commission suggested that if the method can be developed quickly it could be considered prior to any Annex I inclusion for the active substance. If this were not possible, the data would need to be considered at the MS level.

2 Environmental fate and behaviour section

- The majority of data requirements and open points in this area still need to be addressed.

- The RMS informed the meeting that the data and FOCUS modelling provided to demonstrate that the metabolite UR 50604 will not exceed 0.1µg/l in groundwater were not acceptable as the parameters used were not sufficiently 'worst-case'. Additional data will be submitted by the end of 2003 with the RMS to perform further modelling based on these data. The applicant informed the meeting that they had started a lysimeter study but the RMS indicated that this study is not representative of the EU as a whole and so will not be acceptable. This data requirement needs to be addressed prior to Annex I inclusion.

- It was noted that if long-term studies are requested because of higher persistence of the metabolite then this should be reflected in the modelling.

3 Ecotoxicology section

- The applicant proposed to provide a Collembola test to address the long-term risk to earthworms but the meeting considered that this test would be insufficient to address the long-term risk to earthworms. The meeting considered that the applicant should perform a field test and not further reproductive tests and the Commission confirmed that this would be the only way to address this requirement. The applicant was asked to discuss with the RMS what is required. These data are considered essential for Annex I inclusion.

- Data are still required to address the risk to non-target flora and fauna. This was converted into a data requirement by the meeting with the data considered essential for Annex I inclusion.

4 Mammalian toxicology section

- The RMS confirmed that comments had been received from the applicant on the mechanism of tumour induction and that an addendum to the DAR was being prepared. It was concluded that this data requirement needed to be addressed for Annex I inclusion.

- The meeting discussed why no Acute Reference Dose had been set for the active substance. The ECCO Chair confirmed that this issue had been discussed at the specialist ECCO meeting and that the overall mammalian toxicology profile had indicated that no Acute Reference Dose was required.

5 Residues section

- All data requirements and open points have been fulfilled.

6 Recommendations

Within one week, the applicant should provide an estimate as to when the data will be available to address the outstanding data requirements. It is likely that no further progress on the Annex I inclusion of the active substance will be achieved until late 2004.

Appendix 1: Revised evaluation table rev. 0-3 (including complete list of data requirements):

beflubutamid

Classification criteria for data requirements were discussed at the meeting. The group agreed on having three criteria:

- Data requirements essential for unconditional Annex I inclusion;
- Data requirements to be dealt with at Member State level; and
- Data requirements fulfilled.

Appendix 2: Complete list of end points: beflubutamid

Appendix 3: List of studies which were submitted during the evaluation process and were not cited in the draft assessment report: beflubutamid

Appendix 4: Suggested classification and labelling: beflubutamid

Evaluation table Beflubutamid (Hb)

WORKING DOCUMENT – DOES NOT NECESSARILY REPRESENT THE VIEWS OF THE COMMISSION SERVICES

1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
				Section 1 Data requirements: 5 Open points: 1
1.1	A better technical specification which is reflected by the batch analysis data is required or justification for the proposed specification given levels of impurities found in the batches. (IIA 1.11) **A**	01.07.2003 A new specification will be provided and submitted by the end of 2003 taken into account the statistical method of FAO & WHO Spec (2002).	04.08.03 Acceptable, technical specification will be checked after submission.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. The data will be available by the end of 2003.
1.2	A revised technical specification is required when full scale production has started. (IIA 1.11) **A**	01.07.2003 In 1997 and 2000, full scale production has already been started at the three locations as specified in the dossier (UBE, Miteni, Syncia). A revised technical specification taken into account all three of these plants will be provided by end of 2003 (see above).	04.08.03 Acceptable (see 1.1)	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. Dependent on outcome of data requirement 1.1.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
5/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
1.3	The applicant must address biological activity of both isomers **A**	01.07.2003 Only S-isomer has the herbicidal activity. The applicant will submit the report to RMS by the end of 2003.	04.08.03 Acceptable, study will be evaluated after submission.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. RMS to consider whether it is acceptable without justification to approve a compound that is only 50 % or less active material.
	Open point 1.1: RMS to clarify the levels of the fortifications used in the batch analysis			Overview Meeting (16.09.2003): Open point still open.
	Open point 1.2: If applicant provides new batch analysis data from full scale production before Annex I listing, then these will be considered by RMS, otherwise this will need to be dealt with at MS level	01.07.2003 There is an misunderstanding between applicant and RMS: New batch analysis will not be necessary, since full scale production already started at three locations in 1997, 2000 and 2000, respectively. (see above)	04.08.03 Acceptable (see 1.1)	Overview Meeting (16.09.2003): Open point fulfilled. This open point was turned into a data requirement.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
1.7	Applicant to provide new batch analysis data from full scale production. (IIA 1.11) **A** (This data requirement was inserted during the Overview Meeting)			Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
7/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Message 1.1 from ECCO 135 (Phs chem) to ECCO 140 (Overview): Meeting agreed that the Volume C confidential info causes a number of problems for many MS, the suggestions were made to use codes for the impurities and maybe include a key in the Volume C, but this will still cause problems, because the methods have to be considered in conjunction with the tech spec which is only in Volume c . One MS suggested that a summary of the info in Volume C could go in Volume B.			Overview Meeting (16.09.2003): Fulfilled

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
8/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point 1.3: RMS to confirm whether the method of analysis for water had been validated for surface water as only distilled water and HPLC water had been used for the validation.	01.07.2003 The method of analysis had also been validated for surface and ground water.	30.07.03 The method has also been validated for surface and groundwater.	Overview Meeting (16.09.2003): Open point fulfilled.
1.4	The applicant must address the water solubility by the appropriate method	01.07.2003 The column elution method could not be used for such compound as UR-50601 which was found to absorb onto the column elution apparatus (transfer tubing). Repeatability for the water solubility of UR-50601 was actually 6.1 %, 1.7 % and 0.8 %, (10, 20 and 30 degree tests respectively) in the shake-flask method, falling well within required repeatability criteria (15 %).	04.08.03 Acceptable	Overview Meeting (16.09.2003): Data requirement fulfilled. RMS to amend the list of end points.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	~~Open point (1.5) to note for~~ Message 1.2 from ECCO 135 (Phys Chem) to ECCO 137 (Fate): Are there concerns for the difference in the results and do they accept the modelling method. **Answer from ECCO 137 (Fate):** ECCO 137 did not have details of the model used, so could not comment on its acceptability, but agreed that the Henry's Law Constant should be recalculated if the water solubility value that was still to be finalised, subsequently differed.	Nothing to be commented by the applicant.		Overview Meeting (16.09.2003): Fulfilled
	Open point ~~(1.6)~~ 1.4: RMS to include the temperature in the monograph	Nothing to be commented by the applicant.	04.08.03 The monograph will not be updated, the endpoints are updated.	Overview Meeting (16.09.2003): Open point fulfilled.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point ~~1.7~~ 1.5: RMS to amend the typographical error (emulsifiability to read suspensibility)	Nothing to be commented by the applicant	04.08.03 The DAR will not be updated.	Overview Meeting (16.09.2003): Open point still open. The meeting agreed that the DAR should not be updated. Nevertheless, the error needs to be noted somewhere and needs to be corrected.
1.6	Applicant must assess the applicability of multi residue methods for analysis of plant residue A	07.07.2003 Multi-residue method (S19) will be provided by 31.12.2003	30.07.03 Will be evaluated when available.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.
	Open point ~~(1.8)~~ 1.6 : RMS to amend end point sheets for methods in line with the appropriate residue definition		30.07.03 List of endpoints amended for soil.	Overview Meeting (16.09.2003): Open point fulfilled.
	Message 1.3 from ECCO 135 (Phys Chem) to ECCO 138 (Residues): if MRLs are set for animal products, then further			Overview Meeting (16.09.2003): Fulfilled No MRL are needed for animals

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
11/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	methods of analysis will be required			
	Message 1.4 from ECCO 135 (Phys Chem) to ECCO 137 (Fate): If it is concluded that residue definition for soil is parent plus metabolite UR-50604, then confirmatory method for metabolite UR-50604 is required. **Answer from ECCO 137 (Fate) and message to ECCO 140 (Overview)**: The residue definition in soil, water and sediment is proposed as beflubutamid and UR-50604. Therefore, a confirmatory method of analysis for UR-50604 will be required.		30.07.03 According to ECCO 139 the metabolite is included in the residue definition.. Therefore a confirmatory method is required for UR 50604.	Overview Meeting (16.09.2003): Confirmatory methods can be dealt with at MS level. If included in residue definition, need confirmatory method.

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
12/63

2. Environmental fate and behaviour

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
				Section 2 Data requirements: 7 Open points:2
2.1	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.	07.07.03 A report (Takamura 2002) considering the revised application rate of 170 g as./ha and the FOCUS modelling (FocusPelmo ver. 2.2.2) was provided in 09/2002 to RMS and Member States based on the discussion of parameters with RMS for national registration. For this revised calculation following was considered: - the interception of 25 % by the crop cover - all relevant scenarios as suitable for the use of Beflubutamid in cereals - average of normalised degradation rates of all tested soils (incl. Speyer 2.2 both experiments, and Arrow) were used for a.s. (DT_{50}=10.9 days) and metabolite UR-50604 (DT_{50}=3.8	25.07.2003 The calculation of the notifier is not acceptable, because to many ”best – case” assumptions were included. According to our information the metabolite UR 50604 might leach into groundwater under vulnerable environmental conditions. The simulation of leaching behaviour will be recalculated by the RMS according to the FOCUS recommendations taking into account the revised intended uses when missing studies were	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. Some information has been submitted and has been evaluated but is not acceptable. RMS will evaluate when all data available. Further discussion between RMS and NOT needed to clarify input data needed. Data to be submitted at the end of 2003.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		days). - For the Speyer 2.2 soil experiments a detailed argumentation (Anonymous 2002) was provided why degradation rates of 0-30 days instead of 0-120 days were used for the calculation (using Model-maker 4.0 simulation figures of 0-30 days show better fit of the calculated lines of a.s. and metabolite compared to the measured values due to the remarkable decrease of degradation in the latter periods of the laboratory study) - average Koc Values as recommended by the FOCUS guidance were used for a.s. (Koc 1260, 1/n 0.92) and metabolite (Koc 12.3; 1/n 0.87). - Results for UR-50604 using DT50=10.9 days for a.s. and 3.8 days for metabolite, respectively (Max. long-term conc. in gw (µg/L) [80th percentile of UR-50604 in the percolate at 1 m soil depth] Scenario Winter Spring cereal Chateaudun 0.000	received.	
2.1	*continued* 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.			

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
14/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		0.000 Hamburg 0.009 0.000 Jokioinen 0.001 0.000 Kremsmünster 0.000 0.000 Okehampton 0.008 0.000 Piacenza 0.037 - Porto 0.000 0.000 Sevilla 0.000 - Thiva 0.000 -		
	continued			
2.1	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.	- For comparison, Focus-Pelmo calculation was repeated with the averages of normalised degradation rates of all tested soil excluding only the values of the 1st experiment with Speyer 2.2, which was considered as not valid by the applicant because of its exceptional long degradation rate of a.s. compared to the other soils. Average normalised degradation rates correspond to DT_{50}=7.6 days for a.s. and 4.2 days for metabolite. - Results for UR-50604 using DT_{50}=7.6 days for a.s. and 4.2 days		

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
15/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		for metabolite, respectively (Max long-term conc. in gw (µg/L) [80th percentile of UR-50604 in the percolate at 1 m soil depth] Scenario Winter Spring cereal Chateaudun 0.000 0.000 Hamburg 0.020 0.000 Jokioinen 0.003 0.000 Kremsmünster 0.000 0.000 Okehampton 0.018 0.000 Piacenza 0.069 - Porto 0.000 0.000 Sevilla 0.000 - Thiva 0.001 -		
	continued			
2.1	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.	- Conclusion: Although slower degradation of the metabolite in this simulation, no value is reaching the trigger value 0.1 µg/L for groundwater. References as cited above: Takamura, S. 2002: UR-50601		

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		(Beflubutamid): Evaluation of groundwater contamination by the metabolite UR-50604 in soil. Risk assessment at an maximum application rate of 170 g Beflubutamid/ha. UBE Industries, 05.09.2002 Anonymous 2002: ”Supplement to Appendix 1: Calculation of degradation rates of UR-50604 of the revised report: UR-50601 (Beflubutamid). Evaluation of groundwater contamination by the metabolite UR-50604 in soil (Refined Risk Assessment) dated 12 April 2002” – UBE Industries, 30 July 2002		
2.2	Applicant is to submit new PECsoil calculations using the revised application rate of 170 g a.s./ha. (IIIA 9.1.3) **A**	07.07.03 A new PECsoil calculation will be submitted by 31.12.2003.	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
17/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
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) **A**	07.07.03 Applicant will submit the information of the behaviour stability and potential for accumulation of the metabolite UR-50604 in water sediment system by 31.12.2003.	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.
2.4	Applicant is to submit new PECsurface water calculations using the revised application rate of 170 g a.s./ha. (IIIA 9.1.3) **A**	07.07.03 A new PECsurface water calculation will be submitted by 31.12.2003.	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.
2.5	Applicant is to submit new PECsediment calculations using the revised application rate of 170 g a.s./ha. IIIA 9.1.3) **A**	07.07.03 A new PECsediment calculation will be submitted by 31.12.2003.	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
2.6	Applicant is to submit new PECgroundwater calculations using the revised application rate of 170 g a.s./ha in FOCUS modelling. (IIIA 9.2.1) **A**	07.07.03 A report considering the revised application rate of 170 g a.s./ha and the FOCUS modelling was provided in September 2002 to the RMS and Member States (see point 2.1) There was no leaching of the UR-50604 at any of the locations exceeding the trigger value of 0.1 µg/L in groundwater.	25.07.2003 The calculation of the notifier is not acceptable. See comment on 2.1	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion This data requirement is linked to data requirement 2.1.
2.7	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. (IIIA 9.2.1) **A**	07.07.03 See point 2.1. All relevant FOCUS scenarios were regarded in the submitted references.	25.07.2003 The calculation of the notifier is not acceptable because of the chosen input parameters. See comment on 2.1	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. This data requirement is linked to data requirement 2.1.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point 2.1: 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.	07.07.2003: See point 2.1. The difference between the median (Koc 9, 1/n = 0.81) and average (Koc 12.3, 1/n = 0.87) of Koc and Freundlich constant is considered as too small as having a significant effect on the results of the modelling. No value is near the borderline of 0.1 µg/L in groundwater.	25.07.2003 The PECgw will be recalculated by the RMS according to the FOCUS recommendations when missing studies were received.	Overview Meeting (16.09.2003): Open point still open. This open point is linked to data requirement 2.1.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
20/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	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) **A**	07.07.03 Applicant will prepare argumentation of difference in degradation in the environment between two isomers by 31.12.2003.	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Open point still open.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
21/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Message 2.1 from ECCO 137 (Fate) to ECCO 139 (Ecotox): The water-sediment study shows that metabolite UR-50604 was continuing to increase at the study end, in both water and sediment after 100 days. In view of this, ECCO 139 experts are asked to consider whether there are any ecotoxicological issues concerning this metabolite.		25.07.2003 The maximum amount of UR-50604 detected in the water/sediment study was 35 – 43 % in the water phase and 18 - 20 % in sediment. The submitted tests on effects on aquatic organisms demonstrate that UR-50604 is acutely less toxic than beflubutamid. In the opinion of the RMS there is no ecotoxicological concern with respect to the metabolite.	Overview Meeting (16.09.2003): Fulfilled There is no ecotoxicological concern with respect to this metabolite.
	Message 2.2 from ECCO 135 (Phys Chem) to ECCO 137 (Fate): Experts from ECCO 137 asked to comment on whether there are any concerns over the difference in results obtained for Henry's Law Constant and whether the modelling method used is acceptable. **Answer from ECCO 137 (Fate)**: ECCO 137 did not have			Overview Meeting (16.09.2003): No action needed.

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
22/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	details of the model used, so could not comment on its acceptability, but agreed that the Henry's Law Constant should be recalculated if the water solubility value that was still to be finalised, subsequently differed.			

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
23/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Message 2.3 from ECCO 135 (Phys Chem) to ECCO 137 (Fate): ECCO 135 highlighted to ECCO 137 that a confirmatory method of analysis will be required if the environmental residue definition includes metabolite UR-50604. **Answer from ECCO 137 (Fate) and message to ECCO 140 (Overview)**: The residue definition in soil, water and sediment is proposed as beflubutamid and UR-50604. Therefore, a confirmatory method of analysis for UR-50604 will be required.	07.07.03 A confirmatory method of analysis for UR-50604 will be submitted by 31.12.2003.		Overview Meeting (16.09.2003): Still open. Information will be submitted by the end of 2003.

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
24/63

3. Ecotoxicology

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
				Section 3 Data requirements: 3 Open points: 4
	Open point 3.1: 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.	11.07.03 See 3.1-3.8 ff.: Risk assessment will follow until 31.12.2003	25.07.2003 Risk assessment will be revised when missing studies were received.	Overview Meeting (16.09.2003): Open point still open.
	Open point 3.2: RMS to address risk posed to fish and worm eating birds.	11.07.03 See point 3.1	25.07.2003 Studies will be evaluated in one package when received	Overview Meeting (16.09.2003): Open point still open, pending submission of risk assessment by the notifier.
	Open point 3.3: To refine risk assessment for new GAP	11.07.03 See point 3.1	25.07.2003: Risk assessment updated.	Overview Meeting (16.09.2003): Open point still open. For aquatic organisms it is updated but not for the terrestrial vertebrates.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
25/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point 3.4: RMS to update end points for *Lemna*.	11.07.03 See point 3.1	25.07.2003: List of endpoints amended.	Overview Meeting (16.09.2003): Open point fulfilled.
	Open points 3.5: RMS to update end points to indicate that in the bioaccumualtion study the clearance time was lower than 1 day.	11.07.03 See point 3.1	25.07.2003: List of endpoints amended.	Overview Meeting (16.09.2003): Open point fulfilled.
	Open point 3.6: RMS to update NOEC for *Chironimus*	11.07.03 See point 3.1	25.07.2003: List of endpoints updated.	Overview Meeting (16.09.2003): Open point fulfilled.
	Open point 3.7: RMS to correct for solubility with footnote in end point table to say measured concentrations were used.	11.07.03 See point 3.1	25.07.2003: List of endpoints amended.	Overview Meeting (16.09.2003): Open point fulfilled.
	Open point 3.8: Update end points to address new GAP.	11.07.03 See point 3.1	25.07.2003: List of endpoints updated.	Overview Meeting (16.09.2003): Open point fulfilled.

Evaluation table Beflubutamid (Hb)

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Message 3.1 from ECCO 139 (Ecotox) to ECCO 137 (Fate): The DT50 of UR 50604 in the water phase of the sediment/ water study was 13 – 18 days. As its toxicity was also two orders of magnitude lower than the a.s. further information on the chronic risk to fish and aquatic invertebrates was not considered necessary. ***Answer from ECCO 137 (Fate) and message to ECCO 140 (Overview)**: the residue definition in soil, water and sediment is proposed as beflubutamid and UR-50604. Therefore, a confirmatory method of analysis for UR-50604 will be required.*			Overview Meeting (16.09.2003): Response of the Ecotoxicology ECCO meeting 139 to this question from ECCO 137 (Fate): The DT50 of UR 50604 in the water phase of the sediment/water study was 13 – 18 days. As its toxicity was also two orders of magnitude lower than the a.s. further information on the chronic risk to fish and aquatic invertebrates was not considered necessary. Therefore, UR 50604 should not be part of the residue definition.
	Open point 3.9: RMS to update end points as specified.		25.07.2003: List of endpoints updated.	Overview Meeting (16.09.2003): Open point fulfilled.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
27/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point 3.10: RMS to update end points.		25.07.2003: List of endpoints updated.	Overview Meeting (16.09.2003): Open point fulfilled.
3.1	The applicant to address the long-term risk to earthworms from the a.s. and the risk for metabolites. **A**	07.7.03 The applicant will submit the risk assessment to RMS by 31.12.2003 If risk assessment still fails the criteria, further studies are planned for estimation of the risk on soil organisms. The studies are planned to carry out by the step-wise plan as following. 1st Step: Test on Collembola. If TER based on reproduction is < 5, go to 2nd Step: Test on endemic earthworm species with natural soils. Study plan and evaluation criteria will be discussed with RMS. 3rd Step: Field test on earthworms or Litter bag test. Choice of study, study plan and evaluation criteria will be discussed with RMS	25.07.2003 Proposal of the notifier needs to be discussed. Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. Data will be submitted by the end of 2003. Not clear why there is a stepwise procedure outlined in column B. It was pointed out that the collembola issue is being addressed in data requirement 3.2. The earthworm and collembola tests should not be mixed-up. RMS and notifier to discuss whether field studies of earthworms need to be carried out or whether the risk can be assessed by carrying out reproduction studies. The notifier pointed out that field studies can only be conducted in spring and could therefore only be submitted in 2004.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
28/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
3.2	Data are required to address the risk to soil macro-organisms (e.g. study on collembola) **A**	07.07.03 The applicant will submit the report of the Collembola test to RMS by 31.12.2003	25.07.2003 Studies will be evaluated in one package when received.	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion. Study will be available by the end of 2003.
	Open point 3.11: RMS to include non-target flora and fauna in list of end points.		25.07.2003 Studies need to be submitted.	Overview Meeting (16.09.2003): Open point still open. Changed into a data requirement (3.3).
3.3	Applicant to submit study on non-target fauna and flora.			Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.

4. Mammalian Toxicology

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
				Section 4 Data requirements: 1 Open points: 0
	~~Open Point 4.1:~~ Message 4.1 from ECCO 136 (Mamtox) to ECCO 138 (Residues) and ECCO 137 (Fate): Meetings to consider the formation of these metabolites in plant and the environment.			Overview Meeting (16.09.2003): Awaiting response from fate and residues.
4.1	Notifier to provide a commentary on the mechanism of tumour induction and it's relevance of the thyroid follicular tumours to man.	07.07.03 A detailed commentary on these issues (mechanism of tumour induction and it's relevance to human) has been submitted by the applicant as a supplement to the EU dossier in May 2001 to the RMS and on 18 October 2001 to the MS under AII-5.5, Appendix 9 'Mechanistical explanation for the occurrence of thyroid gland follicular tumours of combined chronic	July 25, 2003 The RMS did not receive these comments. Awaiting updated comments by 10.08.03	Overview Meeting (16.09.2003): Data essential for unconditional Annex I inclusion.

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
30/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		toxicity/carcinogenicity study in rats (UBE 044)'. The main conclusion was as follows:		
	continued	”SUBSEQUENT WORK HAS SHOWN THAT THIS MECHANISM OF THYROID TUMOUR FORMATION IS SPECIES SPECIFIC TO THE RAT AND IS ASSOCIATED WITH THE DIFFERENT KINETICS ASSOCIATED WITH HORMONES AND DIFFERENT SENSITIVITIES BETWEEN SPECIES. THE LOW TSH RESPONSE TO THYROTROPHIN RELEASING HORMONE, THE HIGH TSH PLASMA LEVELS, THE GREATER BILIARY EXCRETION OF THYROXINE, THE ABSENCE OF THYROID-BINDING GLOBULIN IN THE PLASMA AND THE SHORT HALF-LIFE OF THYROXINE IN THE RAT COMPARED TO THAT IN MAN, ARE ALL POSSIBLE FACTORS MAKING THE RAT FOLLICULAR CELL MORE VULNERABLE TO		
4.1	Notifier to provide a commentary on the mechanism of tumour induction and it's relevance of the thyroid follicular tumours to man.			

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
31/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
		PROLIFERATIVE EVENTS. SHOULD THIS TYPE OF RESPONSE OCCUR IN A RAT LONG TERM STUDY, IT CAN THEREFORE BE CONSIDERED TO HAVE LITTLE OR NO RELEVANCE IN THE RISK ASSESSMENT FOR MAN." THE COMMENTARY WILL BE UPDATED AND SUBMITTED TO RMS BY 10.08.2003		
	~~Open Point 4.2:~~ Message 4.2 from ECCO 136 (Mamtox) to ECCO 137 (Fate): Meetings to confirm metabolite 50604 < 0.1 ug/litre.			Overview Meeting (16.09.2003): Awaiting reply from fate. 50604 seems to be a significant proportion of environmental residue - all depends on absolute levels.

Evaluation table Beflubutamid (Hb)

5. Residues

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
				Section 5 Data requirements: 0 Open points: 0
~~5.1~~	Open point 5.1: RMS to consider revising the residue definition for some crops, pending investigation of enantiomeric enrichment. The end points should conclude that there are sufficient residue data for Annex I, but there is a need to specify crops for the MRL definition (winter wheat, barley etc.).	11.07.03: UR-50601 is only intended for application in cereals. Investigation of the enantiomeric enrichment in other plants than wheat deemed unnecessary since the decline patterns are similar (significantly not different) in trials in barley and wheat showing a steady decline of residues over time decreasing to < 0.05 mg/kg in all grain and straw samples, equating to pre-harvest intervals ranging form 66 to 116 days. Enrichment of isomers therefore is not likely and therefore a specification for MRL definition deemed not necessary. Applicant agrees with parent compound only as residue definition.	13.08.2003: Since up to now no information is available on possible enrichment of stereochemical isomers of beflubutamid or its metabolites in any crop the comment of the notifier is accepted and no change of the proposed residue definition is necessary. The MRL definition is specified in the end point sheet according to the intended uses.	Overview Meeting (16.09.2003): Open point fulfilled.

Evaluation table Beflubutamid (Hb)

EU RESTRICTED Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
33/63

No.	Column A Conclusions of the ECCO-Peer Review Meeting	Column B Comments from the main data submitter / applicant on the ECCO-Review conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations ECCO-Overview Meeting / Conclusions of the evaluation group
	Open point 5.2: RMS to note the change in the ADI to 0.02 mg/kg bw. (this point was split into an open point and a data requirement)			Overview Meeting (16.09.2003): Open point fulfilled.
~~5.2~~ 5.1	NEDI model (and WHO calculation) will need to be re-calculated (this point was split into an open point and a data reuqirement)	11.07.03 NEDI will be calculated using the ADI of 0.02 mg/kg bw by 30.12.2003	13.08.2003: Recalculation of TMDI and NEDI based on ADI = 0.02 mg/kg bw: TMDI = 0.001 mg/kg bw (5 % ADI) NEDI = 0.0004 mg/kg bw (2 % ADI)	Overview Meeting (16.09.2003): Data requirement fulfilled.

Areas of concern:

Section 1: None.

Section 2: Metabolite UR-50604 is predicted to reach groundwater in concentrations exceeding 0.1 μg/l. Applicant has since reduced the application rate to resolve this. PEC calculations and FOCUS modelling are to be repeated with the revised rate and the relevance of this metabolite addressed, unless it can be shown not to have potential to contaminate groundwater at >0.1 μg/l.

Section 3: Possible risk to terrestrial and aquatic plants. Possible long-term risk to earthworms.

Section 4: The main concern was a lack of any mechanistic data for the thyroid tumours seen in the rat.

Section 5: None.

rapporteur DE

Evaluation table Beflubutamid (Hb) *EU RESTRICTED* Doc. SANCO/10393/2002 rev. 0-2 (16.09.03)
34/63

Overview Meeting (16.09.2003):

- The first provisional authorisation has been granted in Germany on 14th of June 2003.
- A confirmatory method for metabolites is needed. The notifier explained that this would postpone submission of the report by 3 month and submission would be the end of March 2004.
- One Member State pointed out that if long-term studies are requested, high persistence is expected. This needs to be reflected in the modelling.

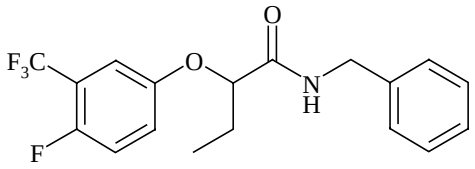
COMPLETE LIST OF ENDPOINTS: BEFLUBUTAMID

2.8.3 Appendix III: Listing of end points

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

Active substance (ISO Common Name)	Beflubutamid
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	Germany

Identity (Annex IIA, point 1)

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

Physical-chemical properties (Annex IIA, point 2)

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

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

16 September 2003

List of uses supported by available data

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests Controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Winter wheat Winter barley Triticale Winter rye	Northern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425 + 0.250 isoproturon Spring: 0.0425 + 0.250 isoproturon	200-400 200-400	0.085 - 0.170 + 0.500 - 1.000 isoproturon 0.085 - 0.170 + 0.500 - 1.000 isoproturon		Co-formulation with isoproturon
Winter wheat Winter barley Durum wheat	Southern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425 + 0.250 isoproturon Spring: 0.0425 + 0.250 isoproturon	200-400 200-400	0.085 - 0.170 + 0.500 - 1.000 isoproturon 0.085 - 0.170 + 0.500 - 1.000 isoproturon		Co-formulation with isoproturon

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)

(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated

16 September 2003

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

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None
with regard to toxicological data	None
with regard to fate and behaviour data	None
with regard to ecotoxicological data	N, R 50/53

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

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

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

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	GC-PND	0.05 mg/kg (cereal grain)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	not relevant	
Soil (principle of method and LOQ)	Beflubutamid LC-MS GC-MS UR 50604 LC-MS	 0.01 mg/kg 0.01 mg/kg 0.01 mg/kg
Water (principle of method and LOQ)	HPLC-UV LC-MS	0.1 µg/l (surface and drinking water) 0.1 µg/l (surface water)
Air (principle of method and LOQ)	HPLC-UV	0.6 µg/m^3
Body fluids and tissues (principle of method and LOQ)	not relevant	

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

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

Rate and extent of absorption	At 35 mg/kg bw rapidly and nearly completely absorbed (>80 %) based on excretion via bile (>66 %) and urine (8 – 16 %). Plasma C_{max}: 6 hours
Distribution	Widely distributed highest levels found in kidneys and liver.
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	Completely excreted within 120 hours mainly via bile (At 35 mg/kg – 66 % (females) and 85 %(males)). Urinary excretion was found to be higher in females.
Metabolism in animals	Extensively metabolised by hydroxylation, cleavage of the amide bond and conjugation as glucuronides (major metabolites: phenoxybutyric acid, hippuric acid)
Toxicologically significant compounds (animals, plants and environment)	Parent compound and major metabolites (to be clarified at the residues/Fate and Behaviour Meetings)

Acute toxicity (Annex IIA, point 5.2)

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

Short term toxicity (Annex IIA, point 5.3)

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

Genotoxicity (Annex IIA, point 5.4)

	No evidence of genotoxic potential. Based on the levels in blood/plasma there was sufficient evidence that the bone marrow would be exposed in the in vivo assay.

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

Target / critical effect	Liver, kidney + thyroid gland (rat)
Lowest relevant NOAEL / NOEL	104-wk oral, rat: 50 ppm (2.2 mg/kg bw/d)
Carcinogenicity	Not carcinogenic in mice. Equivocal increase in thyroid follicular cell tumours in male rats at highest dose (3200 ppm) in the 2 year study. No convincing information on the mechanism of possible tumour induction; relevance to man, if any, considered low because of the high margin of safety between ADI and NOEL for neoplasia..

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	There were no specific effects on reproduction. Impairment of bodyweight development during lactation, delay in age for vaginal opening (F1-females) at parental toxic doses; offspring kidney changes at 3200 ppm.
Lowest relevant reproductive NOAEL / NOEL	2-gen. rat: Reproductive Outcome: 3200 ppm (320 mg/kg bw/day) Parental toxicity; 200 ppm (approx. 17 mg/kg bw/day) Pup development; 200 ppm (approx. 17 mg/kg bw/day)
Developmental target / critical effect	Developmental effects on the kidney/ureter (vestigial and/or losses of renal papilla, dilatated ureter) at maternally toxic doses.
Lowest relevant developmental NOAEL / NOEL	100 mg/kg bw/d (rat, rabbit)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

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

Other toxicological studies (Annex IIA, point 5.8)

No data, not required.

Medical data (Annex IIA, point 5.9)

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

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI	0.02 mg/kg bw	104-wk, oral rat	100
AOEL systemic	0.3 mg/kg bw/d	90-d, rat	100
ARfD (acute reference dose)	Not necessary. Not allocated.	-	-

Dermal absorption (Annex IIIA, point 7.3)

No studies performed; 100% assumed (worst case)

Acceptable exposure scenarios (including method of calculation)

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

2.8.3.4 Appendix III.4: Chapter 4 (residues)

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

Plant groups covered	wheat
Rotational crops	beflubutamid
Plant residue definition for monitoring	beflubutamid
Plant residue definition for risk assessment	beflubutamid
Conversion factor (monitoring to risk assessment)	none

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

Animals covered	lactating goat
Animal residue definition for monitoring	none
Animal residue definition for risk assessment	none
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	yes

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

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

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

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

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

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle Liver Kidney Fat Milk Eggs	no studies required / conducted		

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

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
spring barley	N S	4 x <0.05 mg/kg grain 4 x <0.05 mg/kg grain		0.05 mg/kg	0
spring wheat	N S	1 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0
durum wheat	N	1 x <0.05 mg/kg grain		0.05 mg/kg	0
winter wheat	N S	4 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0

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

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

ADI	0.02 mg/kg bw/d
TMDI (European Diet) (% ADI)	0.001 mg/kg bw (5.2 % ADI)
NEDI (% ADI)	0.0004 mg/kg bw (2 % ADI)
Factors included in NEDI	not applicable
ARfD	not assigned
Acute exposure (% ARfD)	not applicable

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

Crop/processed crop	Number of studies	Transfer factor	% Transference *
no data generated			

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

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

barley, rye, triticale, wheat, durum wheat	0.05 mg/kg
other food of plant origin	0.05 mg/kg

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

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

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

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

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

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

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

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

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

Soil adsorption/desorption (Annex IIA, point 7.1.2)

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

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

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

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

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

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

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

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

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

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

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

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

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

	runoff/erosion)

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

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

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

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

PEC (sediment) **beflubutamid**

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

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

PEC (sediment) **metabolite UR-50604**

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

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

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

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

PEC$_{(gw)}$

Maximum concentration	----
Average annual concentration	< 0.001 µg/L Hamburg, Piacenza

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

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

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

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

PEC (air)

Method of calculation	Not relevant

$PEC_{(a)}$

Maximum concentration	Not relevant

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	Beflubutamid and the major metabolite phenoxybutyric acid (UR50604) (soil (aerobic, anaerobic), water/sediment, groundwater). In soil the metabolite is consired as ecotoxicological

	relevant, but has no potential for accumulation. For groundwater, the metabolite is not relevant regarding ecotoxicology and biological activity. The evaluation of the toxicological relevance of the major metabolite is not yet finished due to missing data.

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

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

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

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

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

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
0.255	Cereals	Herbivorous bird	acute	>285	10
0.255	Cereals	Herbivorous bird	short-term	>185	10
0.255	Cereals	Herbivorous bird	long-term	36	5
0.255	Cereals	Insectivorous bird	acute	>660	10
0.255	Cereals	Insectivorous bird	short-term	>650	10
0.255	Cereals	Insectivorous bird	long-term	125	5
0.255	Cereals	Insectivorous mammal	acute	>710	10
0.255	Cereals	Insectivorous mammal	long-term	114	5

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

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L)
Laboratory tests				
O. mykiss	Active substance	acute	Mortality EC_{50}	1.86
P. promelas	"	long-term	Growth NOEC	0.11
D. magna	"	acute	Immobilization EC_{50}	1.64
"	"	chronic	Reproduction NOEC	0.455
S. capricornutum	"	chronic	Biomass EC_{50}	0.00455
A. flos-aquae	"	chronic	Biomass EC_{50}	>3.31
C. riparius	"	long-term	Emergence NOEC	1.8
L. gibba	"	long-term	Fronds	0.02
C. riparius	"	chronic	Emergenc NOEC	0.56
O. mykiss	Metab. UR-50604	acute	Mortality EC_{50}	>93
D. magna	"	"	Immobilization EC_{50}	>91
S. capricornutum	"	chronic	Biomass EC_{50}	69.2
O. mykiss	ASU 95 510 H	acute	Mortality EC_{50}	39.1
D. magna	"	"	Immobilization EC_{50}	17.3
S. capricornutum	"	chronic	Biomass EC_{50}	0.052
Microcosm or mesocosm tests				
-				

***: with exception of the *C. riparius* test (nominal concentration) all concentrations were given as measured, maximum water solubility of beflubutamid is 3.3 mg/l**

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

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.170	Field crop	*S. capricornutum*	chronic	1	2.8	10
0.170	"	"	"	5	13	10

Bioconcentration

Bioconcentration factor (BCF)	140
Annex VI Trigger for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	0.5 – 0.6 d 2.1 – 2.4 d
Level of residues (%) in organisms after the 14 day depuration phase	< 5

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

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

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

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.170	Cereals	oral	1.7	50
0.170	Cereals	contact	1.7	50

Field or semi-field tests
Not required

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

Species	Stage	Test Substance	Dose g as/ha	Endpoint	Effect %	Annex VI Trigger
Laboratory tests						
T. pyri	Protonymphs	ASU 92530 H	250	Mortality Fecundity	8 9	30
T. pyri	Protonymphs	ASU 95 510 H	255	Mortality Fecundity	31 0	30
A. rhopalosiphi	Adults	ASU 92530 H	250	Mortality Fecundity	0 44	30
A. rhopalosiphi	Adults	ASU 95 510 H	255	Mortality Fecundity	3 13	30
C. carnea	Larvae	ASU 92530 H	250	Mortality Fecundity	6 5	30
C. carnea	Larvae	ASU 95 510 H	510	Mortality Fecundity	18 0	30
P. cupreus	Adults	ASU 92530 H	250	Mortality Food uptake	12 8	30
P. cupreus	Adults	ASU 95 510 H	510	Mortality Food uptake	0 9	30

Field or semi-field tests
not required

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

Acute toxicity	LC_{50} 732 mg as/kg (beflubutamid) (corrected to 366 mg as/kg)
Acute toxicity (Metabolite UR-50604)	LC_{50} 229 mg/kg (corrected to 115 mg)
Reproductive toxicity	NOEC < 0.255 kg as/ha (form. ASU 92 530 H containing 500 g/l beflubutamid), equivalent to < 0.34 mg as/kg, corrected to < 0.17 mg as/kg NOEC 6 l product/ha (form. ASU 95 510 H containing Isoproturon 500 g/l and 85 g/l beflubutamid), equivalent to 0.68 mg as/kg, corrected to 0.34 mg as/kg

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

Application rate (kg as/ha)	test substance	Crop	Time-scale	TER	Annex VI Trigger
0.170	active substance	Cereals	acute	1590	10
0.170	ASU 92530 H	Cereals	long-term	< 0.7	5
0.170	ASU 95510 H	Cereals	long-term	1.5	5

*PEC 0.23 mg as/kg (see chapter B.8.3)

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

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

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

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

LIST OF STUDIES WHICH WERE SUBMITTED DURING THE EVALUATION PROCESS AND WERE NOT SITED IN THE DRAFT ASSESSMENT REPORT: BEFLUBUTAMID

B.1 Identity B.2 Physical and chemical properties B.3 Data on application and further information B.4 Proposals for the classification and labelling B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title source (where different from company) Company[1], report no. GLP or GEP status (where relevant), published or not BBA registration number
-			

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title source (where different from company) Company[1], report no. GLP or GEP status (where relevant), published or not BBA registration number
AIIA-5.3.2; AIIA-5.5	Funaki, E.	2003	Mechanistical explanation for the occurrence of thyroid gland follicular tumours of combined chronic toxicity/ carcinogenicity study in rats and their relevance to man. TSU UR 50601 not GLP, unpublished TOX2003-1546

Codes of company

TSU: Task force von Stähler und UBE

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title source (where different from company) Company[1], report no. GLP or GEP status (where relevant), published or not BBA registration number
-			

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title source (where different from company) Company[1], report no. GLP or GEP status (where relevant), published or not BBA registration number
AIIIA-9.2.1	Takamura, S.	2002	Calculation of degradation rates of UR-50604 of the revised report: UR-50601 (Beflubutamid) Evaluation of groundwater contamination by the metabolite UR-50604 in soil (refined risk assessment) -Supplement to Appendix 1-. TSU not GLP, unpublished BOD2002-561

Codes of company
TSU: Task force von Stähler und UBE

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title source (where different from company) Company[1], report no. GLP or GEP status (where relevant), published or not BBA registration number
-			

[1] Only notifier listed

COMPLETE LIST OF SUGGESTED CLASSIFICATION AND LABELLING: BEFLUBUTAMID

ECCO Peer Review Programme, Round 14, York

1. Classification and labelling:

with regard to physical/chemical data	None
with regard to toxicological data	None
with regard to fate and behaviour data	None
with regard to ecotoxicological data	N, R 50/53

[1] Only notifier listed

ANNEX 2 TO CONCISE OUTLINE REPORT OF ECCO 135 PEER REVIEW MEETING

BEFLUBUTAMID

Rapporteur Member State: GERMANY

Specific comments on the active substance in the section **Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis** are listed below. The conclusions of the meeting were as follows:

1a. Comments received and discussed:

Date	**Supplier**	**File Name**
8 January 2003	United Kingdom	Beflubutamid 135 com01 UK
3 February 2003	Belgium	Beflubutamid 135 com02 BE

1b. Comments received but not discussed (because deadline of submission was not met):

Date	**Supplier**	**File Name**
None		

1c. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
None		

2. **Data on preparations:** Data set is incomplete.

4. **Classification and labelling** None.

5. **Recommended restrictions/conditions for use:** None.

Areas of concern: None.

Appendix 1: ECCO 135 reporting table: BEFLUBUTAMID

Appendix 2: List of end points: BEFLUBUTAMID

Appendix 3: Suggested classification and labelling: BEFLUBUTAMID

Appendix 1: ECCO 135 reporting table Beflubutamid (Hb)

1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
			Section 1 Data requirements: 6 Open points: 8
(i)			
(ii)	Technical specification	A summary of a number of pilot plant production batches were tabled. The RMS stated that in many cases the maximum limits for impurities proposed were much higher than the levels actually found in the batch analysis and that replies from the applicant were that this was pilot plant product. The meeting could not accept the specification as proposed and the applicant must submit a better specification with justifications for any limits they wish to have If the applicant have confirmed that likely plant to go to full scale production is just 1 of the 5 plants seen, then perhaps the results for the other batches should be removed from the monograph or endpoints.	1.1 A better technical specification which is reflected by the batch analysis data is required or justification for the proposed specification given levels of impurities found in the batches. (IIA 1.11) **A** 1.2 A revised technical specification is required when full scale production has started. (IIA 1.11) **A**
(iii)	Biological activity of isomers	The biological effect of both isomers has not been addressed.	1.3 The applicant must address biological activity of both isomers **A**
(iv)	Isomer ratio	The question was raised whether the isomer ratio needed to be specified to reflect the material used in the toxicology testing, However, the meeting agreed that this was a racemic mixture and therefore not required.	
(v)		Discussion about whether methods of analysis for annex II and annex III should go in the confidential info or in the methods chapter of Volume B. LOQ's for the impurities have not been stated and validated and the meeting discussed whether the LOQ's should be proven. Discussion followed as to the requirements of the directives over the information in the guidance documents. Discussion followed whether the LOQ should be proven.	Open point 1.1 RMS to clarify the levels of the fortifications used in the batch analysis

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(vi)		The meeting discussed that if the fortification levels in the batch analysis were at or around the lowest levels in the batches from the pilot plant and that if the levels of these impurities were lower still when the full scale production batches are analysed, then new validation data at these levels will be required for the impurities to reflect the new lower levels. If the data for the full scale production are submitted before Annex I listing, then this will be addressed by the RMS, otherwise the acceptability of the method validation for impurities will have to be addressed at MS level	Open point 1.2, if applicant provides new batch analysis data from full scale production before Annex I listing, then these will be considered by RMS, otherwise this will need to be dealt with at MS level (IIA 1.11)
(vii)		Discussion	Meeting agreed that the Volume C confidential info causes a number of problems for many MS, the suggestions were made to use codes for the impurities and maybe include a key in the Volume C, but this will still cause problems, because the methods have to be considered in conjunction with the tech spec which is only in Volume c . BE suggested that a summary of the info in Volume C could go in Volume B.
(viii)		Questions were raised about the validation of the method for surface water and not for drinking water. The validation data were for distilled water and HPLC water and so the question was raised as to whether the method has actually been validated for surface water.	Open point 1.3. RMS to confirm whether the method of analysis for water had been validated for surface water as only distilled water and HPLC water had been used for the validation.
(ix)	Water solubility	BE asked what the method was used to measure the water solubility . RMS confirmed method used was the flask method of A6, but the water solubility was very low and therefore the column	1.4 The applicant must address the water solubility by the appropriate

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
		elution method is the appropriate method to be used.	method
(x)	Partition co-efficient	Discussion point.	The meeting concluded that the methodology used for this determination was appropriate.
(xi)	Henry's Law	Further to the discussion for the water solubility, the meeting considered that should the water solubility differ from the original result then, the Henry's Law will need to be recalculated. However, it was noted that the data were generated according to a software modelling programme and BE noted that the result from the modelling was very different to the value obtained from the water solubility and vapour pressure.	Open point (1.5) to note for Fate meeting (ECCO 137). Are there concerns for the difference in the results and do they accept the modelling method.
(xii)	Annex III	Discussion	Oxidising properties. The monograph stated that there was not a suitable method for liquids and BE noted there was a FIFRA method available. However, the meeting accepted the case made on the basis of the structure of the compound. The meeting noted there was a draft OECD method oxidising properties for liquids and there may also be a draft EU method as well. UK offered to try and find details of this method.
(xiii)	Surface tension	BE asked for confirmation of the temperature and concentration for the surface tension determination. RMS confirmed the temperature was 20C, but the concentration was not recorded. The meeting accepted that the data point had not been completely fulfilled, but given the preparation was an SC, the meeting were content that no further data on this aspect was required.	Discussion and open point (1.6) for RMS to include the temperature in the monograph

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xiv)	Storage stability	Discussion	BE noted that the accelerated study was conducted at 12 weeks and 35C rather than 14 days at 54C. The RMS confirmed that the preparation thickened up markedly at the higher temperature and the meeting accepted that the 12 weeks at 35C was representative of the 54C/14 days conditions and accepted the data
(xv)	Shelf life data	BE noted the recording of emulsifiabilty data for this formulation and the RMS confirmed this was a typographical error and that it should be suspensibility.	Open point 1.7. RMS to amend the typographical error (emulsifiability to read suspensibility)
(xvi)		FR tabled a comment that the particle size showed that most of the particles were 10 microns and asked whether this should be noted for consideration by toxicology. The meeting agreed that as this formulation was a liquid, this was not necessary	
(xvii)	B5 methods	Initially the residue definition for plants was parent plus one metabolite and the data had shown that these analytes were not analysed by multi residue method. Residue definition in plants is now parent only so will require the company to address the applicability of a multi residue method for the analysis of plant residue.	1.6 Applicant must assess the applicability of multi residue methods for analysis of plant residue
(xviii)		Discussion point	It was noted that the sample numbers for the grain validation were low (n=3), however the RMS confirmed that more fortification levels had been used than in the guidelines and therefore the validation data were considered acceptable

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xix)		Discussion point	It was noted that the company have provided a monitoring method as well as ILV for the method. Therefore, the requirement above is just to assess the applicability of a multi residue method for the analysis of plant residues
(xx)		BE confirmed that the end point should only state the analytes that are in the residue definition. The Chair confirmed that this was desirable	Open point (1.8) for RMS to amend end point sheets for methods in line with the appropriate residue definition
(xxi)		Residues in food of animal origin. No details of methods of analysis for animal products have been submitted or are required.	Note to residue meeting (ECCO 138), if MRLs are set for animal products, then further methods of analysis will be required
(xxii)		Residue definition in soil is parent plus metabolite UR-50604, this is of ecotoxicology concern only and does not apply to water, therefore soil endpoints must refer to parent and metabolite UR-50604. GC-MS method for parent only used at the time as LC/MS/MS not widely available. GC-MS method had 3 m/z ions but did not cover metabolite. The LC/MS/MS method covers metabolite but only 1 m/z ion. Therefore need a confirmatory method for the metabolite UR-50604. If it is concluded that residue definition for soil is parent only, then no further validation for the metabolite UR-50604 is required	Open point for Fate meeting (ECCO 137) If it is concluded that residue definition for soil is parent plus metabolite UR-50604, then confirmatory method for metabolite UR-50604 is required.
(xxiii)		Discussion point	Linearity was not recorded in the draft monograph. However, the rapporteur confirmed that this area was satisfactorily addressed in all areas. This was accepted by the meeting

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xiv)		Discussion point	The meeting noted that very few samples were analysed for each reference point in the air method and that this was not in strict adherence to the guidelines. The meeting agreed to combine the samples from both temperature and humidity conditions and this would give sufficient samples and would enable for example the %RSD to be recorded. The meeting concluded for this case this was an acceptable approach as the results were all similar.

Appendix 2

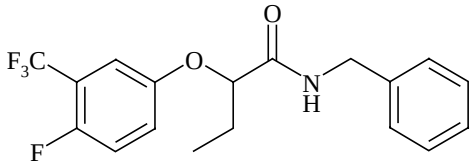
LIST OF END POINTS: **BEFLUBUTAMID**

1 Physical chemical properties section

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

Active substance (ISO Common Name)	Beflubutamid
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	Germany

Identity (Annex IIA, point 1)

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

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	75 °C (99.98 %)
Boiling point (state purity)	Decomposition
Temperature of decomposition	Decomposition begins from 128 °C
Appearance (state purity)	White fluffy powder (99.98 % and 97.46 %)
Relative density (state purity)	1.33 (99.98 %)
Surface tension	66.1 mN/m for a 90 % saturated aqueous solution (19.5 °C)

Vapour pressure (in Pa, state temperature)	$1.1 \cdot 10^{-5}$ Pa at 25 °C	
Henry's law constant (Pa m^3 mol^{-1})	$1.1 \cdot 10^{-4}$ Pa m^3 mol^{-1}	
Solubility in water (g/l or mg/l, state temperature)	$2.30 \cdot 10^{-3}$ g/l at 10 °C $3.29 \cdot 10^{-3}$ g/l at 20 °C $5.03 \cdot 10^{-3}$ g/l at 30 °C Preliminary work showed that the water solubility did not change significantly with pH.	
Solubility in organic solvents (in g/l or mg/l, state temperature)	Acetone	> 600 g/l at 20 °C
	1,2-Dichloroethane	> 544 g/l at 20 °C
	Ethyl acetate	> 571 g/l at 20 °C
	Methanol	> 473 g/l at 20 °C
	n-Heptane	= 2.18 g/l at 20 °C
	Xylene	= 106 g/l at 20 °C
Partition co-efficient (log P_{OW}) (state pH and temperature)	No pH dependency. log $P_{O/W}$ = 4.28 at 21 °C	
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH : 5 no degradation (50°C)	
	pH : 7 no degradation (50°C)	
	pH : 9 no degradation (50°C)	
Dissociation constant	Dissociation is unlikely	
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	281.5 nm	
Photostability (DT_{50}) (aqueous, sunlight, state pH)	DT_{50} 48 d (pH 7, 25°C)	
Quantum yield of direct phototransformation in water at λ > 290 nm	0.044 (pH 7)	
Flammability	Neither highly flammable nor auto flammable	
Explosive properties	Not explosive	

List of uses supported by available data

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests Controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Winter wheat Winter barley Triticale Winter rye	Northern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500 g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-~~0.128~~0.085 + 0.250-~~0.750~~ 0.500 isoproturon Spring: 0.0425-0.085 + 0.250-0.500 isoproturon	200-400 200-400	0.170-~~0.255~~ + 1.0 ~~1.5~~ isoproturon 0.170 + 1.0 isoproturon		Co-formulation with isoproturon
Winter wheat Winter barley Durum wheat	Southern Europe	ASU 95510H	F	Monocotyledon and dicotyledon weeds Autumn: BBCH 11-13 Spring: BBCH 11-29	SC	85 g/L beflubutamid + 500 g/L isoproturon	spraying	Autumn BBCH 11-29 Spring BBCH 13-29	1	-	Autumn: 0.0425-~~0.128~~0.085 + 0.250-~~0.750~~ 0.500 isoproturon Spring: 0.0425-~~0.128~~0.085 + 0.250-~~0.750~~ 0.500 isoproturon	200-400 200-400	0.170-~~0.255~~ + 1.0 ~~1.5~~ isoproturon 0.170-~~0.255~~ + 1.0 ~~1.5~~ isoproturon		Co-formulation with isoproturon

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench

8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None
with regard to toxicological data	None
with regard to fate and behaviour data	None
with regard to ecotoxicological data	N, R 50/53

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

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

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

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	GC-PND	0.05 mg/kg (cereal grain)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	not relevant	
Soil (principle of method and LOQ)	LC-MS GC-MS	0.01 mg/kg 0.01 mg/kg
Water (principle of method and LOQ)	HPLC-UV LC-MS	0.1 µg/l (surface and drinking water) 0.1 µg/l (surface water)
Air (principle of method and LOQ)	HPLC-UV	0.6 µg/m^3
Body fluids and tissues (principle of method and LOQ)	not relevant	

Appendix 3

SUGGESTED CLASSIFICATION AND LABELLING: **BEFLUBUTAMID**

1 Physical chemical properties section

No comments

ANNEX 02 TO CONCISE OUTLINE REPORT OF ECCO 137 PEER REVIEW MEETING

BEFLUBUTAMID

Rapporteur Member State: GERMANY

Specific comments on the active substances in the section **Fate and Behaviour** are listed below. The conclusions of the meeting were as follows:

1a. Comments received and discussed:

Date	**Supplier**	**File Name**
7 March 2003	Denmark	Beflubutamid_137_com01_DK
18 March 2003	United Kingdom	Beflubutamid_137_com02_UK

1b. Comments received but not discussed (because deadline of submission was not met):

Date	**Supplier**	**File Name**
None		

1c. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
None		

2. **Definition of the residues relevant to the environment:** soil & groundwater: beflubutamid and UR-50604 (phenoxybutyric acid); water: beflubutamid and UR-50604 (phenoxybutyric acid); sediment: beflubutamid and UR-50604 (phenoxybutyric acid); air: not discussed.

3. **Data on preparations:** The data set for the plant protection product was considered incomplete.

4. **Classification and labelling:** Not discussed

5. **Recommended restrictions/conditions for use:** None.

Areas of concern: Metabolite UR-50604 is predicted to reach groundwater in concentrations exceeding 0.1 μg/l. Applicant has since reduced the application rate to resolve this. PEC calculations and FOCUS modelling are to be repeated with the revised rate and the relevance of this metabolite addressed, unless it can be shown not to have potential to contaminate groundwater at >0.1 μg/l.

Appendix 1: ECCO 137 reporting table: BEFLUBUTAMID

Appendix 2: List of end points: BEFLUBUTAMID

Appendix 3: Suggested classification and labelling: BEFLUBUTAMID

Appendix 1: ECCO 137 reporting table Beflubutamid (Hb)

2. Environmental Fate and Behaviour

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
			Section 1 Data requirements: 7 Open points: 2
(i)	Rate of degradation in soil -laboratory studies	The rate of degradation was quick (5-8 days) with the exception of Speyer 2.2 soil (DT50 = 118 days). This was attributed by the applicant to low microbial biomass and repeated with a different batch of Speyer 2.2 soil to give a DT50 of 12 days. The meeting agreed with RMS, that the first batch of Speyer 2.2 soil was not microbially dead and other soils e.g. Wick showed greater decrease in microbial biomass during the study. As the study was considered valid, the longer DT50 could not be dismissed as an outlier. Although, it was clarified that the resulting DT50 values were not used in the evaluation, as first order kinetics were not considered adequate for this soil or for Arrow soil, (in first batch of Speyer 2.2 almost no degradation occurred after 30 days). Given the wide range of DT50 values, the experts noted that the DT50 selected for use in the later assessment e.g modelling, would make a difference and as only first order kinetics could be used in FOCUS, some values may have to be recalculated as first order. It was commented that a description of the soil extraction methods would have been useful. Although too late to revise the beflubutamid DAR, this was noted generally for future DAR.	
(ii)	Rate of degradation in soil -field studies	In response to a question from the meeting, RMS proposed that humidity was the most probable explanation for the difference observed in rate of degradation, between the North and South EU field trials. In the North, degradation occurred much faster (DT50 of 15-51 days) compared to in the South (DT50 of 86-103 days).	

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(iii)	Soil adsorption/ desorption	RMS proposed a lysimeter study be requested, unless the applicant demonstrates the mobile metabolite UR-50604 is either not relevant, or will not occur in groundwater > 0.1 µg/l. The meeting considered the 1/n value of 0.57 for the Koc of 6 from Evesham 3 soil was too low to be acceptable, and it was discussed whether this Koc value should be excluded from the average Koc input to groundwater modelling. As this is the lowest of 3 Koc values omitting it gives a higher mean Koc, though the experts noted the exponent (1/n) was more critical than Koc in the model, (omitting this gives a higher, less favourable mean 1/n). It was also commented that recovery of this metabolite in Evesham 3 soil was low (60.3%). It was considered there might be a possible relationship between pH and sorption, as Koc appeared to decrease with higher pH, but 3 values were insufficient evidence of this. If sorption was pH-dependent then a Koc of 9 and 1/n of 0.81 from the Speyer 2.2 soil would be appropriate to use; this is also the median of the 3 soils used. However, reducing the average Koc of 12.3 in the model to 9 was unlikely to significantly alter the results. If the applicant choose to submit a lysimeter study, then pH of the soil used might affect the results, but RMS considered it likely the applicant would opt to establish the non-relevance of the metabolite, rather than perform a lysimeter study. The meeting advised the RMS of two options, either retain the average Koc of 12.3 and 1/n of 0.87, or use the median koc of 9 and 1/n of 0.81, both based on 3 soils including Evesham 3. The important consideration was whether or not the metabolite was relevant following the applicant's assessment, as the values used in modelling its concentration in groundwater were so close. As this was a major arable crop use with a potentially large hectarage to be treated, and given the concentrations predicted in groundwater, it was essential the applicant address this issue. RMS needed to choose appropriate parameters to be input to the FOCUS model after discussion with the applicant and taking the new reduced application rate of 0.17 kg a.s/ha into account. (When recalculated with the lower application rate, at least some scenarios were likely to show concentrations in groundwater <0.1 µg/l, as Piacenza scenario currently showed concentrations twice those of the Hamburg scenario. If results are subsequently borderline, the applicant may be able to consider options such as restrictions, but any relevant metabolite must not be present at > 0.1 µg/l. Relevance of UR-50604 must be considered against the criteria in the latest version (v.10) of the Relevant Metabolites Guidance Document i.e. biological activity, mutagenicity, whether classified as toxic and an aquatic ecotoxicology assessment based on its presence in groundwater, eventually reaching surface water.	2.1 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. Open point 2.1: RMS 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.

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(iv)	PECsoil	PECsoil values to be recalculated using the revised application rate of 170 g a.s./ha instead of 255 g a.s./ha. The meeting noted that the sentence in the end points stating that no PECsoil calculation was carried out for metabolite UR-50604, but non-relevance was demonstrated, was incorrect. RMS is to delete and explain that initial PECsoil was calculated, although TWA PEC was not.	2.2 Applicant is to submit new PECsoil calculations using the revised application rate of 170 g a.s./ha. (IIIA 9.1.3) **A**
(v)	Degradation in water - sediment	The meeting questioned whether a DT50 for metabolite UR-50604 was needed, but considered this would not be possible to obtain from these data, as it was still increasing in the sediment and water phases after 100 days (study end). RMS commented that the parent compound was degraded to very low amounts by the study end, indicating that formation of the metabolite may have been near the maximum amount. It was noted that there was a photolysis DT50 of 60-65 days for UR-50604 in water. The major issue driving the aquatic ecotoxicology risk assessment was the toxicity of the parent compound to algae in surface water and algae were not expected to be as sensitive to UR-50604. However, the experts wanted some further information on the behaviour, stability and potential for accumulation of the metabolite UR-50604 in water-sediment systems. The meeting agreed with the RMS proposals and that RMS should discuss with the applicant, if further information is available on the behaviour of the metabolite UR-50604 in sediment and water. As a first step it was proposed that the applicant should consider the available information e.g. making worst case assumptions for PECsed and PECsw calculations, such as 100% conversion of parent to metabolite, either or both in water or sediment and possible use of the soil DT50. Concerns about accumulation may also be possible to mitigate using Koc values. It was proposed that the ECCO 139 (Ecotox) experts should be asked to consider whether there are any ecotoxicological issues with respect to metabolite UR-50604.	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) **A** Message from ECCO 137 (Fate) to ECCO 139 (Ecotox): The water-sediment study shows that metabolite UR-50604 was continuing to increase at the study end, in both water and sediment after 100 days. In view of this, ECCO 139 experts are asked to consider whether there are any ecotoxicological issues concerning this metabolite.

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(vi)	PECsurface water	PECsurface water values to be recalculated using the revised application rate of 170 g a.s./ha instead of 255 g a.s./ha.	2.4 Applicant is to submit new PECsurface water calculations using the revised application rate of 170 g a.s./ha. (IIIA 9.1.3) **A**
(vii)	PECsediment	PECsediment values to be recalculated using the revised application rate of 170 g a.s./ha instead of 255 g a.s./ha.	2.5 Applicant is to submit new PECsediment calculations using the revised application rate of 170 g a.s./ha. (IIIA 9.1.3) **A**
(viii)	PECgroundwater	PECgroundwater values to be recalculated using the revised application rate of 170 g a.s./ha instead of 255 g a.s./ha. RMS to clarify whether re-modelling of laboratory soil degradation data with ModelMaker was performed by applicant (as stated in DAR) or RMS (as stated in end points). The meeting asked the RMS to include more details in the end points under method of calculation of PECgw, such as DT50 values used for metabolite and type of kinetics for field studies. It was noted that the choice of DT50 used for UR-50604 made a difference as to whether concentrations of the metabolite in groundwater exceeded 0.1 µg/l for the most sensitive FOCUS scenarios e.g. Hamburg and Piacenza.	2.6 Applicant is to submit new PECgroundwater calculations using the revised application rate of 170 g a.s./ha in FOCUS modelling. (IIIA 9.2.1) **A**

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(ix)	PECgroundwater	Parent beflubutamid was not predicted to exceed 0.1 µg/l in groundwater. The only major soil metabolite, UR-50604, showed potential to contaminate groundwater above 0.1 µg/l limit. There was some discussion of different parameterisation possibly giving different results, (e.g. RMS had excluded the Speyer 2.2 DT50 of 118 days from the average normalised DT50 of 12 days used), however the overall situation of concern over the mobile metabolite was unlikely to change. To achieve a good optimisation of fit for the Speyer 2.2 groups, the normalised DT50s had only been calculated over 0-30 days, instead of up to 120 days as for the other soils. This was considered inappropriate as greater than 25%AR parent remained in Speyer 2.2 soils at 120 days. It was proposed that groundwater PECs when re-calculated should use a DT50 based on longer than 30 days of data for Speyer 2.2 soils. The applicant also excluded the DT50 value from the Arrow soil, on grounds of declining microbial activity. The meeting agreed with RMS that Arrow soil DT50 should be taken into account as microbial biomass measured was in the same order as for the other soils and the values had not been evaluated as outliers. The meeting considered that all relevant FOCUS scenarios, not just Hamburg and Piacenza should be used for both parent and metabolite. RMS to discuss these points with the applicant, assess data provided and update the list of end points with all results from all the relevant FOCUS scenarios. The experts noted that the relationship between the parent compound and metabolite should be also be taken into account for the groundwater assessment. For example, if a higher DT50 value was used for parent, then lower amounts of metabolites would be formed, as assuming faster degradation for parent was more worst-case for formation of the metabolite, UR-50604. Although it was noted that use of average degradation values was in accordance with FOCUS guidance, the meeting considered that in this case presenting a worst case range of values that might be expected was reasonable and could be helpful in guiding the applicant on a way forward. There was a suggestion that FOCUS PEARL model should be used as well as PELMO, but the meeting noted the current view was not to specify which FOCUS model to use.	2.7 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. (IIIA 9.2.1) **A**
(x)	Fate and behaviour in air	The meeting agreed with the RMS conclusions that long range transport of beflubutamid in air was not expected. It was noted that the end points referenced data on aqueous photolysis under the headings for ‘Direct photolysis in air’ and ‘Quantum yield of direct phototransformation’. RMS is to replace this with ‘No information/ data provided’.	

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xi)	Fate and behaviour of Isomers.	Following ECCO 135 (Chemistry) the applicant was required to address the biological effect of isomers. ECCO 137 (Fate) discussed whether there were any environmental fate implications. It was considered that a difference in fate profile of the 2 isomers for parent and metabolite UR-50604 could not be ruled out. Physical properties are unlikely to differ between them but there may be differences in biological degradation in terms of reactions with enzymes. Differences in relative proportions of optical isomers were observed in results of the sediment-water study and were attributed to possible selective degradation of R-isomer or isomerisation of R to S- in aqueous phase. (RMS clarified that a method of analysis used in the sediment-water study was able to elucidate differences in partitioning of the isomers, with no clear trend of one being degraded to a greater extent than the other). This also needs to be addressed for soil and the role of the isomers should be checked to see if they make any difference to the assessment, particularly where results are borderline, e.g. concerning risk to groundwater. (RMS added that for PECgw, bulk data were used, with no differentiation between stereoisomers, so if concentrations were <0.1 µg/l for the racemate, they should also be < 0. 1 µg/l for each isomer). The meeting agreed that RMS should consider whether all the issues associated with parent and the major metabolite UR-50604 each having 2 isomers have been addressed. 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.	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) **A**
(xii)	Residue definition	The meeting agreed that residue definition of parent beflubutamid and UR-50604 (phenoxybutyric acid) in soil and water. RMS is to delete reference to relevance of UR-50604 in the end points as this was still to be elucidated.	

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xiii)	Message from ECCO 135 (Chemistry) to ECCO 137 (Fate): Experts from ECCO 137 asked to comment on whether there are any concerns over the difference in results obtained for Henry's Law Constant and whether the modelling method used is acceptable.	Henry's Law Constant was generated according to a software modelling programme and was also derived from water solubility and vapour pressure, with different results. ECCO 137 experts were asked for their views. The meeting did not have details of the model used, so were unable to comment on its acceptability. The meeting noted that the water solubility value was currently not valid and was to be addressed further, therefore should the result for water solubility be different, the Henry's Law Constant would need to be recalculated.	Message from ECCO 135 (Chemistry) to ECCO 137 (Fate): Experts from ECCO 137 asked to comment on whether ther are any concerns over the difference in results obtained for Henry's Law Constant and whether the modelling method used is acceptable. Answer from ECCO 137 (Fate): ECCO 137 did not have details of the model used, so could not comment on its acceptability, but agreed that the Henry's Law Constant should be recalculated if the water solubility value that was still to be finalised, subsequently differed.

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(xiv)	Message from ECCO 135 (Chemistry) to ECCO 137 (Fate): ECCO 135 highlighted to ECCO 137 that a confirmatory method of analysis will be required if the environmental residue definition includes metabolite UR-50604.	ECCO 135 noted that if the metabolite UR-50604 was included in the environmental residue definition, then a confirmatory method of analysis will be required. ECCO 137 have included parent beflubutamid and metabolite UR-50604 in the residue definition for soil, water and sediment. Therefore, a confirmatory method of analysis for this metabolite is required.	Message from ECCO 135 (Chemistry) to ECCO 137 (Fate): ECCO 135 highlighted to ECCO 137 that a confirmatory method of analysis will be required if the environmental residue definition includes metabolite UR-50604. Answer from ECCO 137 (Fate) and message to ECCO 140 (Overview): the residue definition in soil, water and sediment is proposed as beflubutamid and UR-50604. Therefore, a confirmatory method of analysis for UR-50604 will be required.

Appendix 2

LIST OF END POINTS: **BEFLUBUTAMID**

2 Fate and behaviour section

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

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

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

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

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

Soil adsorption/desorption (Annex IIA, point 7.1.2)

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

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

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

$PEC_{(s)}$ mg/kg	Single application Actual	Single application Time weighted average
Initial	0.340	---
Short term24 h	0.338	0.339
2 d	0.335	0.338
4 d	0.331	0.335
Long term7 d	0.324	0.332
28 d	0.282	0.310
50 d	0.243	0.289
100 d	0.173	0.247

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

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

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

PEC$_{(sw)}$ µg/l	Single application Actual	Single Application Time weighted average
Initial	3.40	3.40
Short term24 h	3.28	3.34
2 d	3.17	3.28
4 d	2.96	3.17
Long term7 d	2.66	3.02
14 d	2.09	2.69
21 d	1.64	2.41
28 d	1.28	2.17
42 d	0.79	1.79

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

PEC (sediment) beflubutamid

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

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

PEC (sediment) metabolite UR-50604

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

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

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

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

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

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

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

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

PEC (air)

Method of calculation	Not relevant

$PEC_{(a)}$

Maximum concentration	Not relevant

Definition of the Residue (Annex IIA, point 7.3)

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

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

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

Appendix 3

SUGGESTED CLASSIFICATION AND LABELLING: **BEFLUBUTAMID**

2 Fate and behaviour section

Hazard symbol		Not discussed
Risk phrase		Not discussed
Safety phrase		Not discussed

This version does not reflect the outcome of the meeting. However, an updated version is not available at the moment.

ANNEX 02 TO CONCISE OUTLINE REPORT OF ECCO 139 PEER REVIEW MEETING

BEFLUBUTAMID

Rapporteur Member State: GERMANY

Specific comments on the active substances in the section **Ecotoxicology** are listed below. The conclusions of the meeting were as follows:

1a. Comments received and discussed:

Date	**Supplier**	**File Name**
20-3-03	INRA	Beflubutamid_139_com01_FR
6-5-03	KEMI	Beflubutamid_139_com02_SE
1-5-03	Danish Environmental Protection Agency	Beflubutamid_139_com03_DK
24-3-03	CTB	Beflubutamid_139_com04_NL
8-5-03	PSD	Beflubutamid_139_com05_UK
27-5-03	BE	Beflubutamid_139_com06 BE

1b. Comments received but not discussed (because deadline of submission was not met):

Date	**Supplier**	**File Name**
None		

1c. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
None		

2. **Definition of the residues of ecotoxicological relevance:** Water: active substance. Soil: active substance, metabolite UR 50604

3. **Data on preparations:** Dossier incomplete.

4. **Classification and labelling:** N, R50/53.

5. **Recommended restrictions/conditions for use:** Only for use in spring on winter wheat. 5 m buffer zone required to protect non-target plants.

Areas of concern: Possible risk to terrestrial and aquatic plants. Possible long-term risk to earthworms.

Appendix 1: ECCO 139 reporting table: BEFLUBUTAMID

Appendix 2: List of end points: BEFLUBUTAMID

Appendix 3: Suggested classification and labelling: BEFLUBUTAMID

Appendix 1: ECCO 139 reporting table Beflubutamid (Hb)

3. Ecotoxicology

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
			Section 3 Data requirements: 2 Open points: 11
(i)	GAP	A revised GAP was notified, the new proposed rate was up to 170 g a.s./ha for use in spring on winter wheat (DAR considers spring and autumn use at 170 – 255 g a.s./ha). Proposed product contains beflubutamid and ipu.	
(ii)	Birds/Mammals	Using the new application rate (170 g a.s./ha) and EPPO (1992), the TER is above the trigger-value of 5 for long-term risk to mammals. However, conducting the risk assessment in accordance with new guidelines raised concerns but the meeting did not believe that they were of sufficient concern to request further information. The Commission clarified that, as no real concern was raised and a decision can be made on inclusion of this a.s. in Annex I, based on the EPPO guidance, the assessment was considered acceptable. The meeting requested that the RMS should carry out a risk assessment to determine the long-term risk to mammals using the new guidance. As the log Pow > 3 the meeting requested that the RMS considered the risk to fish and worm eating birds. Metabolite UR 50604 low toxicity compared to a.s. for birds and mammals. Therefore the risk posed by this metabolite was considered acceptable. The comments of Sweden, the Netherlands, the UK and Belgium were taken into account.	Open point 3.1: 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. Open point 3.2: RMS to address risk posed to fish and worm eating birds. Open point 3.3: To refine risk assessment for new GAP

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(iii)	Aquatic life	A risk to algae was highlighted at the old GAP that was managed through the use of a buffer zone. It was likely that the new GAP would be acceptable without the use of a 5 m buffer zone. As regards metabolites, only UR 50604 was considered. Concerns had been raised by both Denmark and ECCO 137 with respect to the risk posed to aquatic life from this metabolite. The meeting noted that the DT50 in the water phase of the sediment/water study was 13 – 18 days and that it was nearly two orders of magnitude less toxic than the parent to *Daphnia magna* and fish. Therefore, the meeting concluded that further information on the chronic risk to fish and *Daphnia magna* for UR 50604 was not needed. Regarding further information on sediment dwelling organisms, it was noted that the parent compound did not trigger the need for a *Chironimid* study and therefore this factor together with only 21% partitioning to sediment indicated that risk posed was likely to be low. It was further noted that if algae and *Lemna* were of concern then the risk management measures required to protect these organisms would also afford further protection to other aquatic life and the risk regarding UR 50604. It was noted that UR 50604 was a potential ground water metabolite, the RMS highlighted that on the basis of new modelling data it was unlikely to occur at concentrations greater than 0.1 µg/l. Therefore this, together with the available toxicity data indicated that the metabolite was of no toxicological concern. The comments Denmark and the Netherlands were taken into account.	Open point 3.4: RMS to update end points for *Lemna*. Open points 3.5: RMS to update end points to indicate that in the bioaccumualtion study the clearance time was lower than 1 day. Open point 3.6: RMS to update NOEC for *Chironimus* Open point 3.7: RMS to correct for solubility with footnote in end point table to say measured concentrations were used. Open point 3.8: Update end points to address new GAP. Message from ECCO 137 (Fate): The DT50 of UR 50604 in the water phase of the sediment/water study was 13 – 18 days. As its toxicity was also two orders of magnitude lower than the a.s. further information on the chronic risk to fish and aquatic invertebrates was not considered necessary.
(iv)	Honeybees	Acute and contact data had been considered and these indicated a low risk to bees. The UK highlighted an inconsistency between the risk assessment and the endpoint table regarding the HQ, i.e. in the endpoint table it is presented as 1.275 whereas in the DAR it is quoted as 2.55.	Open point 3.9: RMS to update end points as specified.

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(v)	Non-target arthropods	Data on a range of non-target arthropods had been submitted and the results from the *T. pyri* and *A. rhopalosiphi* studies naturally raised concerns. However, mortality of *T. pyri* was only 5.4% once a correction for control mortality had been made. The sub-lethal effects on *A. rhopalosiphi* were 44%. According to recent knowledge and due to a lack of effects with the proposed formulation (a.s. + IPU) on other non-target arthropods the meeting felt on balance (using a weight of evidence approach) that the risk was considered to be acceptable for *A. rhopalosiphi*. The comments of the UK and the Netherlands were taken into account.	Open point 3.10: RMS to update end points.
(vi)	Earthworms	The acute risk was considered to be acceptable. The first two long-term studies conducted with the formulation were not considered to be valid. Two new studies submitted (conducted with single a.s. formulation and a.s. + IPU formulation) resulted in TERs of 1 and 3.75. Both studies, therefore, highlighted a long-term risk to earthworms. Further data were requested to address the long-term risk to earthworms. It was noted that the metabolite was more acutely toxic than the a.s. and no corresponding TERs had been calculated. It was requested that further information should be submitted to address the risk posed by the metabolite. The comments of Sweden, Belgium, the Netherlands and the UK were taken into account.	3.1 The applicant to address the long-term risk to earthworms from the a.s. and the risk for metabolites. (A)
(vii)	Soil macro-organisms	The comment of Belgium that the DT90field > 100 days and effects on reproduction of earthworms were observed was taken into account. Consequently the meeting considered the need for a collembola or litter bag test. As the DT was between 143 – 180 days a collembola study was requested.	3.2 Data are required to address the risk to soil macro-organisms (e.g. study on collembola) (A)
(viii)	Soil microbial processes	The meeting highlighted no concerns.	
(ix)	Non target flora and fauna	Data for 6 species using formulation resulted in an EC50 for the most sensitive species of 14.8 g a.s./ha. Using this risk mitigation (5 m) gave acceptable TERs (>5). Risk management levels to be considered at MS level. The metabolite UR 50604 showed low herbicidal activity and hence no risk was perceived.	Open point 3.11: RMS to include non-target flora and fauna in list of end points.
(x)	Sewage	A study was submitted which indicated the EC50 was greater than 100 mg/l and hence no concerns.	
(xi)	Classification	N, R50 & R53	
(xii)	Residue definition	Water phase: active substance. Soil: active substance, UR 50604	

Appendix 2

LIST OF END POINTS: **BEFLUBUTAMID**

3 Ecotoxicology section

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

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

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
0.255	Cereals	Herbivorous bird	acute	>285	10
0.255	Cereals	Herbivorous bird	short-term	>185	10
0.255	Cereals	Herbivorous bird	long-term	36	5
0.255	Cereals	Insectivorous bird	acute	>660	10
0.255	Cereals	Insectivorous bird	short-term	>650	10
0.255	Cereals	Insectivorous bird	long-term	125	5
0.255	Cereals	Insectivorous mammal	acute	>710	10
0.255	Cereals	Insectivorous mammal	long-term	114	5

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

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/L) *
Laboratory tests				
O. mykiss	Active substance	acute	Mortality EC_{50}	1.86
P. promelas	”	long-term	Growth NOEC	0.11
D. magna	”	acute	Immobilization EC_{50}	1.64
”	”	chronic	Reproduction NOEC	0.455
S. capricornutum	”	chronic	Biomass EC_{50}	0.00455
A. flos-aquae	”	chronic	Biomass EC_{50}	> 3.31
C. riparius	”	long-term	Emergence NOEC	1.8
L. gibba	”	long-term	Fronds EC_{50}	0.02
C. riparius	”	chronic	Emergence NOEC	0.56
O. mykiss	Metab. UR-50604	acute	Mortality EC_{50}	>93
D. magna	”	”	Immobilization EC_{50}	>91
S. capricornutum	”	chronic	Biomass EC_{50}	69.2
O. mykiss	ASU 95 510 H	acute	Mortality EC_{50}	39.1
D. magna	”	”	Immobilization EC_{50}	17.3
S. capricornutum	”	chronic	Biomass EC_{50}	0.052
Microcosm or mesocosm tests				

***: with exception of the *C. riparius* test (nominal concentration) all concentrations were given as measured, maximum water solubility of beflubutamid is 3.3 mg/l**

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

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
0.170	Field crop	*S. capricornutum*	chronic	1	2.8	10
0.170	”	”	”	5	13	10

Bioconcentration

Bioconcentration factor (BCF)	140
Annex VI Trigger for the bioconcentration factor	100
Clearance time (CT_{50})	0.5 – 0.6 d
(CT_{90})	2.1 – 2.4 d
Level of residues (%) in organisms after the 14 day depuration phase	< 5

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

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

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

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.170	Cereals	oral	1.7	50
0.170	Cereals	contact	1.7	50

Field or semi-field tests
Not required

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

Species	Stage	Test Substance	Dose g as/ha	Endpoint	Effect %	Annex VI Trigger
Laboratory tests						
T. pyri	Protonymphs	ASU 92530 H	250	Mortality Fecundity	8 9	30
T. pyri	Protonymphs	ASU 95 510 H	255	Mortality Fecundity	31 0	30
A. rhopalosiphi	Adults	ASU 92530 H	250	Mortality Fecundity	0 44	30
A. rhopalosiphi	Adults	ASU 95 510 H	255	Mortality Fecundity	3 13	30
C. carnea	Larvae	ASU 92530 H	250	Mortality Fecundity	6 5	30
C. carnea	Larvae	ASU 95 510 H	510	Mortality Fecundity	18 0	30
P. cupreus	Adults	ASU 92530 H	250	Mortality Food uptake	12 8	30
P. cupreus	Adults	ASU 95 510 H	510	Mortality Food uptake	0 9	30

Field or semi-field tests
not required

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

Acute toxicity	LC_{50} 732 mg as/kg (beflubutamid) (corrected to 366 mg as/kg)
Acute toxicity (Metabolite UR-50604)	LC_{50} 229 mg/kg (corrected to 115 mg)
Reproductive toxicity	NOEC < 0.255 kg as/ha (form. ASU 92 530 H containing 500 g/l beflubutamid), equivalent to < 0.34 mg as/kg, corrected to < 0.17 mg as/kg NOEC 6 l product/ha (form. ASU 95 510 H containing Isoproturon 500 g/l and 85 g/l beflubutamid), equivalent to 0.68 mg as/kg, corrected to 0.34 mg as/kg

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

Application rate (kg as/ha)	test substance	Crop	Time-scale	TER	Annex VI Trigger
0.17	active substance	Cereals	acute	1590	10
0.17	ASU 92530 H	Cereals	long-term	> 0.7	5
0.17	ASU 95510 H	Cereals	long-term	1.5	5

*PEC 0.23 mg as/kg (see chapter B.8.3)

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

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

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

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

Appendix 3

SUGGESTED CLASSIFICATION AND LABELLING: **BEFLUBUTAMID**

3 Ecotoxicology section

Hazard symbol	**N**	Dangerous for the environment
Risk phrase	**R50**	Very toxic to aquatic organisms
	R 53	May cause long-term adverse effects in the aquatic environment

ANNEX 2 TO CONCISE OUTLINE REPORT OF ECCO 136 PEER REVIEW MEETING

BEFLUBUTAMID

Rapporteur Member State: GERMANY

Specific comments on the active substances in the section **Mammalian toxicology** are listed below. The conclusions of the meeting were as follows:

1a. Comments received and discussed:

Date	**Supplier**	**File Name**
17 February 2003	UK	COM 01 UK
25 February 2003	Belgium	COM 02 BE
3 March 2003	Netherlands	COM 03 NL

1b. Comments received but not discussed (because deadline of submission was not met):

Date	**Supplier**	**File Name**
-	-	-

1c. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
-	-	-

2. **Residues relevant to worker safety:** Parent compound and major metabolites (to be clarified at the residues meeting)..

3. **Data on preparations:** The data package submitted for ‘’Herbaflex” was considered to be complete.

4. **Classification and labelling:** The experts provisionally proposed not to classify beflubutamid pending, further information from the applicant on the mechanism of thyroid tumour induction and it's relevance to man.

5. **Recommended restrictions/conditions for use:** None at present.

Areas of concern: The main concern was a lack of any mechanistic data for the thyroid tumours seen in the rat..

Appendix 1: ECCO 136 reporting table: BEFLUBUTAMID

Appendix 2: List of end points: BEFLUBUTAMID

Appendix 3: Suggested classification and labelling: BEFLUBUTAMID

Appendix 1: ECCO 136 reporting table Active substance (Beflubutamid)

4. Mammalian toxicology

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(i)	General	The UK commented that the product Herbaflex contains two active substances, beflubutamid and isoproturon. It was noted that the RMS should consider the possible toxic effects from the presence of two active substances. The UK considered that some further reasoning was required to address whether there are possible additive and/or synergistic effects. The UK notes that both substances affect the liver (isoproturon is reported to cause hepatocyte degeneration).	
(ii)	Rate and extent of absorption	The meeting noted that the majority of radioactivity was excreted the bile (>66% at a dose of 35 mg/kg bw).	
(iii)	Distribution	The meeting considered that beflubutamid was widely distributed with the highest levels found in kidneys and liver.	
(iv)	Rate and extent of excretion	It was noted that urinary excretion of radioactivity was higher in females, than males.	
(v)	Toxicologically significant compounds	The meeting considered that toxicologically the most significant compounds, were the parent compound and major metabolites. This would need to be clarified at the residues/Fate and Behaviour Meetings.	Open Point 4.1: ECCO residues/Fate and Behaviour Meetings to consider the formation of these metabolites in plant and the environment.

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(vi)	Short-term toxicity: lowest relevant oral NOAEL	Comments from BE and NL were discussed. It was considered that based upon the data available in this 90 day mouse study, it is questionable whether the effects on the liver at the lowest dose should be considered as really adverse. Although it was also noted that there was a dose related increase in centrilobular hepatocyte hypertrophy. Members considered the high background levels of methaemoglobin, and an apparent dose relationship for this effect seen in the 90 day rat study. However this finding was not considered a major issue. Overall the critical NOAEL was considered to be 400 ppm (30 mg/kg bw/day) from the 90-day rat study.	
(v)	Genotoxicity	Based on all genotoxicity studies it was agreed that it can be concluded that the active substance was not genotoxic	
(vi)	Long term toxicity and carcinogenicity	The meeting noted there was a treatment-related increased incidence of thyroid follicular tumours in male rats the RMS considered that this was without relevance to humans. However the Notifier had provided no reasoning for considering the tumours to be without relevance to humans. Although no marked concerns were expressed by members it was felt that the Notifier should address this point.	Data requirement 4.1: Notifier to provide a commentary on the mechanism of tumour induction and it's relevance of the thyroid follicular tumours to man.
	Other toxicological studies	It was noted that data on metabolite 50604 were not required as levels were <0.1ug/l however this would need to be confirmed by E-fate ECCO	Open Point 4.2: ECCO Fate and Behaviour Meetings to confirm metabolite 50604 <0.1ug/litre.
(vii)	ADI	The meeting agreed an ADI of 0.02 mg/kg bw/d based on the NOAEL of 2 mg/kg bw/d in the 2 year rat study. A standard safety factor of 100 was considered appropriate.	
(viii)	AOEL	The meeting agreed an AOEL of 0.3 mg/kg bw/d based on the NOAEL of 30 mg/kg bw/d in the 90 day rat study and using a safety factor of 100. Correction for oral absorption was not required.	
(ix)	ARfD	Based on the toxicological profile of beflubutamid no ARfD was considered necessary.	
(x)	Dermal absorption	A default of 100% was assumed.	
(xi)	Operator exposure	Intended uses considered acceptable with the addition of PPE.	
(xii)	Worker exposure	Intended uses considered acceptable	

Appendix 2

LIST OF END POINTS: **Beflubutamid**

4 Mammalian toxicology section

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

Rate and extent of absorption:	At 35 mg/kg bw rapidly and nearly completely absorbed (>80%) based on excretion via bile (>66%) and urine (8 - 16%). Plasma C_{max}: 6 hours
Distribution:	Widely distributed highest levels found in kidneys and liver.
Potential for accumulation:	No evidence for accumulation
Rate and extent of excretion:	Completely excreted within 120 hours mainly via bile (At 35 mg/kg - 66% (females) and 85%(males)). Urinary excretion was found to be higher in females.
Metabolism in animals	Extensively metabolised by hydroxylation, cleavage of the amide bond and conjugation as glucuronides (major metabolites: phenoxybutyric acid, hippuric acid)
Toxicologically significant compounds (animals, plants and environment)	Parent compound and major metabolites (to be clarified at the residues/Fate and Behaviour Meetings)

Acute toxicity (Annex IIA, point 5.2)

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

Short-term toxicity (Annex IIA, point 5.3)

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

Genotoxicity (Annex IIA, point 5.4)	No evidence of genotoxic potential. Based on the levels in blood/plasma there was sufficient evidence that the bone marrow would be exposed in the *in vivo* assay.

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

Target/critical effect	Liver(rat and mouse); kidney + thyroid gland (rat)
Lowest relevant NOAEL / NOEL	104-wk oral, rat: 50 ppm (2.2 mg/kg bw/d)
Carcinogenicity	Not carcinogenic in mouse. Slight increase in thyroid follicular cell tumours at highest dose (3200 ppm) in rat 2 year study . Information required on the mechanism of tumour induction and its relevance to man.

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	There were no specific effects on reproduction. Impairment of bodyweight development during lactation, delay in age for vaginal opening (F1-females) at parental toxic doses; offspring kidney changes at 3200 ppm.
Lowest relevant reproductive NOAEL / NOEL	2-gen. rat: Reproductive Outcome: 3200 ppm (320 mg/kg bw/day) Parental toxicity; 200 ppm (approx. 17 mg/kg bw/day) Pup development; 200 ppm (approx. 17 mg/kg bw/day)
Developmental target / critical effect	Developmental effects on the kidney/ureter at maternally toxic doses (rat). There was no evidence of teratogenic effects.
Lowest relevant developmental NOAEL / NOEL	100 mg/kg bw/d (rat, rabbit)

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

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

Other toxicological studies (Annex IIA, point 5.8)

	No data, not required

Medical data (Annex IIA, point 5.9)

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

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI	0.02 mg/kg bw	104-wk, oral rat	100
AOEL	0.3 mg/kg bw/d	90-d, rat	100
ARfD (acute reference dose)	Not necessary, not allocated	-	-

Dermal absorption (Annex IIIA, point 7.3)

No studies performed; 100% assumed (worst case)

Acceptable exposure scenarios (including method of calculation)

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

Appendix 3

SUGGESTED CLASSIFICATION AND LABELLING: BEFLUBUTAMID

4 Mammalian toxicology section

No classification required pending, further information from the applicant on the mechanism of thyroid tumour induction and it's relevance to man.

ANNEX 02 TO CONCISE OUTLINE REPORT OF ECCO 138 PEER REVIEW MEETING

BEFLUBUTAMID

Rapporteur Member State: GERMANY

Specific comments on the active substances in the section **Residues** are listed below. The conclusions of the meeting were as follows:

1a. Comments received and discussed:

Date	**Supplier**	**File Name**
23 April 2003	The Netherlands	Beflubutamid 138 com01 NL

1b. Comments received but not discussed (because deadline of submission was not met):

Date	**Supplier**	**File Name**
None		

1c. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
None		

2. **Definition of the residues relevant to MRLs:** Beflubutamid for specified crops. Possible revision in other crops, pending investigation of enantiomeric enrichment.

3. **Data on preparations:** The data set for the plant protection product was considered complete.

4. **Classification and labelling:** Not discussed.

5. **Recommended restrictions/conditions for use:** None

Areas of concern: None

Appendix 1: ECCO 138 reporting table: BEFLUBUTAMID

Appendix 2: List of end points: BEFLUBUTAMID

Appendix 3: Suggested classification and labelling: BEFLUBUTAMID

Appendix 1: ECCO 138 reporting table Beflubutamid (Hb)

5. Residues

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
			Section 5 Data requirements: 0 Open points: 2
(i)	General	Uses proposed in cereals at GS 11 – 29 (autumn or spring). Winter wheat, barley, rye, triticale in northern Europe and winter wheat, barley and durum wheat in southern Europe.	
(ii)	Plant metabolism	Winter wheat metabolism studies were submitted to represent the intended uses. Significant residues were found in young plants, and were still detectable at harvest. Most residues were in the straw (TRR straw 1.0mg/kg; TRR grain 0.04mg/kg). The residue was mainly parent beflubutamid, but included a number of metabolites. The main metabolite was UR-5064 (0.2mg/kg in straw; 0.01mg/kg in grain), plus another four metabolites which were detectable in straw only (<0.001mg/kg in grain). There was some concern over the higher residues indicated in the metabolism study compared with the residue trials. It was generally considered that this was due to the later application timing in the metabolism study (GS33; outside the proposed GAP) compared with the residue trials (GS29)	
(iii)	Rotational crops	Residue data were available in succeeding crops of carrot and wheat (see point vii).	

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(iv)	Crop residue definition (for monitoring and risk assessment)	It was suggested that parent and metabolite UR-5064 should constitute the residue for monitoring and risk assessment. The metabolite was not of toxicological concern, however, and it was agreed that the residue definition should be the parent compound only. There was some concern over metabolism in other crops where the possibility of selective cleavage of the isomers should be taken into account. This was not a concern in wheat.	Open point 5.1: RMS to consider revising the residue definition for some crops, pending investigation of enantiomeric enrichment. The end points should conclude that there are sufficient residue data for Annex I, but there is a need to specify crops for the MRL definition (winter wheat, barley etc.).
(v)	Animal metabolism	The parent compound and metabolite UR-5064 were also found in animal studies (lactating goats; labeled parent compound; ~90% recovery. In terms of TRR, 80% of compound was excreted; 0.2% in milk; 9% in GI tract and with low levels in other organs. It was noted that residues reached a plateau rapidly after feeding.	
(vi)	Animal residue definition (for monitoring and risk assessment)	Parent compound only. It was concluded, however, that animal feeding studies were not necessary (see point viii).	
(vii)	Residues in succeeding crops	Labeled parent (phenoxy label; more stable part of the molecule) was applied to soil in accordance with the proposed GAP. In carrot, the main residue was metabolite UR-5064 and parent compound; levels were low (0.03mg/kg) in both foliage and roots. In wheat the residue was not completely characterised with low levels in grain (0.01mg/kg), but more in straw (0.10mg/kg).	
(viii)	Residues from livestock feeding studies	Low residues in grain (<LOQ). Some general concern over feeding treated straw to animals (see general point XX). It was agreed, however, that animal feeding studies were not necessary if straw was dismissed as a significant component of the diet.	
(ix)	Residue trials	Supervised residue trials were conducted on a range of cereals. At harvest the total residue was below the LOQ in grain and soil, and at 0.6 – 0.3mg/kg in straw.	

No.	Subject	Discussion ECCO-Peer Review Meeting	Recommendations ECCO-Peer Review Meeting (Annex point)
(x)	Consumer risk assessment	There had been a slight change to the ADI (to 0.02mg/kg bw)	Open point 5.2: RMS to note the change in the ADI to 0.02mg/kg bw. NEDI model (and WHO calculation) will need to be re-calculated

Appendix 2

LIST OF END POINTS: **BEFLUBUTAMID**

5 Residues section

Appendix III.4: Chapter 4 (residues)

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

Plant groups covered	wheat
Rotational crops	carrot, wheat
Plant residue definition for monitoring	beflubutamid (provisional, inclusion of metabolite UR-50604 questionable)
Plant residue definition for risk assessment	beflubutamid (provisional, inclusion of metabolite UR-50604 questionable)
Conversion factor (monitoring to risk assessment)	none

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

Animals covered	lactating goat
Animal residue definition for monitoring	none
Animal residue definition for risk assessment	none
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	yes

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

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

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

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

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

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes/no	Poultry: yes/no	Pig: yes/no
Muscle Liver Kidney Fat Milk Eggs	no studies required / conducted		

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

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
spring barley	N S	4 x <0.05 mg/kg grain 4 x <0.05 mg/kg grain		0.05 mg/kg	0
spring wheat	N S	1 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0
durum wheat	N	1 x <0.05 mg/kg grain		0.05 mg/kg	0
winter wheat	N S	4 x <0.05 mg/kg grain 2 x <0.05 mg/kg grain		0.05 mg/kg	0

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

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

ADI	0.8 mg/kg bw/d
TMDI (European Diet) (% ADI)	0.23 mg/kg bw (4.7 %)
NEDI (% ADI)	not calculated
Factors included in NEDI	not applicable
ARfD	not assigned
Acute exposure (% ARfD)	not applicable

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

Crop/processed crop	Number of studies	Transfer factor	% Transference *
no data generated			

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

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

grain of barley, oats, rye, triticale, wheat	0.05 mg/kg
other food of plant origin	0.05 mg/kg

Appendix 3

SUGGESTED CLASSIFICATION AND LABELLING: **BEFLUBUTAMID**

5 Residues section

Not discussed