Conclusion regarding the peer review of the pesticide risk assessment of the active substance

bifenox

finalised: 29 November 2007

SUMMARY

Bifenox is one of the 79 substances of the third stage, part A, of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

Belgium being the designated rapporteur Member State submitted the DAR on bifenox in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 4 July 2005. The peer review was initiated on 25 January 2006 by dispatching the DAR for consultation of the Member States and the sole applicant Feinchemie Schwebda. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed on during a written procedure in August - September 2006. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in March 2007.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 25 September 2007 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as a herbicide as proposed by the applicant on winter wheat and barley, full details of the gap can be found in the attached list of end points.
The representative formulated product for the evaluation was "Milan", a suspension concentrate (SC), the formulation also contains another active substance pyraflufen-ethyl.

Adequate methods are available to monitor all compounds given in the respective residue definition where these could be set. Residues in cereals can be determined with a multi-method (The German S19 method has been validated). For the other matrices only single methods are available to

[1] OJ No L 224, 21.08.2002, p. 25 as last amended by Commission Regulation 1095/2007, OJ L 246, 21.9.2007, p.19

determine residues of bifenox in soil and air and bifenox and aminobifenox acid[2] in water. The ground water residue definition is not finalised and further methods for bifenox acid may be required. Also it is not yet clear if methods will be required for products of animal origin.
Sufficient analytical methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. The technical specification can not be agreed on at this time as the analytical data do not support the proposed values.

In mammalian metabolism studies oral absorption of bifenox occurred in the first 48 hours after dosing and is sex and dose dependent. Bioavailability reached 29% and 53% in male and female rats respectively, after a single oral low dose. When the dose was increased, urinary excretion was reduced suggesting saturation of absorption. Based on urinary excretion, oral absorption is estimated to be 25%. No potential for accumulation was observed. Metabolism occurred by nitro-reduction and O-demethylation. Acute oral toxicity of bifenox is low in rats, however, classification with Xn, R22 – Harmful if swallowed, is required based on the oral LD_{50} found in mice (1540 and 1780 mg/kg bw in males and females respectively). No classification is required for dermal or inhalation toxicity; bifenox is not a skin or eye irritant and is not a skin sensitizer. Animals exposed to bifenox developed mild signs of porphyria as suggested by small-altered blood parameters (in rats and dogs), kidney toxicity (rat), and some altered clinical chemistry, which could suggest hepatotoxicity (rat and dog). Bifenox showed no potential for genotoxicity. Upon long-term exposure, no clear toxic effects were demonstrated in either rats or mice, which was found a limitation factor by the experts of PRAPeR 19 to conclude on the carcinogenic potential of bifenox; according to the available results, no carcinogenic potential was observed. Bifenox produced no adverse effects on fertility, slight/marginal effects on reproduction/development were observed at parental toxic doses, and no teratogenic effects were seen. No potential for neurotoxicity was evidenced. The acceptable daily intake (ADI) was set at 0.3 mg/kg bw/day and the acute reference dose (ARfD) at 0.5 mg/kg bw considering an assessment factor of 100; the acceptable operator exposure level (AOEL) was set at 0.125 mg/kg bw/day considering an assessment factor of 400 (correction of 25% for oral absorption). Dermal absorption was 1% when handling the concentrate representative formulation (Milan) and 4% when handling an in-use field dilution. According to the representative uses of Milan, and considering only the bifenox component of the formulation, the estimated operator exposure was below the AOEL when personal protective equipment (PPE) as gloves during mixing/loading and application are used according to the UK POEM model; according to the German model calculations, exposure was below the AOEL even without the use of PPE. Exposure of workers and bystanders was estimated to be also below the AOEL.

The metabolism of bifenox was investigated in winter wheat. Upon an early application (BBCH 13) bifenox was extensively and completely metabolised through hydroxylation into bifenox acid[3] and

[2] aminobifenox acid: 5-(2,4-dichlorophenoxy)-2-anthranilate acid
[3] bifenox acid :5-(2,4-dichlorophenoxy)-2-nitrobenzoic acid

the major metabolite hydroxybifenox acid[4] followed by conjugation with glucose. Identification of metabolites was based on residues in straw as the residues in grains were very low. The results of supervised residue trials indicated that, when bifenox is applied at a later growth stage (BBCH 29), unchanged bifenox is still a significant residue in straw. As the notified GAP allows for applications between BBCH 13 and 29, a significant variation in the composition of the residues may occur. Hydroxybifenox acid was not found in the rat and therefore it could not be concluded whether it needs to be included in the residue definition for risk assessment. The experts of PRAPeR 20 concluded that the levels of hydroxybifenox acid residues that could be expected in cereal crops having received an early application were not sufficiently addressed by residue trial data and further trials are needed.

In a rotational crop study significant residue levels were found in edible crops parts. However, the study had some draw backs that didn't allow finalising the assessment of whether these residues are relevant for consumer and livestock exposure and therefore further data are required.

Significant residue may also occur in the diet of ruminants; however no livestock metabolism data were submitted that would address the nature of potentially occurring residues in food of animal origin. In an available feeding study with goats, only milk was analysed for residues of bifenox, but residue levels and the potential of accumulation in tissues and organs was not investigated. Bifenox is considered a fat soluble compound. Therefore further data are required to address residues in food of animal origin.

The consumer dietary intake and risk assessment cannot be finalised pending data submission to address the identified data gaps. While the consumer exposure to residues of bifenox in grains (all below the LOQ) is expected to be insignificant (<1% of the ADI and ARfD respectively), the exposure to residues in food of animal origin and rotated crops cannot be assessed due to lack of data.

In soil under aerobic conditions bifenox exhibits low to moderate persistence forming the major soil metabolite bifenox acid (accounting for up to 79% of applied radioactivity (AR)) which exhibits moderate to high persistence. Mineralisation of both the chlorophenyl and nitrophenyl rings to carbon dioxide was relatively limited accounting for 3.8-8% AR after 90-92 days. The formation of unextractable residues was a significant sink, accounting for 28-41 % AR after 90-92 days. Bifenox is immobile or exhibits low mobility in soil, bifenox acid exhibits high to medium mobility in soil. There was no indication that adsorption of either bifenox or bifenox acid was pH dependant.

In dark natural sediment water systems bifenox degraded exhibiting low persistence in both water and sediment to the metabolite aminobifenox[5] in sediment which exhibited moderate persistence and to aminobifenox acid in water. In mesocosm studies (light exposed) low levels of 2,4-dichlorophenol were produced which exhibited low persistence. The terminal metabolite, CO2, was a small sink in the material balance accounting for a maximum of 4.9 % AR at 105 days (study end). Unextracted sediment residues were the major sink representing 60-64 % AR at study end. The necessary surface water and sediment exposure assessments were appropriately carried out using the agreed FOCUS

[4] hydroxybifenox acid: 5-(2,4-dichloro-?-hydroxy-phenoxy)-2-nitrobenzoic acid
[5] aminobifenox: 5-(2,4-dichlorophenoxy)-2-aminobenzoic acid methyl ester

scenarios approach for bifenox at steps 1-4, with spray drift mitigation being applied at step 4. For the metabolites aminobifenox, aminobifenox acid, 2,4-dichlorophenol and [bifenox acid that may leach from soil to surface water] appropriate FOCUS step 1 and 2 calculations were carried out. These values are the basis for the risk assessment discussed in this conclusion.

The potential for groundwater exposure from the applied for intended uses by bifenox above the parametric drinking water limit of 0.1 µg/L, was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios. However for the metabolite bifenox acid, in geoclimatic regions represented by the Okehampton and Piacenza FOCUS groundwater scenarios contamination of groundwater above the 0.1 µg/L limit cannot be excluded and a metabolite non relevance assessment was triggered for this metabolite. The conclusion of this assessment using the available toxicological information was that bifenox acid was not relevant with respect to groundwater. However information on pesticidal activity of bifenox acid against target weeds is required before the groundwater non relevance assessment can be finalised.

The acute and long-term risk to birds and the acute risk to mammals were assessed as low in the first tier-risk assessment. The long-term risk to mammals needed refinement. The suggested refinement based on wood mouse (*Apodemus sylvaticus*) as a focal species and the PD and measured residues were accepted by the meeting of experts but not the suggested PT values. The long-term TER of 5 is not met without PT refinement. Therefore, a data gap for submission of further data to refine the risk was identified in the experts' meeting. Bifenox is very toxic to aquatic organisms with algae driving the risk assessment. No TER met the Annex VI trigger based on FOCUS step3 PECsw. A mesocosm study was submitted. A NOAEC of 4 µg bifenox/L and a safety factor of 2-3 was agreed in the meeting of experts. Risk mitigation measures such as a no-spray buffer zone of 10 m is required to achieve a TER of >3 and a no-spray buffer zone of 5 m is required to achieve TERs >2 for all FOCUS step4 scenarios. A range of non-target arthropods was tested. *Typhlodromus pyri* reacted very sensitive in the standard glass-plate test. In an extended laboratory study it was shown that adverse effects in the off-field area are <50%. Hence the risk to predatory mites was considered to be sufficiently addressed. A long-term/reproduction study with bifenox and earthworms was not considered necessary since the DT_{90} values were in the range of 28-107 days and only one application per year is proposed. However a chronic study with another formulation containing additionally two other active substances was submitted by the applicant. No effects were observed at the highest tested application rate which is about 5 times the suggested field rate. No long-term/reproduction study with earthworms was submitted for the metabolite bifenox acid for which DT_{90} values ranged from 80-517 days. It is very likely that bifenox-acid was formed in the long-term test with the formulation but it is uncertain if it reached amounts comparable to the PECsoil. Taking into account that no effects were observed in the long-term study at an application rate of up to 5 times the suggested field rate and that no acute effects were observed in the study with bifenox-acid no further studies with earthworms are considered necessary. No studies with bifenox and other soil non-target micro-organisms were triggered. The need for studies with bifenox-acid was discussed in the experts´ meeting. It was agreed that no study is required if the long-term risk to earthworms is sufficiently addressed. The risk to

bees, soil non-target micro-organisms, non-target plants and biological methods of sewage treatment were assessed as low.

Key words: bifenox peer review, risk assessment, pesticide, herbicide

TABLE OF CONTENTS

BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Bifenox is one of the 79 substances of the third stage, part A, covered by the Regulation (EC) No 1490/2002 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Belgium submitted the report of its initial evaluation of the dossier on bifenox, hereafter referred to as the draft assessment report, to the EFSA on 4 July 2005. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions and the rapporteur Member State submitted a revised version of the draft assessment report. In accordance with Article 11(2) of the Regulation (EC) No 1490/2002 the revised version of the draft assessment report was distributed for consultation on 25 January 2006 to the Member States and the main applicant Feinchemie Schwebda as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed during a written procedure in August - September 2006 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings in March 2007. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place with representatives from Member States on 25 September 2007 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 11(4) of the Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received;
- the resulting reporting table (rev. 1-1 of 12 October 2006)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation;
- the evaluation table (rev. 2-1 of 27 September 2007).

Given the importance of the draft assessment report including its addendum (compiled version of November 2007 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Bifenox is the ISO common name for methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate (IUPAC).

Bifenox belongs to the class of nitrophenyl ether herbicides such as fomesafen and lactofen. Bifenox is taken up via leaves, emerging stems and roots. It acts by cellular membrane disruption and by inhibition of photosynthesis.

The representative formulated product for the evaluation was "Milan", a suspension concentrate (SC), the formulation also contains another active substance pyraflufen-ethyl.

The evaluated representative use is as a herbicide as proposed by the applicant on winter wheat and barley, full details of the gap can be found in the attached list of end points (Summary of representative uses evaluated appendix 1). The environmental peer review noted that the prescribed growth stage application window (BBCH 13-29) may happen before March (November-December). In agreement with the representative use table, the available environmental risk assessment has only assessed spring (mid March) applications. Autumn applications are not covered by the available assessment.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

At the moment no minimum purity of bifenox as manufactured can be given, because further clarification is needed. Also the technical specification in general can not be concluded on as the analytical data do not support the proposed values. According to the FAO specification 413/TC/S/F (1992) the minimum purity should not be less than of 950 g/kg. In the meeting of experts the proposed technical specification was rejected as it was not supported by the available data. After the meeting of experts the rapporteur produced an addendum proposing a specification which is in line with the batch analysis however, this was rejected by the applicant. This means that the data gap identified by the meeting of experts remains and the applicant needs to provide a justification to support their specification. For this reason there is no agreed specification for this compound. The mammalian toxicology meeting of experts were able to accept the original specification and also the specification that is in the addendum because the levels presented are within the original specification. However, the ecotoxicology meeting of experts were unable to accept it and a data gap was raised.

The technical material contains 2,4-dichloroanisol and 2,4-dichlorophenol, which have to be regarded as relevant impurities. The maximum content in the technical material given in the FAO specification is 6 g/kg for 2,4-dichloroanisole and 3 g/kg for 2,4-dichlorophenol. These levels were agreed by the mammalian toxicology meeting of experts but were not agreed by the ecotoxicology meeting of experts. There may also be other relevant impurities but this is the subject of a data gap.

The content of bifenox in the representative formulation is 500 g/L (pure).

Beside the specification, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of bifenox or the respective formulation. However, the following data gaps were identified:
A justification for the limits in the specification is required.
GLP analysis of 5 batches for nitrosamine content.

The main data regarding the identity of bifenox and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of bifenox in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material and the relevant impurities in the formulation.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. bifenox in food of plant origin (cereals, only); bifenox in soil and air and bifenox and aminobifenox acid[6] in surface water.

Residues in food of plant origin can be determined with a multi-method (the German S19 method has been validated).
The method for soil was by GC-MS with an LOQ of 0.02 mg/kg, for water there were two GC-MS methods for bifenox with an LOQ of 0.1 µg/kg and 0.05 µg/kg. There was also a GC-ECD method available for bifenox in water with an LOQ of 0.05 µg/kg. The metabolite aminobifenox acid in water was analysed by LC-MS/MS with an LOQ of 0.1 µg/kg. The residue definition for ground water is not finalised and further methods may be required for bifenox acid. For air the method of analysis was by GC-ECD with an LOQ of 10 µg/m^3.
It can not be concluded if an analytical method for products of animal origin is required as there are data gaps identified in the residues section. A method of analysis for body fluids and tissues is not required as the active substance is not classified as toxic or very toxic.

2. Mammalian toxicology

Bifenox was discussed during the PRAPeR Expert's Meeting on mammalian toxicology in March 2007 (PRAPeR 19, Round 4).
No analysis of the impurities present in the batches used for the toxicological studies is available. The Experts considered reasonable to assume that the batches used in the toxicological studies were similar to the proposed technical specifications in the DAR and agreed that the proposed technical specification was adequately covered by the batches used in the toxicological studies.
EFSA note:
RMS proposed a revised technical specification for the current source (see addendum to volume 4, dated June 2007), which would still be covered by the batches used in the toxicological studies; however this specification has not been peer-reviewed. Therefore, while the technical specifications are not agreed on, no conclusion can be drawn on the compliance of the batches used in the toxicological studies with the current manufactured material.

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Oral absorption occurred in the first 48 hours after dosing and was sex and dose dependent. Bioavailability reached 29% and 53% in males and females respectively, after a single oral low dose. When the dose was increased, urinary excretion was reduced suggesting saturation of absorption. Based on urinary excretion, oral absorption is estimated to be 25%. The only tissues shown to have significant radioactivity levels seven days after dosing were the kidneys and liver, no evidence of retention in tissues was observed. Bifenox appeared mostly unchanged in faeces but was completely

[6] 5-(2,4-dichlorophenoxy)-2-anthranilate acid

metabolised in urine samples. Metabolism occurred by nitro-reduction and O-demethylation leading to formation of **aminobifenox**[7] (in faeces) and **bifenox acid**[8] (in urine).

2.2. ACUTE TOXICITY

Acute oral toxicity of bifenox is low in rats (LD_{50} oral >5000 mg/kg bw), but the lower oral LD_{50} found in mice (1540 and 1780 mg/kg bw in males and females respectively) was considered to require classification with **Xn (Harmful), R22 – Harmful if swallowed**. No classification is required for dermal or inhalation toxicity; bifenox is not a skin or eye irritant and did not show sensitisation properties in a Magnusson & Kligman test.

2.3. SHORT TERM TOXICITY

Protoporphyrinogen oxidase, a membrane-bound flavoenzyme that catalyzes the final reaction of the common branch of the haem and chlorophyll biosynthesis pathways in plants, is the molecular target of diphenyl ether-type herbicides such as bifenox.

In mammals, protoporphyrinogen oxidase IX is one of the enzymes involved in haem (porphyrin) synthesis. Its inhibition could result in liver, dermal and kidney toxicity, apparently due to accumulation of haem precursors. In humans porphyrias are relatively uncommon inherited or acquired disorders, in which clinical manifestations are attributable to a disturbance of haem synthesis (porphyrin metabolism), usually associated with endogenous or exogenous stressors. Only limited information is available in the open literature to extrapolate from experimental animals to assess the potential risks of specific chemicals for humans.

Oral short term toxicity of bifenox was assessed in 90-day dietary studies in rat and mice, and in a one-year dog study; as the mice study was quite incomplete, it couldn't be used for the final evaluation. In rats, the target organs appeared to be blood, kidney and liver, as suggested by slightly decreased RBC parameters with partial compensation, brownish-red urine and pyelonephritis causing death at the top dose of 2500 mg/kg bw/day, and liver enlargement and altered clinical chemistry at 900 mg/kg bw/day and up. The NOAEL was the dose level of 300 mg/kg bw/day based on liver effects observed at the next higher dose level. Dogs exposed to bifenox over a 52-week period, showed signs of blood toxicity at interim sacrifice and liver toxicity at terminal sacrifice at the top dose of 1000 mg/kg bw/day. The NOAEL was the dose level of 145 mg/kg bw/day.

Percutaneous administration of bifenox to rats for 28 consecutive days at dose level up to 1000 mg/kg bw/day produced at the highest dose a slight decreased body weight gain and food consumption and signs of liver changes. The NOAEL was the next lower dose level of 150 mg/kg bw/day.

2.4. GENOTOXICITY

Although structurally related to the genotoxic carcinogen nitrofen, bifenox showed no potential for genotoxicity or clastogenicity, when tested *in vitro* in *Salmonella typhimurium*, in chromosomal aberration test in CHO cells, in gene mutation test in the TK locus of L5178Y TK+/- mouse

[7] aminobifenox: 5-(2,4-dichlorophenoxy)-2-aminobenzoic acid methyl ester
[8] bifenox acid: 5-(2,4-dichlorophenoxy)-2-nitrobenzoic acid

lymphoma cells, in the CHO/HGPRT mammalian cell forward gene mutation test or in primary rat hepatocytes UDS assay, or *in vivo*, in a mouse bone marrow micronucleus assay and a metaphase analysis in rat bone marrow. The inactivity of bifenox may be explained by a steric interference of carboxyl-moiety in ortho position next to the nitro group with enzymes (acetyltransferases, sulfotransferases), which activate the N-hydroxylamine intermediate to highly reactive O-conjugates.

2.5. LONG TERM TOXICITY

After long-term exposure, in both rats and mice, no clear toxic effects were demonstrated up to the top dose of 252 mg/kg bw/day in rats and 188 mg/kg bw/day in mice. The selection of dose levels was discussed in the light of the validity of both studies by the experts. In the rat study, reduced body weight gain at the top dose was < 10% (6% in males and females) and not statistically significant together with reduced food consumption. The meeting concluded that these effects are not adverse; therefore the NOAEL was set at 252 mg/kg bw/day (5000 ppm). In the mice study, the NOAEL was agreed to be the dose level of 30 mg/kg bw/day (200 ppm) based on small effects on haematological parameters (reduced platelets and reticulocytes counts) at 188 mg/kg bw/day (1000 ppm). The meeting discussed the relevance of histopathological findings in the mice's kidneys and concluded that they were not toxicologically relevant. Bifenox showed no carcinogenic effects in either species. The meeting concluded that the long-term studies could be considered acceptable in terms of risk assessment, but are of limited quality to conclude sufficiently on the carcinogenic profile of the substance.

2.6. REPRODUCTIVE TOXICITY

In a two-generation study in rats, the parental (systemic) and reproductive NOAEL were 44.5 mg/kg bw/day (750 ppm) based on decreased pup and litter weight at weanling in F1 and F2 generation and slightly reduced implantation rate at the top dose of 276 mg/kg bw/day dose level (4500 ppm) in the presence of slight parental toxicity (decreased body weight gain).

Two developmental studies were performed in rabbits (the second study was presented in an addendum to the DAR) and one in the rat, additional information was found in the open literature on mice. In the rat study, the top dose of 3600 mg/kg bw/day caused clinical signs such as salivation, staining of the mouth and patchy hair loss. A marginally higher incidence of foetuses with large fontanelle was also noted at the high dose. Based on these findings, the maternal and foetal NOAEL were the dose level of 900 mg/kg bw/day.

In rabbits, maternal toxicity was evident at doses much lower than those inducing slight toxic effects in rats, dogs and mice. In the first study, the dose level of 200 mg/kg bw/day resulted in maternal mortality and compound-related clinical signs of toxicity. This dose level elicited a slight increased incidence of angulated hyoid alae in foetuses, which was not replicated in the second study. In the second study, the dose level of 160 mg/kg bw/day induced slight maternal body weight loss and clinical signs as hypoactivity, cyanotic appearance and ataxia, no effects on developmental parameters were observed. However a NOAEL for developmental effects of 160 mg/kg bw/day was proposed as maternal death at higher doses reduced the number of viable litters, making the evaluation of developmental effects not possible. Considering both studies and dose spacing, the

overall NOAEL for maternal toxicity was 50 mg/kg bw/day and the NOAEL for developmental toxicity was 160 mg/kg bw/day based on the slight increased incidence of hyoid alae angulated at 200 mg/kg bw/day.
The study reported in the open literature suggested that developmental toxicity was not seen in mice.
Bifenox do not require classification for reproductive or developmental toxicity.

2.7. NEUROTOXICITY

No studies were conducted. Bifenox do not belong to chemical groups known to induce neurotoxicity, no concern was raised from the other general studies, and therefore no study is required.

2.8. FURTHER STUDIES

Cytotoxic and porphyrinogenic effects of bifenox and other diphenyl ethers were studied in cultured rat hepatocytes. No concentration-dependent decrease in viability was observed in the bifenox-treated hepatocytes at a concentration up to 1.0 mM. The maximum porphyrin accumulation was observed at 0.25 mM for bifenox (21-fold). The predominant species was protoporphyrin IX in all of the diphenyl ethers-treated cultures. These results suggest that bifenox inhibits protoporphyrinogen oxidase, resulting in the accumulation of protoporphyrin IX.

Metabolites

The main plant metabolite **hydroxybifenox acid**[9] was not found in the rat metabolism, but was considered by the RMS as a detoxification step of the parent molecule. However the experts considered that no conclusion on the toxicological profile of this metabolite could be reached on the basis of the data provided. Therefore, a new data gap was set for information on the toxicological profile of the main plant metabolite hydroxybifenox acid.

EFSA note: The relevance of the groundwater metabolite **bifenox acid**[10] was not discussed at the expert meeting, however, this metabolite was identified as the main metabolite in rat urine (see 2.1), so its toxicity is covered by the studies where bifenox was dosed and it is not expected to be more toxic than bifenox. Therefore, it can be considered as a non-relevant groundwater metabolite, according to the criteria pertaining to toxicology set in the Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater (Sanco/221/2000-rev.10 of February 25, 2003).

Impurities

The relevance of the impurity **2,4-dichlorophenol** present in technical bifenox was discussed by the experts. The impurity is classified as "Toxic in contact with skin, Harmful if swallowed and Corrosive – causes burns" in Annex I to Directive 67/548/EEC. In the FAO specification, a maximum limit of 3 g/kg is proposed for this impurity. The bifenox batches used in the toxicological studies are in accordance with FAO specification with a minimum purity of 97%. The meeting confirmed that

[9] hydroxybifenox acid: 5-(2,4-dichloro-?-hydroxy-phenoxy)-2-nitrobenzoic acid
[10] bifenox acid: 5-(2,4-dichlorophenoxy)-2-nitrobenzoic acid

this impurity is of toxicological relevance and agreed with the maximum limit of 3 g/kg already proposed in FAO specification.

The impurity **2,4-dichloroanisole,** the methyl ether of 2,4-dichlorophenol and result from the methylation of the latter, was confirmed by the experts as being toxicologically relevant and the maximum limit proposed in the FAO specification was agreed.

The meeting noted that the technical material may contain **nitrosamines** (but further batch analysis is required according to GLP – see chapter 1).

2.9. MEDICAL DATA

A medical surveillance from a bifenox production site in France did not indicate clear compound related effects. Bifenox is a protoporphyrinogen oxidase inhibitor, and accumulation of photoreactive by-products, the porphyrins can occur, causing cutaneous photosensitivity and dermopathic manifestations.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

ADI

The **ADI for bifenox was established at 0.3 mg/kg bw/day** based on the NOAEL of 30 mg/kg bw/day from the carcinogenicity study in mice and an assessment factor of 100.

AOEL

Initially in the DAR, the Rapporteur Member State proposed an AOEL of 0.360 mg/kg bw/day, based on the 1-year oral dog study (NOAEL = 145 mg/kg bw/day), considering dose spacing used in the studies. The experts considered that the two-generation rat study (NOAEL = 44.5 mg/kg bw/day) would support the selection of the overall NOAEL from the developmental rabbit studies (NOAEL = 50 mg/kg bw/day).

The AOEL was set at 0.125 mg/kg bw/day, based on the overall NOAEL of 50 mg/kg bw/day from the developmental rabbit studies, which is supported by the two-generation rat study, considering a safety factor of 100 and a correction factor for oral absorption of 25%.

ARfD

Initially in the DAR, RMS proposed to use the developmental rabbit NOAEL of 20 mg/kg bw/day to calculate the ARfD, however as the Applicant provided the second developmental rabbit study, the overall NOAEL could be set at 50 mg/kg bw/day.

The ARfD was set at 0.5 mg/kg bw, considering the NOAEL of 50 mg/kg bw/day from the developmental rabbit studies and an assessment factor of 100.

2.11. DERMAL ABSORPTION

The formulation tested in an *in vitro* dermal absorption study is equivalent to the representative formulation (Milan SC formulation). The experts agreed on values for dermal absorption of 4% for

the dilution and 1% for the concentrate formulation based on the comparative *in vitro* study using rat and human skin after an 8-hour exposure and a 24-hour sampling period.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product Milan is a suspension concentrate formulation containing 500 g/L of bifenox and 9 g/L of pyraflufen-ethyl. The assessment below has only considered the bifenox component of the formulation. Since there is no agreed procedure for performing combined assessments for more than one a.s., combined exposure to bifenox and pyraflufen-ethyl has to be taken into account at Member State level. Consequently, the risk assessment for the formulation cannot be concluded for the operators, workers and bystanders.

Operator exposure

Milan is recommended as an herbicide for post-emergence application to control broad-leaved weeds in winter cereals. The estimations are based on standard tractor-mounted spraying equipment for field crops. Milan is to be applied at a maximum rate of 1.5 L product/ha corresponding to 0.75 kg bifenox/ha, application volume of 100 L/ha, work rate of 50 ha/day.

According to the UK POEM model calculations, the exposure of operators is below the AOEL only if PPE (gloves during mixing & loading and application) are used. According to the German model, the exposure is below the AOEL even when no PPE are worn; using the standard assumptions of the German model (i.e. 20 ha/day work rate), a still lower level of exposure would be estimated.

Estimated operator exposure presented as % of AOEL (0.125 mg/kg bw/day) after application of Milan, according to calculations with the UK POEM model and German model. The default for body weight of operator is 60 kg for UK POEM and 70 kg for the German model. A work rate of 50 ha/day was used for either models.

Tractor-mounted (field crop)	No PPE	With PPE*
UK POEM	182	32
German model	45	29

*PPE: gloves during mixing, loading and application.

Worker exposure

Milan is applied in cereals at early growth stages, which generally do not require cultivation work after application. According to a German re-entry model approach, a transfer factor of 3000 cm^2 x kg a.i./ha, work rate of 6 ha/day and a penetration factor through clothing of 0.05 when using PPE (gloves, long sleeved shirt and long trousers) were used to assess the worker exposure. Exposure of workers was estimated to be below the AOEL, even when no PPE are used.

Estimated worker exposure presented as % of AOEL (0.125 mg/kg bw/day)

Field crop (cereals)	No PPE	With PPE*
Worker exposure	53	2.6

*PPE: gloves, long sleeved shirt and long trousers.

Bystander exposure

Two approaches for the calculation of bystander exposure are proposed in an addendum to the DAR. It can be estimated that bystander exposure would reach at most 2.2% of the AOEL (0.125 mg/kg bw/day), assuming a drift deposition for an 8 m distance in field crop of 0.13%, an exposed area of the skin of 0.4225 m^2/person/day and a body weight of 70 kg.

3. Residues

Bifenox was discussed by the experts in residues in the PRAPeR meeting in March 2007 in Parma (PRAPeR 20, Round 4).

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism of bifenox was investigated in winter wheat with test substance ^{14}C labelled in either the chlorophenyl-ring or the nitrophenyl-ring. The application rate was comparable (*ca* 1.2 N) with the proposed cGAP rate, however the application was made at the three to four leaves stage (BBCH 13/14) while the cGAP permits a latest time of application at the end of tillering (BBCH 29). Samples were taken before plant maturity (forage, hay) and at the over-ripe stage (grain, straw). The meeting of experts agreed that the metabolism study can be considered sufficiently representative to support the notified use.

At harvest, the total amount of radioactive residues (TRR) in wheat grain was less than 0.01 mg/kg for both labels whereas the level of the residues in straw accounted for 0.18 and 0.26 mg/kg respectively for the two labelling moieties. In forage, total residues of up to 2.7 mg/kg were found. In average 80% of the TRR could be extracted from forage, hay and straw samples. The residual unextracted radioactivity was not further investigated. More than 90% of the extractable residues in forage and hay and around 80% of the extractable residues in straw could be identified. The major compound of the forage residues was bifenox (44-56 % TRR). However, no bifenox was present in the hay and straw samples. The major compounds were identified as hydroxybifenox acid (position of the hydroxygroup not determined) and a tentatively characterised compound, the glucose conjugate of hydroxybifenox acid. From grain, only 40- 49 % of the TRR could be extracted, and due to the very low level of the TRR in grains (0.006 mg/kg) no further identification was attempted.

In winter wheat, bifenox was extensively and completely metabolised via hydroxylation steps to bifenox acid and a hydroxy-derivative of bifenox acid followed by conjugation with glucose forming conjugates of the hydroxybifenox acid compound. There was no significant difference between the

two radiolabels, indicating that, as far as residues in wheat were investigated, the bifenox ether linkage remained intact.

Based on the available metabolism data it was agreed that with regard to the notified representative use the residue definition for grain should be bifenox for risk assessment and monitoring purposes by default since the TRR in grain was below the trigger value for identification of 0.01 mg/kg. It is however noted that for other uses in cereals that may lead to significant residue levels in the grain further data will be necessary to refine the residue definition. The experts discussed also the relevant residue in potential feed items, which appeared to be dependent of the growth stage of the plant at application. The vast majority of the hay and straw residues were made up by hydroxybifenox acid, free or conjugated with glucose (together 65-74% TRR), in forage it accounted for around 24% TRR. The toxicity of the non rat metabolite hydroxybifenox acid is unknown and therefore the experts could not conclude if it should be considered in the residue definition for forage and straw for risk assessment purposes (refer to paragraph 2.8). Also no conclusion could be drawn with regard to a residue definition applicable to rotational crops (refer to 3.1.2 below).

A number of residue trials with bifenox in winter wheat and winter barley carried out in representative cereal growing areas in northern and southern Europe over two decades were submitted, but not all of them support the notified GAP in terms of the application rate. In the trials selected for assessment of the representative use the time of application varied between the growth stages BBCH 24 and 31. Bifenox was the residue analysed for in all trials. In a limited number of trials, the most recent ones, also 5-hydroxybifenox acid[11] was analysed for. All selected residue trials were supported by sufficient storage stability data and validated analytical methods. In wheat and barley grain no residues above LOQ were found, but in straw residues of bifenox up to 0.49 mg/kg could be detected. With the exception of one wheat forage sample no residues of 5-hydroxybifenox acid were detected if analysed for.

When comparing the results of the metabolism study and the supervised residue trials the experts noted that when bifenox is applied at a later growth stage, as occurred in the residue trials, unchanged bifenox is still the significant residue in cereal straw, and that when bifenox is applied at an earlier growth stage, as in the metabolism study, the metabolites hydroxybifenox acid (hydroxy-group position not confirmed) and its glucose conjugates are the significant residues in straw.

However, the notified GAP allows for applications between BBCH 13 and 29 and hence significant variation in the composition of the residues may occur. There was some concern that not all the available trials were analysed for hydroxybifenox acid metabolite (substituted at any position, 4 trials in wheat and barley, respectively) and no trials with an application at early growth stage, where hydroxybifenox acid might be present, were in the data set. Therefore the experts concluded that the applicant should provide 4 additional residue trials where application is made at BBCH 14 and samples are analysed for bifenox and hydroxybifenox acid (all possible substitution positions) including its conjugates at harvest and at interim time points. These additional trials will also be

[11] 5-hydroxybifenox acid: 5-(2,4-dichloro-5-hydroxy-phenoxy)-2-nitrobenzoic acid

useful for defining the ratio of the hydroxybifenox acid metabolite including its conjugates to bifenox which then can be used in the further risk assessment.

Data concerning the effects of industrial cereals processing on the residue levels were not required mainly as no significant residues (greater than 0.1 mg/kg) occurred in cereal grains at harvest which would be processed.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Bifenox DT_{90} values calculated in field degradation conditions ranged between 27 and 106 days. For the major soil metabolite bifenox acid the highest potential accumulation was estimated by EFSA (using a decline DT_{50} of 269.7 days - refer to paragraph 4.1.2 of this document).
Therefore, studies in succeeding and rotational crops are needed to address the potential for uptake of residues from soil in the crops rotated with the treated cereal crops.
In the submitted study the application rates were not included and the RMS calculated these from the reported concentration in soil, assuming a density of 1.5 kg/L and a soil depth of 20 cm. The estimated application rates are 2.4-8 N. However the plant back intervals were too long (120 and 570 days) and moreover the crops were not harvested mature. Total residues above 0.01 mg/kg were found in edible crop parts e.g. in radish roots (0.07 mg/kg at *ca* 4 N rate) but also in wheat and spinach. There was no identification of the residues and it was possible that there would be relevant residues above 0.01 mg/kg in edible plant parts even at the 120 day plant back period. It is therefore expected that with shorter plant back periods even higher TRR levels would be found. The experts concluded that the study does not sufficiently address residues in rotational crops and a new rotational crop study with shorter plant back intervals and a sufficient rate of identification of residues is needed.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

The residue trials showed that significant residues (>0.1 mg/kg) could occur in livestock total diet. Moreover, bifenox is fat soluble. Taking all information into consideration the meeting of experts agreed that a metabolism study with ruminants is required to address potentially occurring residues in food of animal origin (new data gap). It should be considered if the study needs to include dosing with hydroxybifenox acid (depending on its mammalian toxicity and the new residue trials) as well as bifenox.
A feeding study in lactating goats was still provided. Unlabelled bifenox (approx. 1 mg/kg bw) was administered to the animals for 14 consecutive days. However, no analysis of the goat tissues was performed. In all the analysed milk matrices the residue levels of bifenox were at or below the LOQ of the analytical method (0.01 mg/kg), with individual samples having slightly higher residues (up to 0.05 mg/kg).
However, the available feeding study with goats is of subordinate importance, as the relevant residues in animal matrices haven't been clarified by metabolism data, and residue levels in organs and tissues and therewith the potential of bifenox to accumulate in tissue haven't been investigated. Moreover,

according to current guidance treatment should last for at least 28 days. Therefore, depending on the outcome of the metabolism study a new ruminant feeding study may be required, too.

Since no significant residues are expected in poultry diet (grains), no metabolism or feeding studies are required for poultry.

3.3. CONSUMER RISK ASSESSMENT

The consumer dietary intake and risk assessment cannot be finalized pending data submission to address the identified data gaps for further residue trials, rotational crops studies, and the ruminant metabolism and possibly feeding study.
While the consumer exposure to residues of bifenox in grains (all below the LOQ) is expected to be insignificant (<1% of the ADI and ARfD respectively), the exposure to residues in food of animal origin and rotated crops cannot be assessed due to lack of data.

It is noted that in groundwater potentially used as drinking water the metabolite bifenox acid may exceed 0.1 µg/L. Bifenox acid is not expected to be of higher toxicity than bifenox, i.e. it is a 'non-relevant' groundwater metabolite with regard to the hazard assessment (refer to paragraph 2.8). From a risk management point of view the exposure of consumers to "non-relevant" metabolites at levels less than 0.75 µg/L is considered acceptable (threshold of concern approach)[12] and therefore, currently no further consumer exposure or risk assessment is required.

Nevertheless, it should be mentioned that for the notified use with the combi-formulation containing besides bifenox also pyraflufen-ethyl, the consumer risk assessment could not be completed, since no assessment with regard to pyraflufen-ethyl residues was carried out.

3.4. PROPOSED MRLS

The RMS proposed the MRL in wheat and barley grain should be set at 0.05 mg/kg even though the analytical method is validated at a level of 0.01 mg/kg. In the majority of trials (21) no residues above the LOQ of 0.01 mg/kg were found. The experts considered that there are three older residue trials (1987) with an LOQ of 0.05 mg/kg in grain. But it is very likely that the real residue in these trials would not exceed 0.01 mg/kg. It is therefore possible to set the MRL at either 0.01 mg/kg or 0.05 mg/kg in wheat and barley grain.

4. Environmental fate and behaviour

Bifenox was discussed at the PRAPeR experts' meeting for environmental fate and behaviour PRAPeR 17 in March 2007.

[12] Guidance document SANCO/221/2000 rev.20 on the assessment of the relevance of metabolites in ground water of substances regulated under council directive 91/414/EEC

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Soil experiments (4 different soils) were carried out under aerobic conditions in the laboratory (20°C 45% maximum water holding capacity (MWHC) in the dark. The formation of residues not extracted by methanol or methanol:water were a sink for the applied chlorophenyl ring-^{14}C-radiolabel (28.4-41% of the applied radiolabel (AR) after 90-92 days). Mineralisation to carbon dioxide of this radiolabel accounted for 5.6-8 % AR after 76-119 days. These values for the nitro phenyl radiolabel (only 1 soil studied) were 39% and 3.8%AR at 90 days respectively. The major (>10AR) extractable breakdown product present was bifenox acid (max. 50.8-78.7%AR at 10-56 days).

Data on anaerobic degradation in soil were not available. However these data are not necessary to complete an assessment for the applied for representative use in this case, that is only spring application to cereals, due to the timing of application and relative impersistence of the active substance in soil. In a laboratory soil photolysis study, no novel photodegradation products were identified, and the degradation of parent bifenox was slower in irradiated samples than in the dark controls.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The rate of degradation of bifenox was estimated from the results of the studies described in 4.1.1 above. DT_{50} were: 4-17.7 days (single first order non linear regression, 20°C 45% MWHC, 4 different soils). After normalisation to FOCUS reference conditions[13] (20°C and -10kPa soil moisture content) this range of single first order DT_{50} remained unchanged (geometric mean that is appropriate for use in FOCUS modelling 8.3 days) (see addendum to the DAR).

The major (> 10 %AR) degradation product, bifenox acid was applied as test substance to 3 soils and incubated in the laboratory (aerobic dark 20°C 45%MWHC). Single first-order DT_{50} values from these studies were calculated to be 24-88 days. In the addendum to the DAR where a kinetic assessment for bifenox acid from the studies (4 soils) where parent bifenox was dosed was reported, degradation rates of 49-156 days were estimated (The graphs of the kinetic fitting used to obtain these values, which were available to the meeting of experts, can be found in the EFSA addendum). The appropriate value to use for this metabolite in FOCUS modelling is a geometric mean value after normalisation to FOCUS reference conditions from all 7 soils of 56.3 days. In the addendum the RMS presented data for laboratory soil incubations for the minor soil metabolites aminobifenox acid (max 0.8%AR) and aminobifenox (max 1.2%AR). Though provided by the applicant, an assessment of the rate of soil degradation for this metabolite was not triggered and the data were not requested from the applicant by the peer review process. These studies were not considered by the meeting of experts, did not need to be relied upon, have not been peer reviewed and were considered gratuitous.

[13] Using section 2.4.2 of the generic guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

Though not formally triggered field soil dissipation studies (bare soil) were provided from 4 sites in the USA (Florida, Nebraska, Virginia and New Jersey) where applications were made between April and July. Using the residue levels of parent bifenox determined over the whole core sampled (either 0-15 or 0-8cm (New Jersey) soil layer), single first order DT_{50} were 8.3-32.1 days.

The longest available laboratory bifenox single first order soil DT_{50} of 17.7 days was agreed by the experts from the Member States for use in PEC soil calculations. For the major soil metabolite accumulated bifenox acid PEC soil calculations were made using the pattern of decline in the laboratory experiment dosed with bifenox (sandy loam 9917soil) where the observed formation fraction of 58% and longest laboratory single first order decline DT_{50} of 269.7 days (estimated by EFSA after the meeting of experts from day 56 onwards) results in the highest potential accumulation. This was the approach for calculating this PEC recommended by the experts. The resulting PEC can be found in appendix 1 (plateau concentration bifenox acid).

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The adsorption / desorption of bifenox was investigated in 7 soils in satisfactory batch adsorption experiments. Calculated adsorption $K_f oc$ values varied from 500 to 23000 mL/g, (mean 7143 mL/g) (1/n 0.77 – 1.1, mean 0.96). There was no evidence of a correlation of adsorption with pH.

The adsorption / desorption of bifenox acid was investigated in three soils in Dutch guideline batch adsorptions experiments. Calculated adsorption $K_f oc$ values were 130-155 mL/g (mean 143.3 mL/g) (1/n 0.79 – 0.89, mean 0.84). There was no evidence of a correlation of adsorption with pH.

The adsorption / desorption of aminobifenox (formed in aerobic sediment water studies) was investigated in three soils in Dutch guideline batch adsorptions experiments. Calculated adsorption $K_f oc$ values were 3697-5024 mL/g (mean 4444 mL/g) (1/n 0.70 – 0.77, mean 0.74). There was no evidence of a correlation of adsorption with pH.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Bifenox was essentially stable under sterile hydrolysis conditions at 25°C at pH 4 and 7. At pH 9 a single first order DT_{50} of 4 days was calculated. The metabolite bifenox acid was the major breakdown product formed and this was stable to further hydrolysis.

In a laboratory study where the aqueous photolysis of bifenox was investigated under sterile pH 5 conditions, a rate of degradation (single first order DT_{50}) of 2.18 days equated to summer sunlight at 40°N was determined. Bifenox degraded to 2.4-dichlorophenol which accounted for 79%AR after 72 hours in this test system. This rate of degradation is slower than was observed in the biologically active water sediment study where the water pH was 7.9-9. In an outdoor pond (mesocosm study)

dosed with bifenox at 0.001- 0.016mg/L where some photolysis would have occurred, 2,4-dichlorophenol was determined at a maximum of 5.2% applied molar bifenox equivalents (see addendum) indicating that 2,4-dichlorophenol would be expected to only be a minor degradation product of bifenox in natural surface water systems. In this study degradation rates of 2.4-dichlorophenol were relatively rapid (single first order DT_{50} estimated as 10.4 days). These values from the mesocosm study were agreed by the experts as appropriate to use in FOCUSsw calculations at steps 1&2.

A ready biodegradability test (OECD 301B) indicated that bifenox is 'not readily biodegradable' using the criteria defined by the test.

In water-sediment studies (2 systems studied at 20°C in the laboratory, sediment pH 7.5, water pH 7.9-9) bifenox degraded rapidly in both the water and sediment (√first order whole system DT_{50} 0.1 days). The metabolite aminobifenox (max. 64-67 % AR at 24-48 hours after treatment, in sediment) only accounted for a maximum of 6.4%AR in the water phase and was estimated to dissipate in sediment with a DT_{50} of 25 days (2^{nd} order, from maximum concentration 48 hours after treatment, DT_{90} 227 days) or40 days (√first order, from maximum concentration 24 hours after treatment, DT_{90} 444 days). Aminobifenox acid accounted for maxima of 10.6%AR at 14 days and 12.5%AR at 24 hours in the water phase but was not present in sediment extracts. The terminal metabolite, CO_2, accounted for only 3.7-4.9 %AR of the dichlorophenyl ring radiolabel by 105 days. Residues not extracted from sediment by acetonitrile and acetonitrile:water were a significant sink representing 60-64%AR at study end (105 days). The experts agreed that for bifenox water and sediment DT_{50} of 0.11 days (whole system values) were acceptable for use as FOCUSsw scenario calculation input (strictly speaking single first order values of ca. 0.36 days and not $\sqrt{1^{st}}$ order values should have been used). For aminobifenox the kinetic assessment used to derive water and sediment DT_{50} of 45.1 days (longest whole system value calculated using the observed decline from the maximum occurrence and single first order kinetics as clarified in footnote e of table B.8.6.2-27 of the addendum) was used for the FOCUSsw step 2 calculations. For aminobifenox acid (formed in the sediment water system) and bifenox acid (that may leach from soil) default sediment water system DT_{50} of 1000 days were agreed for use in the FOCUSsw step 2 calculations.

FOCUS surface water modelling was evaluated up to step 4 for bifenox and step 2 for the metabolites aminobifenox, aminobifenox acid, 2,4-dichlorophenol and [originating from soil bifenox acid] in an addendum. The peer review agreed these PEC surface water and sediment as presented in the addendum were appropriate for use in risk assessment. At step 4 the only mitigation considered was no spray drift buffer zones of 5 and 10m that were implemented following the methods prescribed by FOCUSsw guidance.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The applied for representative use of Spring applications (15th March) to winter cereals was simulated using FOCUS PEARL 2.2.2 using the following input parameters: bifenox single first order DT_{50} 8.3 days, K_{foc} 7143 mL/g (K_{fom} 4143 mL/g), 1/n=0.96; bifenox acid single first order DT_{50} 56.3 days, formation fraction from bifenox 100%, K_{foc} 143.3 mL/g (K_{fom} 83.1 mL/g), 1/n=0.84

Parent bifenox was calculated to be present in leachate leaving the top 1m soil layer at 80th percentile annual average concentrations of <0.001µg/L. For bifenox acid this range was 0.001-0.29µg/L, with the 0.1µg/L parametric drinking water limit being exceeded at the Piacenza (0.29µg/L) and Okehamption (0.11µg/L) scenarios (see addendum to the DAR, the input file summary out output files for the PEARL simulations, which were available to the meeting of experts, are contained in the EFSA addendum.).

4.3. FATE AND BEHAVIOUR IN AIR

The vapour pressure of bifenox ($4.74x10^{-8}$ Pa at 20°C) means that bifenox would be classified under the national scheme of The Netherlands as very slightly volatile, indicating losses due to volatilisation would not be expected. Based on the results of 4 laboratory wind tunnel experiments where bifenox formulations were applied to soils and French beans, it was estimated that only up to 1.3% of the bifenox applied was lost to the air compartment in 24 hours. Calculations using the method of Atkinson for indirect photooxidation in the atmosphere through reaction with hydroxyl radicals resulted in an atmospheric half life estimated at 12 hours (assuming an atmospheric hydroxyl radical concentration of $5x10^5$ radicals cm^{-3}) indicating the small proportion of applied bifenox that will volatilise would be unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Bifenox was discussed at the experts' meeting for ecotoxicology (PRAPeR 18) in March 2007. Based on a message from the expert meeting on physical-chemical properties a data gap was identified for the applicant to submit an evaluation whether the batches used in the ecotox tests are in compliance with the technical specification from the new source and an assessment of the ecotoxicological relevance of the impurities 2,4-dichloroanisol and 2,4-dichlorophenol. An aquatic risk assessment for impurity 2,4-dichlorophenol (also a major photoysis metabolite) was submitted by the applicant. The endpoints from IUCLID database and from US-EPA were used in the risk assessment. It was decided in the experts´ meeting that the endpoints need to be validated and a data gap was identified to submit the references and information for each endpoint. The full analytical profile of the batches used for ecotox testing is unknown. Hence, the technical specification proposed by the applicant has been considered inappropriate and the RMS proposed a revised technical specification, which is based on the 5-batch analysis results of the current Chinese source and which is in agreement with the comments received during the expert meeting on physical-chemical properties. Refer to not-peer-

reviewed confidential addendum to Vol.4(C) of June 2007. The proposal of the RMS was not agreed by the applicant. Therefore no agreed technical specification is currently available

5.1. RISK TO TERRESTRIAL VERTEBRATES

The representative use evaluated for the product 'Milan' is as a herbicide applied to winter cereals at post emergence in spring. An acute toxicity study with the product 'Milan' does not indicate that the product is significantly more toxic than expected from the content of bifenox. The risk to generic species, representing a large herbivorous bird, an insectivorous bird, small herbivorous mammal and an insectivorous mammal was assessed according to SANCO/ 4145/2000 for one application of 0.75 kg bifenox per hectare.

All first tier TER values for birds are above the Annex VI triggers, hence indicating a low risk. The TER values for insectivorous mammals and the acute TER for herbivorous mammals were all above the triggers. However the long-term TER value for a small herbivorous mammal was 0.4 and hence needed further consideration.

A refined assessment of long-term risk to herbivorous mammals was presented in the addendum of January 2007. The exposure was refined by using measured residue data from field trials with winter wheat. The experts' meeting agreed to use the mean residue value from the trials performed with an application rate of approximately 0.75 kg a.s./ha. Further refinement steps of PD and PT considering wood mouse as the focal species was discussed in the experts' meeting. Wood mouse (*Apodemus sylvaticus*) was agreed as a focal species as well as the suggested PD refinement. However the experts considered the proposed PT values as not sufficiently supported by the submitted information. The use of an interception factor for estimation of residues on invertebrates was considered not appropriate by the experts. A new risk assessment based on the recommendations from the experts´ meeting was presented in an updated (not peer-reviewed) addendum from June 2007. The long-term TER of 2.28 is below the Annex VI trigger of 5. Further risk refinement is required.

The risk to earthworm- and fish-eating birds and mammals is considered to be low since the TER values calculated according to SANCO/4145/2000 are well above the Annex VI triggers.

An assessment of risk from consumption of contaminated drinking water was not considered necessary by the RMS, as for the evaluated use no application to leafy crops is intended.

5.2. RISK TO AQUATIC ORGANISMS

Based on the available acute toxicity data, the proposed classification of bifenox is "very toxic to aquatic organisms". The most sensitive organisms are green algae and aquatic plants with EC_{50} values of 0.000175 mg/L (*Scenedesmus subspicatus*) and 0.0021 mg/L (*Lemna gibba*). The formulation 'Milan' was not significantly more toxic to green algae than expected based on the content of bifenox.

The first tier acute TER values for aquatic organisms were calculated based on PEC_{sw} caused by spray drift in a ditch at different distances from the treated field. For algae the TER was calculated to 0.7 with a 30 m buffer zone. No assessment of long-term risk was presented in the DAR. The RMS considered the risk to be low due to the rapid dissipation of bifenox from the water phase. However, repeated exposure from bifenox and/or the soil metabolite bifenox-acid (DT_{90} 83-294 d) due to drainage and run-off events cannot be excluded. In the addendum of January 2007 a new risk assessment using PEC_{sw} values from FOCUS Step 3 and 4 modelling was presented. With risk mitigation measures comparable to 10 m spray free zones a long-term TER of 10.8 is obtained for fish in the worst case scenario R3 stream.

The risk assessment for invertebrates, algae and aquatic plants was refined based on results from an outdoor mesocosm study evaluated in the addendum of January 2007. The study was discussed by Member State experts and it was agreed that even though the formulation used in the study contained additional active substances, the effects observed were most probably related to the exposure to bifenox. The RMS proposed a NOAEC of 8 µg a.s/L based on effects to phyto/zooplankton and macrophytes. However the abundance of *Lemna* was increased by a factor of 10 at this concentration until the end of the test. Pronounced short-term effects on phytoplankton were also observed at this concentration and functional endpoints like pH and oxygen level were lower than in the controls up to 71 and 64 days after treatment. The meeting agreed on a NOAEC of 22 µg formulated product/L which corresponds to a NOAEC of 4 µg/L. An assessment factor of 2-3 was proposed by the meeting. Based on the NOAEC of 4 µg a.s./L a no-spray buffer zone of 10 m is required to achieve a TER of >3 and a no-spray buffer zone of 5 m is required to achieve TERs >2 for all FOCUS step4 scenarios.

No metabolites above 10% were detected in the water phase in the water/sediment study except aminobifenox acid which reached a maximum of 12.7% after 1d. The toxicity of aminobifenox to aquatic organisms is about 1 order of magnitude lower to fish, daphnids and Chironomus and about 4 orders of magnitude lower to algae compared to bifenox. Bifenox acid is more persistent in soil than bifenox and has a higher potential to move to surface water. It is however of low acute toxicity to fish and the risks to invertebrates, algae and aquatic macrophytes are considered to be covered by the mesocosm study.

2,4 dichlorophenol was identified as a major photolysis metabolite. No studies were submitted but the applicant used endpoints from IUCLID database and from US-EPA in the risk assessment presented in the addendum. The TERs were well above the triggers of 100 and 10 with FOCUS step1 PECsw values for all aquatic organisms. The long-term endpoints were compared to time weighted PECsw however this was not further justified and therefore considered as not appropriate. Based on the maximum initial PECsw the long-term TERs are also above the trigger of 10 except a long-term endpoint observed in one test with *O. mykiss* where the resulting TER is 9.94. However the TER of 9.94 is close to the trigger of 10 and taking into account that the TER calculation is based on a FOCUS step1 PECsw and a second long-term endpoint for *O. mykiss* is available which resulted in a

TER of 409 the long-term risk to fish is considered to be low. In the meeting of experts it was decided that the information provided by the applicant should be validated.

Bifenox partitions into sediment, and was found in amounts up to 32% in the water/sediment studies already on day 0. Also the metabolite aminobifenox was found in sediment up to 67% after 2 days. Studies with *Chironomus riparius* are available for both bifenox and the metabolite. The 28-d NOECs were reported as 0.015 mg bifenox/L and 0.1 mg aminobifenox/L. The TER value for bifenox was above the trigger of 10 in the worst case scenario R3 (stream) if a buffer zone of 10m is applied. The risk from aminobifenox is considered to be low since the initial PECsw is about 21 times less than the NOEC.

The bioconcentration factor for whole fish was determined to 1500. However, the clearance time is short (CT_{50}=1.4 days) and the level of residues after 28 days was only 2%. Therefore, the risk for bioconcentration is considered to be low.

5.3. RISK TO BEES

The acute oral and contact toxicity of bifenox and the formulation 'Milan' to bees is low. The HQ-values are well below the Annex VI trigger of 50 and the risk is considered to be low.

5.4. RISK TO OTHER ARTHROPOD SPECIES

Laboratory studies with the two standard species *Typhlodromus pyri* and *Aphidius rhopalosiphi* showed 100% mortality for *T. pyri* while no mortality was observed for *A. rhopalosiphi*. The application rate in the study with *A. rhopalosiphi* was somewhat lower than the recommended, but it is not likely that the recommended rate would have resulted in effects above the trigger. Additional studies with glass plate or sand as substrate are available with *Poecilius cupreus, Aleochara bilineata Coccinella septempunctata* and *Pardosa sp*. also with an application rate of 1.33 L Milan/ha. The only significant effect observed for these species was a 25.1% reduction in reproductive performance for *C. septempunctata.* Extended laboratory studies are available with *A. rhopalosiphi, Hypoaspis aculeifer* and *Chrysoperla carnea.* No effects above the ESCORT II trigger of 50% were observed.

The RMS did not consider *T. pyri* as a representative species for cereals and therefore no extended laboratory study was requested. However, *T. pyri* should be seen also as a sensitive indicator species for species outside the treated field. The LR_{50} from an extended laboratory study presented in the addendum of January 2007 was 24 g a.s./ha. The off-field drift rate at 1 m was calculated to 10.4 g bifenox with an uncertainty factor of 5. Thus the off-field effect is <50% and the risk off-field was considered to be low by the experts' meeting. Overall it is concluded that the risk to non-target arthropods is low for the representative use evaluated.

5.5. RISK TO EARTHWORMS

The acute toxicity of bifenox and the formulation 'Milan' to earthworms is low and the TER values calculated based on initial PEC_{soil} (0.75 mg bifenox/kg soil) are well above the Annex VI trigger. A long-term/reproduction was not considered necessary by the RMS since the field DT_{90} values for bifenox in soil were determined to be in the range of 28-107 days and only one application is proposed. A chronic study with another formulation (EXP 30535, containing 255 g bifenox/L, 75.2 g ioxynil/L and 293 g mecoprop-P/L) is available and summarised in the addendum of January 2007. No effects were observed at the highest test concentration, corresponding to 5.1 mg bifenox/kg soil. The NOEC was divided by 2 to correct for the high organic content of the artificial soil. The TER based on the corrected NOEC and an initial PEC_{soil} is 3.4. The experts agreed that the long-term risk to earthworms can be regarded as addressed and no further studies would be necessary considering that the NOEC is based on the highest tested concentration and no effects were observed at an application rate of 5 times the suggested field rate.

The metabolite bifenox-acid was detected in amounts up to 63.8% of applied after 14 days in the aerobic soil degradation study. The acute toxicity is low, and the acute TER is well above the trigger. Since the DT_{90} is in the range 80-517 days a reproduction study with the metabolite bifenox-acid should be considered. A long-term (reproduction) study with earthworms was conducted with the formulation EXP 30535. Due to the short DT_{50} (maximum of 17.7 days) of bifenox in soil it was suggested by the RMS that potential effects on earthworm reproduction are covered by the study with the formulation containing bifenox. It was discussed in the meeting of experts whether the risk from bifenox-acid is covered by the long-term study with the formulation. It is likely that bifenox-acid was formed in the test system but at which amounts is uncertain and it is not possible to conclude on whether the concentration of bifenox-acid reached the PECsoil. However taking into consideration that no effects were observed in the long-term study at an application rate of 5 times the suggested field rate and that no effects were observed with bifenox-acid in the acute 14-d study EFSA agrees to the weight of evidence approach suggested by the RMS.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

No studies are available and are not considered necessary for bifenox since the field DT_{90} values were in the range of 28-107 days. For the metabolite bifenox-acid DT_{90} values ranged from 80-517 days. A study with collembola or mites would be triggered if effects on soil micro-organisms of >25% or a TERlt earthworm of <5 is observed. No effects >25% on soil micro-organisms were detected for bifenox-acid. In the meeting of experts it was concluded that no study with other soil non-target macro-organisms is required if the long-term risk to earthworms is addressed. A range of non-target arthropods was tested. Predatory mites were very sensitive to bifenox but the soil dwelling mite *Hypoaspis aculeifer* was not. Taking all information into account no study with collembola and bifenox-acid is considered necessary.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects on soil respiration and nitrification were tested with bifenox, the soil metabolite bifenox-acid and the formulation 'Milan'. No deviation >25% from the control was observed after 28 days at concentrations of about 6 times the maximum PECs. Hence the risk to non-target soil micro-organisms is considered to be low.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

Vegetative vigour and seedling emergence studies with two monocotyledonous (*Avena sativa, Allium cepa*) and four dicotyledonous (*Beta vulgaris, Brassica napus, Daucus carota, Glycine max*) are available to assess the risk to non-target plants. Effects on shoot fresh weight was observed in both types of studies with the lowest ED_{50} being 0.214 L 'Milan'/ha obtained in the vegetative vigour study. The TER value calculated based on 2.77% spray drift at one meter from the field meets the Annex VI trigger of 5 (TER=5.14) suggesting a low risk to non-target plants from exposure to bifenox.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

No inhibitory effects on respiration of activated sewage sludge was observed at a concentration of 1000 mg bifenox/L. It is not expected that the concentration of bifenox would reach levels >1000 mg/L in sewage treatment plants if applied according to the GAP. Therefore the risk to biological methods of sewage treatment is considered to be low.

6. Residue definitions

Soil

Definitions for risk assessment: bifenox, bifenox acid[14]

Definitions for monitoring: bifenox

Water

Ground water

Definitions for exposure assessment: bifenox, bifenox acid

Definitions for monitoring: bifenox, further data are identified as being required before it can be concluded if bifenox acid needs to be included in the monitoring residue definition or not.

[14] bifenox acid: 5-(2,4-dichlorophenoxy)-2-nitrobenzoic acid

Surface water

Definitions for risk assessment:

surface water: bifenox, aminobifenox acid[15], bifenox acid, 2,4-dichlorophenol

sediment: aminobifenox[16]

Definitions for monitoring: aminobifenox acid as a marker as the DT_{90} of bifenox in water is <3 days.

Air

Definitions for risk assessment: bifenox

Definitions for monitoring: bifenox

Food of plant origin

Definitions for risk assessment: bifenox (by default, applicable for cereal grain and the notified cGAP only), inconclusive for cereal straw and rotational crops due to lack of data

Definitions for monitoring: bifenox (by default, applicable for cereal grain and the notified cGAP only), inconclusive for rotational crops due to lack of data

Food of animal origin

Definitions for risk assessment: inconclusive due to lack of data

Definitions for monitoring: inconclusive due to lack of data

[15] aminobifenox acid: 5-(2,4-dichlorophenoxy)-2-anthranilate acid

[16] aminobifenox: 5-(2,4-dichlorophenoxy)-2-aminobenzoic acid methyl ester

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Bifenox	Low to moderate persistence Single first order DT_{50} 4-17.7 days (20°C, 45%MWHC soil moisture) Single first order DT_{50} 8.2-32 days (USA field studies)	Low acute toxicity to earthworms (LC_{50} >1000 mg/kg soil) and low risk to earthworms and soil micro-organisms
Bifenox acid	Moderate to high persistence Single first order DT_{50} 24-156 days (20°C, 45%MWHC soil moisture)	Low acute toxicity to earthworms (LC_{50} >1000 mg/kg soil), low risk to earthworms and soil micro-organisms

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
Bifenox	low mobility to immobile K_{foc} 500-23000 mL/g	No.	Yes	Yes	Very toxic to aquatic organisms (LC/EC_{50} fish = 0.67 mg/L, daphnia = 0.66 mg/L, 0.000175 mg/L)

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
Bifenox acid	high to medium mobility K_{foc} 130-155 mL/g	Yes at 2 FOCUS scenarios. Piacenza 0.29µg/L, Okehampton 0.11µg/L. No at the remaining 7 FOCUS groundwater scenarios	No information submitted, information required	Not relevant. Toxicity comparable to parent compound	Low toxicity and low risk to aquatic organisms.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Bifenox (water and sediment)	See 5.2.
Aminobifenox acid (water only)	About 1 order of magnitude less toxic to fish and daphnids and about 4 orders of magnitude less toxic to algae compared to bifenox. The risk to aquatic organisms was considered to be covered by the risk assessment for bifenox and the endpoint from the mesocosm study.
Aminobifenox (sediment only)	About 1 order of magnitude less toxic to chironomus compared to bifenox. The risk to sediment dwelling organisms was considered to be low.
Bifenox acid (water only, from soil)	Low toxicity and low risk to aquatic organisms
2,4-dichlorophenol (water only, from mesocosm)	Based on endpoints from IUCLID and US-EPA data base the risk was assessed as low. However the endpoints need further validation.

Air

Compound (name and/or code)	Toxicology
Bifenox	LC_{50} inhalation, rat > 0.91 mg/L (highest obtainable concentration, no classification required)

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- A justification must be provided to support the proposed minimum purity of the active substance and the maximum content of the impurities (relevant for all uses evaluated, data gap identified by the meeting of experts 13-16 03 2007, date of submission unknown, refer to chapter 1).
- A GLP 5 batch analysis study with analysis for total nitrosamine content (relevant for all uses evaluated, data gap identified by the meeting of experts 13-16 03 2007, date of submission unknown, refer to chapter 1).
- Once the technical specification has been agreed on, confirmation whether the batches used in the toxicological studies were in compliance with the technical specification from the current source (relevant for all uses evaluated; data gap identified by RMS in the addendum to volume 4, dated June 2007; submission date unknown; refer to chapter 2).
- Information on the toxicological profile of hydroxybifenox acid (hydroxy substitution position/s to be confirmed), the main plant metabolite found in cereal forage and straw (relevant for all representative uses evaluated, data gap identified by the meeting of experts PRAPeR 19; submission date unknown; refer to point 2.8).
- The applicant to provide 4 additional residue trials where application is made at BBCH 14 and samples are analysed for bifenox and hydroxybifenox acid (hydroxy substitution position/s to be confirmed) including its conjugates at harvest and at interim time points (relevant for all representative uses evaluated; data gap identified by the meeting of experts PRAPeR 20; submission date unknown; refer to point 3.1.1).
- A new rotational crop metabolism study is required (relevant for all representative uses evaluated; data gap identified by the meeting of experts PRAPeR 20; submission date unknown; refer to point 3.1.2).
- A ruminant metabolism study with bifenox is required. The applicant has to consider if the study should include dosing with hydroxybifenox acid as well (relevant for all representative uses evaluated; data gap identified by the meeting of experts PRAPeR 20; submission date unknown; refer to point 3.2).
- Depending on the outcome of ruminant metabolism study a ruminant feeding study may be required (relevant for all representative uses evaluated; data gap identified by the meeting of experts PRAPeR 20; submission date unknown; refer to point 3.2).
- The long-term risk to herbivorous mammals needs further refinement (relevant for all uses evaluated; data gap identified in the meeting of experts (PRAPeR 18) in March 2007; no submission date proposed by the notifier; refer to point 5.1).
- Evaluation whether the batches used in the ecotox tests were in compliance with the technical specification from the current source and an assessment of the ecotoxicological relevance of the impurities 2,4-dichloroanisol and 2,4-dichlorophenol (relevant for all uses evaluated; data gap identified in the meeting of experts (PRAPeR 18) in March 2007 following a comment from PRAPeR 16; no submission date proposed by the notifier; refer to point 5).

- Applicant to submit information/study summaries and references for each endpoint for the metabolite 2,4-dichlorophenol used in the aquatic risk assessment (relevant for all uses evaluated; data gap identified in the meeting of experts (PRAPeR 18) in March 2007; no submission date proposed by the notifier; refer to point 5.2).
- Information on the pesticidal activity of the potential groundwater metabolite bifenox acid against target weeds is required to complete the groundwater relevance assessment (relevant for all representative uses evaluated in geoclimatic conditions represented by the Piacenza and Chateaudun FOCUS groundwater scenarios; data gap identified by EFSA; submission date unknown; refer to point 6).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as a herbicide as proposed by the applicant on winter wheat and barley, full details of the gap can be found in the attached list of end points.

The representative formulated product for the evaluation was "Milan", a suspension concentrate (SC), the formulation also contains another active substance pyraflufen-ethyl.

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in cereals can be determined with a multi-method (The German S19 method has been validated). For the other matrices only single methods are available to determine residues of bifenox in soil and air and bifenox and aminobifenox acid in water. The ground water residue definition is not finalised and further methods for bifenox acid may be required. Also it is not yet clear if methods will be required for products of animal origin.

Sufficient analytical methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. The technical specification can not be agreed on at this time as the analytical data do not support the proposed values.

Oral absorption of bifenox occurs in the first 48 hours after dosing and is sex and dose dependent. Based on urinary excretion, oral absorption is estimated to be 25%. No potential for accumulation is observed. Metabolism occurs by nitro-reduction and O-demethylation. Acute oral toxicity of bifenox is low in rats, however, classification with Xn, R22 – Harmful if swallowed, is required based on the oral LD_{50} found in mice. No classification is required for dermal or inhalation toxicity; bifenox is not a skin or eye irritant and is not a skin sensitizer. Animals exposed to bifenox developed mild signs of porphyria as suggested by small-altered blood parameters (in rats and dogs), kidney toxicity (rat), and some altered clinical chemistry, which could suggest hepatotoxicity (rat and dog). Bifenox showed no potential for genotoxicity. Upon long-term exposure, no clear toxic effects were demonstrated in

either rats or mice, which was found a limitation factor by the experts of PRAPeR 19 to conclude on the carcinogenic potential of bifenox; according to the available results, no carcinogenic potential was observed. Bifenox produced no adverse effects on fertility, slight/marginal effects on reproduction/development were observed at parental toxic doses, and no teratogenic effects were seen. No potential for neurotoxicity was evidenced. The acceptable daily intake (ADI) is set at 0.3 mg/kg bw/day and the acute reference dose (ARfD) at 0.5 mg/kg bw considering an assessment factor of 100; the acceptable operator exposure level (AOEL) is set at 0.125 mg/kg bw/day considering an assessment factor of 400 (correction of 25% for oral absorption). Dermal absorption is 1% when handling the concentrate representative formulation (Milan) and 4% when handling an in-use field dilution. According to the representative uses of Milan, and considering only the bifenox component of the formulation, the estimated operator exposure was below the AOEL when personal protective equipment (PPE) as gloves during mixing/loading and application are used according to the UK POEM model; according to the German model calculations, exposure is below the AOEL even without the use of PPE. Exposure of workers and bystanders is estimated to be also below the AOEL. A new data gap was identified by the meeting of experts (PRAPeR 19) on information of the toxicological profile of hydroxybifenox acid, the main plant metabolite.

The metabolism of bifenox was investigated in winter wheat. Upon an early application (BBCH 13) bifenox was extensively and completely metabolised through hydroxylation into bifenox acid and the major metabolite hydroxybifenox acid followed by conjugation with glucose. Identification of metabolites was based on residues in straw as the residues in grains were very low. The results of supervised residue trials indicated that, when bifenox is applied at a later growth stage (BBCH 29), unchanged bifenox is still a significant residue in straw. As the notified GAP allows for applications between BBCH 13 and 29, a significant variation in the composition of the residues may occur. Hydroxybifenox acid was not found in the rat and therefore it could not be concluded whether it needs to be included in the residue definition for risk assessment. The experts of PRAPeR 20 concluded that the levels of hydroxybifenox acid residues that could be expected in cereal crops having received an early application were not sufficiently addressed by residue trial data and further trials are needed.

In a rotational crop study significant residue levels were found in edible crops parts. However, the study had some draw backs that didn't allow finalising the assessment of whether these residues are relevant for consumer and livestock exposure and therefore further data are required.

Significant residue may also occur in the diet of ruminants; however no livestock metabolism data were submitted that would address the nature of potentially occurring residues in food of animal origin. In an available feeding study with goats, only milk was analysed for residues of bifenox, but residue levels and the potential of accumulation in tissues and organs was not investigated. Bifenox is considered a fat soluble compound. Therefore further data are required to address residues in food of animal origin.

The consumer dietary intake and risk assessment cannot be finalised pending data submission to address the identified data gaps. While the consumer exposure to residues of bifenox in grains (all

below the LOQ) is expected to be insignificant (<1% of the ADI and ARfD respectively), the exposure to residues in food of animal origin and rotated crops cannot be assessed due to lack of data.

The information available on the fate and behaviour in the environment is sufficient to carry out an appropriate environmental exposure assessment at the EU level. For the applied for intended uses, the potential for groundwater exposure by bifenox above the parametric drinking water limit of 0.1 µg/L, is low. However for the metabolite bifenox acid, in geoclimatic regions represented by the Okehampton and Piacenza FOCUS groundwater scenarios contamination of groundwater above the 0.1 µg/L limit cannot be excluded and a metabolite non relevance assessment is necessary for this metabolite. The available toxicological data indicate that bifenox acid can be considered not relevant for groundwater, however information on pesticidal activity of bifenox acid against target weeds is required before the groundwater non relevance assessment can be finalised.

The risk to birds was assessed as low as well as the acute risk to mammals. However the long-term risk to mammals needed refinement. The suggested refinement based on wood mouse (*Apodemus sylvaticus*) as a focal species, PD and measured residues were accepted by the meeting of experts but not the PT values. Further data are required to address the long-term risk to herbivorous mammals. Bifenox is very toxic to aquatic organisms with algae driving the risk assessment. No TER met the Annex VI trigger based on FOCUS step3 PECsw. A mesocosm study was submitted and discussed in the meeting of experts. A NOAEC of 4 µg bifenox/L and a safety factor of 2-3 was agreed to be used in the risk assessment. Risk mitigation measures such as a no-spray buffer zone of 10 m is required to achieve a TER of >3 and a no-spray buffer zone of 5 m is required to achieve TERs >2 for all FOCUS step4 scenarios. A range of non-target arthropods was tested. *T. pyri* reacted very sensitive in the standard glass-plate test. In an extended laboratory study it was shown that adverse effects in the off-field area are <50% and the risk to predatory mites was considered as sufficiently addressed. A long-term/reproduction study with bifenox and earthworms was not considered necessary since the DT_{90} values were in the range of 28-107 days and only one application is proposed. However a chronic study with another formulation containing additionally two other active substances was submitted by the applicant. No effects were observed at the highest tested application rate which is about 5 times the suggested field rate. No long-term/reproduction study with earthworms was submitted for the metabolite bifenox acid for which DT_{90} values ranged from 80-517 days. It is very likely that bifenox acid was formed in the test with bifenox but it is uncertain if it reached concentrations comparable to the PECsoil. Taking into consideration that no effects were observed in the long-term study at an application rate of up to 5 times the suggested field rate and that no acute effects were observed in the study with bifenox-acid no further studies with earthworms are considered necessary. No studies with bifenox and other soil non-target micro-organisms were triggered. The need for studies with bifenox-acid was discussed in the experts´ meeting. It was agreed that no study is required if the long-term risk to earthworms is sufficiently addressed.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- Risk mitigation measures such as a no-spray buffer zone of 10 m are required to protect aquatic organisms (refer to point 5.2.)

Critical areas of concern

- The minimum purity of the active substance is not agreed and also the specification for impurities is not finalised.
- The operator and worker exposure assessment for pyraflufen-ethyl and combined risk assessment for the formulation (bifenox + pyraflufen-ethyl) could not be concluded and are to be considered at MS level.
- No conclusion on the toxicological profile of the main plant metabolite hydroxybifenox acid (for which the hydroxy substitution position in the structure has not been confirmed) could be reached on the basis of the data provided.
- The consumer exposure and risk assessment is not finalised.
- The long-term risk to herbivorous mammals needs further refinement

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

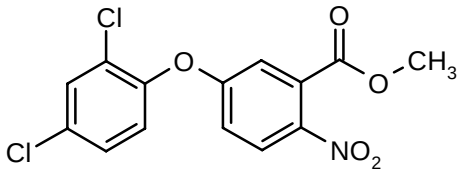
Active substance (ISO Common Name) ‡	Bifenox
Function (e.g. fungicide)	Herbicide

Rapporteur Member State	Belgium
Co-rapporteur Member State	None

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	Methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate
Chemical name (CA) ‡	Methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate
CIPAC No ‡	413
CAS No ‡	42576-02-3
EC No (EINECS or ELINCS) ‡	EINECS: 255-894-7
FAO Specification (including year of publication) ‡	413/TC/S/F (1992), published in AGP:CP/308 (1994): purity: "the Bifenox content shall be declared (not less than 970 g/kg) and, when determined, the content obtained shall not differ from that declared by more than ± 20 g/kg" impurities: max. 3 g/kg 2,4-dichlorophenol max. 6 g/kg 2,4-dichloroanisole max. 10 g/kg loss on drying
Minimum purity of the active substance as manufactured ‡	970 g/kg (commercial plant) ***open***
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	2,4-dichlorophenol (2,4-DCP): max. 3 g/kg 2,4-dichloroanisole (2,4-DCA): max. 6 g/kg These maximum levels were agreed by the mammalian toxicology meeting of experts but not the ecotoxicology meeting of experts.
Molecular formula ‡	$C_{14}H_9Cl_2NO_5$
Molecular mass ‡	342.14

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Structural formula ‡	 **Bifenox**

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	Melting endotherm from 86.0 to 87.7 °C (99.9%)
Boiling point (state purity) ‡	No boiling (decomposition) (99.9%)
Temperature of decomposition (state purity)	Decomposition from 398.6 °C (99.9%)
Appearance (state purity) ‡	Pale yellow crystalline granular solid, no characteristic odour (99.9%); pale yellow powdery solid, no characteristic odour (98.4%)
Vapour pressure (state temperature, state purity) ‡	4.74 x 10^{-8} Pa at 20°C (99.9%)
Henry's law constant ‡	> 1.62 x 10^{-4} $Pa.m^3.mol^{-1}$ at 20°C (98.4% - 99.9%)
Solubility in water (state temperature, state purity and pH) ‡	pH 4, 20°C: < 0.1 mg/L (98.4%)
	unadjusted pH, 20°C: < 0.1 mg/L (98.4%)
	pH 9, 20°C: < 0.1 mg/L (98.4%)
Solubility in organic solvents ‡ (state temperature, state purity)	At 20°C in g/L (98.4%) hexane 3.1 toluene 320 dichloromethane > 1000 (not performed analytically) methanol 23 n-octanol 10 acetone > 500 ethyl acetate 440 acetonitrile 330
Surface tension ‡ (state concentration and temperature, state purity)	Not required
Partition co-efficient ‡ (state temperature, pH and purity)	pH unadjusted, 20-25°C: log Pow = 3.64 (range 3.55 to 3.73) (99.9%)
	Effect of pH does not need to be addressed (no dissociation in water)
Dissociation constant (state purity) ‡	Not relevant (no acidic of basic function or other substituent included in the molecule which could be dissociated in water)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	In methanol (99.9%): λ_{max} 284.5 nm; ε = 8.980 x 10^3 L.mol^{-1}.cm^{-1} λ_{max} 436.0 nm; ε = 1.74 x 10^2 L.mol^{-1}.cm^{-1} in 17.6% v/v methanol in water (99.9%): λ_{max} 301.5 nm; ε = 8.633 x 10^3 L.mol^{-1}.cm^{-1} λ_{max} 437.0 nm; ε = 2.90 x 10^2 L.mol^{-1}.cm^{-1}
Flammability ‡ (state purity)	Not highly flammable (98.4%); not auto-flammable (98.4%)
Explosive properties ‡ (state purity)	Not explosive (98.4%)
Oxidising properties ‡ (state purity)	Not oxidising (97.8%)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of representative uses evaluated *

Crop and/ or situation	Member State or Country	Product name	F G or I	Pests or Group of pests controlled	Preparation		Application				Application rate per treatment			PHI (days)	Remarks
(a)			(b)	(c)	Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min)	g as/hL min – max (l)	water L/ha min – max	g as/ha min – max (l)	(m)	
Winter wheat, winter barley	North and South Europe	Milan	F	Broad leaved weeds	SC	B: 500 P: 9	Tractor mounted boom sprayer	Post emergence in spring BBCH 13 to BBCH 29	1	Not applicable	B: 188 – 750 P: 3 – 13.5	100 - 400	B: 750 P: 13.5	Not appli-cable	[1]

B: Bifenox; P: Pyraflufen-ethyl

[1] The minimum purity is not finalised, the technical specification is missing; the consumer risk assessment could not be completed; the long-term risk to herbivorous mammals needs further refinement.

Remarks:					
	(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)		(i)	g/kg or g/l
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)		(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
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)		(l)	PHI - minimum pre-harvest interval
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		(m)	Remarks may include: Extent of use/economic importance/restrictions
	(f)	All abbreviations used must be explained			
	(g)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench			
	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated			

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.2: Methods of Analysis

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

Technical as (analytical technique)	HPLC-UV CIPAC Method 413/TC/M/3 is available
Impurities in technical as (analytical technique)	HPLC-UV, CIPAC MT 17.2, conductometric titration, Relevant impurities (2,4-DCP and 2,4-DCA): HPLC-UV
Plant protection product (analytical technique)	HPLC-UV, CIPAC Method 413/SC/M/3 is available Relevant impurities (2,4-DCP and 2,4-DCA): HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Bifenox (by default, applicable for cereal grain and the notified cGAP only), *inconclusive for rotational crops due to lack of data*
Food of animal origin		*Inconclusive due to lack of data*
Soil		Bifenox
Water	surface	Aminobifenox acid as a marker as the DT_{90} of bifenox in water is <3 days
	drinking/ground	Bifenox a*nd aminobifenox acid as provisional residue definition*
Air		Bifenox

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Multi-method DFG S19 (modified): GC-ECD, conf. by GC-MS (Bifenox); LOQ = 0.01 mg/kg (cereal grain and green plant), resp. 0.05 mg/kg (straw)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	***Pending the necessity of feeding study in ruminants***
Soil (analytical technique and LOQ)	Single method: GC-MS (Bifenox); LOQ = 0.02 mg/kg

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Water (analytical technique and LOQ)	Single method: GC-MS (Bifenox); LOQ = 0.1 µg/L (surface water) LC-MS/MS (aminobifenox acid); LOQ = 0.1 µg/L (surface water) Single method: GC-ECD, conf. by GC-MS (Bifenox); LOQ = 0.05 µg/L (ground water, drinking water) Further data may be required for ground water.
Air (analytical technique and LOQ)	Single method: GC-ECD (Bifenox); LOQ ≈ 10 µg/m³ (warm, humidified air)
Body fluids and tissues (analytical technique and LOQ)	Not required (active substance is not classified as toxic or highly toxic)

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	None

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.3: Impact on Human and Animal Health

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

Rate and extent of oral absorption ‡	25% (based on urinary excretion within 48 h)
Distribution ‡	Large, highest level in excretory organs
Potential for accumulation ‡	No evidence for accumulation
Rate and extent of excretion ‡	29.1-52.6% via urine; 63-46% via faeces within 48 h for males and females respectively
Metabolism in animals ‡	Quantitative estimation is not possible; nitro-reduction and O-demethylation are involved
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound and metabolites
Toxicologically relevant compounds ‡ (environment)	Parent compound and metabolites

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	>5000 mg/kg bw	
Mouse LD_{50} oral ‡	Male: 1540 mg/kg bw Female: 1780 mg/kg bw	**Xn; R22**
Rat LD_{50} dermal ‡	>2000 mg/kg bw	
Rat LC_{50} inhalation ‡	> 0.91 mg/L (whole body, dust exposure, 4h, highest obtainable concentration)	
Skin irritation ‡	Non- irritant	
Eye irritation ‡	Non- irritant	
Skin sensitisation ‡	Non- sensitiser (M&K test)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Liver, blood	
Relevant oral NOAEL ‡	1year, dog study: 145 mg/kg bw/day	
Relevant dermal NOAEL ‡	28-day rat: 150 mg/kg bw/day	
Relevant inhalation NOAEL ‡	Not relevant- not required	

Genotoxicity ‡ (Annex IIA, point 5.4)

……..	Weight of evidence suggests no genotoxic potential	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Target/critical effect ‡	Blood (decreased reticulocytes and platelets) (mice)	
Relevant NOAEL ‡	30 mg/kg bw/day; 2-year, mouse 252 mg/kg bw/day; 2-year, rat	
Carcinogenicity ‡	No carcinogenic potential up to the highest dose tested	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Reduced implantation rate and decreased pup and litter weight at parental toxic dose (decreased body weight gain) in the rat	
Relevant parental NOAEL ‡	44.5 mg/kg bw/day	
Relevant reproductive NOAEL ‡	44.5 mg/kg bw/day	
Relevant offspring NOAEL ‡	44.5 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡	Marginally higher incidence of foetuses with large fontanelle at maternal toxic dose (clinical signs), rat; Slight increased incidence of angulated hyoid alae at maternal toxic dose (death, clinical signs, reduced body weight gain and food consumption), rabbit.	
Relevant maternal NOAEL ‡	Rat: 900 mg/kg bw/day Rabbit: 50 mg/kg bw/day	
Relevant developmental NOAEL ‡	Rat: 900 mg/kg bw/day Rabbit: 160 mg/kg bw/day	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data, not necessary	
Repeated neurotoxicity ‡	No data, not necessary	
Delayed neurotoxicity ‡	No data, not necessary	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	Cytotoxic and porphyrinogenic effects of bifenox were studied in cultured rat hepatocytes. Results suggest that bifenox inhibits protoporphyrinogen oxidase, resulting in the accumulation of protoporphyrin IX.
Studies performed on metabolites or impurities ‡	Information on the toxicological profile of the main plant metabolite, hydroxy-bifenox acid is required. (new data gap identified at PRAPeR 19) 2 impurities (2,4-dichlorophenol and 2,4-dichloroanisole) are toxicologically relevant, maximum limits proposed in FAO specifications are agreed.

Medical data ‡ (Annex IIA, point 5.9)

……..	No detrimental effects on health in manufacturing personnel

Summary (Annex IIA, point 5.10)	**Value**	**Study**	**Safety factor**
ADI ‡	0.3 mg/kg bw/day	Mouse, 2-year study	100
AOEL ‡	0.125 mg/kg bw/day	Rabbit, developmental, supported by the rat, 2-generation study	400*
ARfD ‡	0.5 mg/kg bw	Rabbit, developmental study	100

*correction for low oral absorption (25%)

Dermal absorption ‡ (Annex IIIA, point 7.3)

Milan (500 g bifenox/L SC formulation)	Concentrate: 1% Spray dilution: 4% Comparative *in-vitro* (human/rat skin) study

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Exposure scenarios (Annex IIIA, point 7.2)

Operator	The estimated exposure for Milan according to the UK POEM (application rate 0.75 kg a.i./ha) by tractor mounted sprayer equipment (field crop) was below the AOEL only if PPE are worn. According to the German model, estimated exposure was below the AOEL even if no PPE are worn: UK POEM model: Without PPE: 182% PPE (gloves M&L and application): 32% German model: Without PPE: 45% PPE (gloves M&L and application): 29%
Workers	According to German re-entry approach, estimated exposure was below the AOEL even if no PPE are worn: Without PPE: 53% With PPE (gloves, long sleeved shirt & long trousers): 2.6%
Bystanders	Estimated exposure (without PPE): 2.2%

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

	RMS/peer review proposal	
Bifenox	Xn	Harmful
	R22	Harmful if swallowed

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.4: Residues

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

Plant groups covered	Cereals (Supported uses: winter wheat and winter barley)
Rotational crops	*A new rotational crop study is required.*
Metabolism in rotational crops similar to metabolism in primary crops?	*Open*
Processed commodities	None
Residue pattern in processed commodities similar to residue pattern in raw commodities?	-
Plant residue definition for monitoring	Bifenox (only assessed for cereal grains)
Plant residue definition for risk assessment	Bifenox (only applicable to cereal grains)[17]
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	*None. A ruminant metabolism study is required.*
Time needed to reach a plateau concentration in milk and eggs	*Open*
Animal residue definition for monitoring	*Pending the results of the ruminant metabolism study*
Animal residue definition for risk assessment	*Pending the results of the ruminant metabolism study*
Conversion factor (monitoring to risk assessment)	*Open.*
Metabolism in rat and ruminant similar (yes/no)	*Open*
Fat soluble residue: (yes/no)	Yes, according to the log P*ow* value of 3.64

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

……..	In the available studies, the plant back intervals were too long and the crops were not harvested mature. It is not excluded that residues above 0.01 mg/kg would occur in the edible plant parts and therefore identification is requested. A new rotational crop metabolism study is required.

[17] For feed items (other than grains) it might be considered to include bifenox-5'-hydroxy-acid. Further residue trial data are required.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

……..	-Residues of bifenox in winter wheat plants, grain and straw can be considered as stable under frozen storage conditions for a period of 170 days. -Residues of Bifenox-5'-hydroxy acid are considered as stable in wheat and barley straw, plants and grain for up to 24 months (after storage at –22°C).

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

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Yes -Dairy cattle: 0.14 mg/kg diet. -Beef cattle: 0.32 mg/kg diet.	No	No
Potential for accumulation (yes/no):	Yes – Log P_{ow}: 3.64	Not relevant	Not relevant
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	*Study required.*	Not required.	Not required.
	Feeding studies Residue levels in matrices: Mean (max) mg/kg		
Feeding rate in cattle and poultry studies	*Pending the outcome of the metabolism study, a feeding study may be required.*	Not required.	Not required.
Muscle	*Open*		
Liver			
Kidney			
Fat			
Milk			
Eggs			

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Winter wheat	N	-grain: <0.003, 5x <0.01, 2x <0.02, <0.05 mg/kg -straw [18]*: bifenox: <0.006, 4x <0.02, 0.04, <0.05, 0.10, 0.49 mg/kg bifenox-5'-hydroxy-acid: 2x <0.015 mg/kg	Samples of whole green plants at day 0 as well as samples of ears, plants with ears removed, straw and grains at different PHIs up to normal harvest time were analysed for parent compound. The trials were performed in accordance with the critical GAP.	0.01* mg/kg, optional 0.05* mg/kg		0.01* mg/kg
	S	-grain: 3x <0.003, 5 x <0.01mg/kg -straw *: <0.006, 5x <0.02, 0.07, 0.19 mg/kg				
Winter barley	N	-grain: 2x <0.003, 3x <0.01, 2 x <0.05mg/kg -straw*: bifenox:2x <0.006, 2x <0.02, 0.028, 0.063, 0.15 mg/kg bifenox-5'-hydroxy-acid: 2x <0.015 mg/kg				
	S	-grain: 4x <0.01mg/kg -straw*: <0.006, 2x <0.02, 0.18 mg/kg				

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

[18] * For straw/ forage it might be considered to include bifenox-5'-hydroxy-acid in the residue definition for risk assessment. Further residue trial data are required to enable a decision.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

ADI	0.3 mg/kg b.w./day	
TMDI (% ADI) according to WHO European diet	0.055 %, wheat and barley grain only potential residue exposure from rotational crops and food of animal origin not considered as assessment inconclusive	
TMDI (% ADI) according to national (to be specified) diets	-German 4-6 years old girl (0.13 %), -UK adult, infant, toddler, 4-6 years, 7-10 years, 11-14 years, 15-18 years, vegetarians, elderly (<1%).	
IEDI (WHO European Diet) (% ADI)	-	
NEDI (specify diet) (% ADI)	-	
Factors included in IEDI and NEDI	Not applicable.	
ARfD	0.5 mg/kg bw/day	
IESTI (% ARfD) wheat and barley grain only; potential residue exposure from rotational crops and food of animal origin not considered as assessment inconclusive	<u>UK adults</u>: - Wheat wholemeal: 0.06% - Wheat bran: 0.03% - Wholemeal bread 0.17% - Barley: 0.15% - Wheat: 0.14%	<u>UK children</u>: - Wheat wholemeal: 0.12% - Wheat bran: 0.05% - Wholemeal bread 0.42% - Barley: 0.018% - Wheat:0.25%
NESTI (% ARfD) according to national (to be specified) large portion consumption data	-	
Factors included in IESTI and NESTI	Not applicable.	

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

Not required.

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

Wheat grain	0.01* mg/kg or 0.05* mg/kg
Barley grain	0.01* mg/kg or 0.05* mg/kg

* LOQ

Note: Intended use on winter wheat and barley only.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	5.6-8.0 % after 90-92 d, [Chloro phenyl – U14C] – label (n=4) 3.8% after 90 d, [Nitro phenyl – U14C] – label (n=1) 6.3% after 120 d, [Nitro phenyl – U14C] – label (n=1)
Non-extractable residues after 100 days ‡	28-41 % after 90-92 d, [Chloro phenyl – U14C] – label (n=4) 39% after 90 d, [Nitro phenyl – U14C] – label (n=1) 46.1% after 120 d, [Nitro phenyl – U14C] – label (n=1)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	Bifenox-acid – max 50.8-78.7 % at 10-56 d (n=4)

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

Anaerobic degradation ‡	Not required in the case of the representative use of spring application to cereals
Mineralization after 100 days	Not required
Non-extractable residues after 100 days	Not required
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Not required
Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Mineralisation 1.1% after 30 d Non-extractable residues 10.8% after 30 d Metabolites Bifenox-acid 16.5% after 30 d [Chloro phenyl – U14C] – label Degradation in irradiated samples was slower than in dark controls

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)	
Method of calculation	Laboratory: single first order decay
Laboratory studies (range or median, with n value, with r^2 value)	Bifenox DT_{50lab} (20°C, aerobic): 4-18 d (n = 4, r^2= 0.93-0.99), geomean after normalising = 8.3 days Bifenox-acid DT_{50lab} (20°C, aerobic): 24-156 d (n = 7, r^2= 0.85-0.99), geomean after normalising = 56.3 days.
	Bifenox DT_{90lab} (20°C, aerobic): 13.3-59.8 d (n = 4, r^2= 0.52-0.90) Bifenox-acid DT_{90lab} (20°C, aerobic): 79.7-517 d (n = 3, r^2= 0.85-0.99)
	Bifenox DT_{50lab} (10°C, aerobic): 55 d (n=1, r^2=0.99)
	DT_{50lab} (20°C, anaerobic): not required
	degradation in the saturated zone: not required
Field studies (state location, range or median with n value)	DT_{50f}: Florida, bare soil, 8.3 d (n = 1, r^2 not determined) 1st order kinetics ; Nebraska, bare soil, 12.2 d (n = 1, r^2 not determined) 1st order kinetics ; Virginia, bare soil, 16.7 d (n = 1, r^2 not determined) 1st order kinetics ; New Jersey, bare soil, 32.1 d (n = 1, r^2 not determined) 1st order kinetics.
	DT_{90f}: Florida, bare soil, 27.7 d ; Nebraska, bare soil, 40.6 d ; Virginia, bare soil, 55.4 d ; New Jersey, bare soil, 106.6 d.
Soil accumulation and plateau concentration ‡	Not required for bifenox, calculated accumulation factor of 1.63 for bifenox acid, see bifenox acid PEC soil endpoint for details.

Laboratory studies ‡

Parent/metabolite	Anaerobic conditions
Not required	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Bifenox ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Sandy loam	2.09	5.3 (in water)	/	/	169	8070	1.117
Loamy sand	0.75	6.6 (in water)	/	/	33.6	4477	1.055
Clay loam	1.51	7.6 (in water)	/	/	73.3	4853	1.113
Sand	0.17	7.5	/	/	0.925	500	0.7657
Sandy loam	0.81	6.9	/	/	36.1	4 400	0.8900
Silt loam	1.16	7.4	/	/	54	4 700	0.7707
Sandy clay loam	0.64	7.3	/	/	146	23 000	0.9938
Arithmetic mean/median						7143	0.96
pH dependence, Yes or No			No				

Bifenox-acid ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Humic sand soil	2.50	5.7	/	/	3.62	145	0.89
Loam soil	0.81	7.3	/	/	1.26	155	0.85
BBA 2.1	0.52	5.6	/	/	0.68	130	0.79
Arithmetic mean/median						143.3	0.84
pH dependence (yes or no)			No				

Aminobifenox ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Humic sand soil	2.50	5.7	/	/	115	4611	0.77
Loam soil	0.81	7.3	/	/	40.8	5024	0.74
BBA 2.1	0.52	5.6	/	/	19.3	3697	0.70
Arithmetic mean/median						4444	0.74
pH dependence (yes or no)			No				

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

Column leaching ‡	Not required
Aged residues leaching ‡	Not required

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Lysimeter/ field leaching studies ‡	Not required

PEC (soil) (Annex IIIA, point 9.1.3)

Parent	
Method of calculation	DT_{50} (d): 17.7 days (worst-case DT_{50} from lab studies) Kinetics: 1st order
Application data	Crop: winter cereals Growth stage: BBCH 13-29 % plant interception: 25% Application rate(s): 750 g as/ha Number of applications: 1/year Depth / bulk density of soil layer: 5 cm / 1.5 g/cm³

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.750		/	
Short term	24h	0.721	0.736	/	/
	2d	0.694	0.721	/	/
	4d	0.641	0.694	/	/
Long term	7d	0.570	0.656	/	/
	28d	0.251	0.456	/	/
	50d	0.106	0.329	/	/
	100d	0.015	0.188	/	/
Plateau concentration		Not relevant			

Bifenox-acid	
Method of calculation	Molecular weight relative to the parent: 328/342
Application data	Application rate assumed: 568.2 g as/ha (assumed bifenox-acid is formed at a maximum of 79% of the applied dose with no crop interception)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.57		/	
Plateau concentration	With a single first order DT_{50} 269.7 days (estimated rate of decline from day 56 in sandy loam 9917soil laboratory study) soil application rate 312.9g/ha (750x0.58x0.75x328/342) a maximum PEC of 0.68mg/kg is calculated (calculated steady state level before final application 0.27mg/kg)			

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 4 and 5, 25°C: hydrolytically stable (99.2% radiochemical purity)
	pH 7, 25°C: DT_{50} = 265 d (99.2% radiochemical purity) Bifenox acid accounted for 22% AR at 90 days
	pH 9, 25°C: DT_{50} = 4 d (99.2% radiochemical purity) Bifenox acid accounted for 100% AR at 15 days
Photolytic degradation of active substance and metabolites above 10 % ‡	pH 5, 20°C: DT_{50} = 24.4 hrs (continuous artificial light) (99.2% radiochemical purity) DT_{50} was ca. 2.18 days when equated to natural summer sunlight at 40°N. 2,4-dichlorophenol accounted for 79% AR after 72 hours
Quantum yield of direct phototransformation in water at Σ > 290 nm	1.25×10^{-3} molecules degraded.photon^{-1} (99.2% radiochemical purity)
Readily biodegradable ‡ (yes/no)	No The max. cumulated CO_2 generated is 14% of the amount of CO_2 that theoretically can be generated from the test material at day 28.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Degradation in water / sediment

Bifenox	Distribution: system I: max. 1.6% in water after 0.25 d and max. 32.4% in sediment after 0 d system II: max. 3.5% in water after 0 d and max. 17.2% in sediment after 0 d									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	St. (r^2)	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
"Bickenbach" brook (system I)	7.9	7.5	20	0.11– 1.17	n.c	n.c.	n.c.	n.c.	n.c.	First order square root
"Unter Widdersheim" brook (system II)	8.1	7.5	20	0.11–1.22	n.c	n.c.	n.c.	n.c.	n.c.	First order square root
Geometric mean				0.11-1.20						

Degradation in water / sediment

Aminobifenox	Distribution system I: max. 5.8% in water after 0.25 d and max. 63.7% in sed after 1 d system II: max. 6.4% in water after 0.25 d and max. 66.7% in sed after 2 d									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	St. (r^2)	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
"Bickenbach" brook (system I)	7.9	7.5	20	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
"Unter Widdersheim" brook (system II)	8.1	7.5	20	45.1(decline from maximum occurrence)	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
Geometric mean										

n.c. = not calculated

Aminobifenox acid	Distribution system I: max. 10.6% in water after 14 d; not detected in sediment system II: max. 12.7% in water after 1 d; not detected in sediment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Mineralization and non extractable residues

Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed. max x % after n d (end of the study)
"Bickenbach" brook (system I)	7.9	7.5	3.7% after 105 days	Max. 60.2% after 105 days	Max. 60.2% after 105 days
"Unter Widdersheim" brook (system II)	8.1	7.5	4.9% after 105 days	Max. 63.8% after 105 days	Max. 63.8% after 105 days

Aquatic mesocosm study

2,4-DCP	Distribution: max. 5.2% in water after 7 d ; no amount in sediment Degradation: DT_{50} in water phase of 10 days

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

Bifenox Parameters used in FOCUSsw step 1, 2 and 3	Molecular weight (g/mol): 342 Water solubility (mg/L): 0.1 Koc (L/kg): 7143 DT_{50} soil (d): 8.3 DT_{50} water/sediment system (d): 0.11 DT_{50} water (d): 0.11 DT_{50} sediment (d): 0.11
Aminobifenox acid Parameters used in FOCUSsw STEP1-2	Molecular weight (g/mol): 298 Water solubility (mg/L): 6.263 Koc (L/kg): 10 DT_{50} soil (d): 1.8 DT_{50} water/sediment system (d): 1000 DT_{50} water (d): 1000 DT_{50} sediment (d): 1000 Max. occurrence in soil: 0.8% Max. occurrence in water/sediment: 12.7%

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Bifenox acid Parameters used in FOCUSsw STEP1-2	Molecular weight (g/mol): 328 Water solubility (mg/L): 1000 Koc (L/kg): 143 DT_{50} soil (d): 1000 DT_{50} water/sediment system (d): 1000 DT_{50} water (d): 1000 DT_{50} sediment (d): 1000 Max. occurrence in soil: 79% Max. occurrence in water/sediment: 7.8%
2,4-dichlorophenol Parameters used in FOCUSsw STEP1-2	Molecular weight (g/mol): 163 Water solubility (mg/L): 4500 Koc (L/kg): 10 DT_{50} soil (d): 1000 days DT_{50} water/sediment system (d): 10.4 DT_{50} water (d): 10.4 DT_{50} sediment (d): 10.4 Max. occurrence in soil: - Max. occurrence in water/sediment: 5.2%
Aminobifenox Parameters used in FOCUSsw STEP1-2	Molecular weight (g/mol): 312 Water solubility (mg/L): 0.88 Koc (L/kg): 4444 DT_{50} soil (d): 5.8 DT50 water/sediment system (d): 45.1 DT50 water (d): 45.1 DT50 sediment (d): 45.1 Max. occurrence in soil : 1.2% Max. occurrence in water/sediment : 72.4%
Application rate	Crop: winter cereals Number of applications: 1 Interval (d): / Application rate(s): 750 g as/ha Depth of water body: 30 cm Application window: Spring Crop interception (%): 25

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Bifenox

Initial PEC values for bifenox obtained from each scenario at STEP 1, 2 and 3

Waterbody	Location	Application date	PECsw (µg/L)	PECsed (µg/kg)
Step 1	-	March – May	**30.6527**	**1.7E+03**
Step 2	North	March – May	**6.8975**	182.2453
	South	March – May	6.8975	**364.4906**
Step 3 Ditch	D1	7 Mach 1982	4.700	0.597
	D2	12 March 1986	**4.781**	**0.606**
	D3	29 February 1992	4.708	0.527
	D6	5 March 1986	4.719	0.353
Step 3 Stream	D1	7 March 1982	3.198	0.059
	D2	12 March 1986	4.197	**0.530**
	D4	1 March 1985	3.839	0.190
	D5	1 March 1978	3.709	0.081
	R1	17 March 1984	3.121	0.440
	R3	1 March 1980	**4.368**	0.452
	R4	5 March 1984	3.110	0.231
Step 3 Pond	D4	1 March 1985	**0.162**	**0.024**
	D5	7 March 1978	**0.162**	0.017
	R1	17 March 1984	**0.162**	0.022

FOCUS Step 4 output showing PECsw initial values for bifenox on winter cereals

Waterbody	Location	Application date	Date of PECsw initial	Step 3 1 m (µg/L)	Step 4 5 m (µg/L)	Step 4 10 m (µg/L)
Ditch	D1	7 March 1982	7 March 1982	4.700	1.270	0.676
	D2	12 March 1986	12 March 1986	**4.781**	**1.292**	**0.687**
	D3	29 February 1992	29 February 1992	4.708	1.273	0.677
	D6	5 March 1986	5 March 1986	4.719	1.276	0.678

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Waterbody	Location	Application date	Date of PECsw initial	Step 3 1 m (µg/L)	Step 4 5 m (µg/L)	Step 4 10 m (µg/L)
Stream	D1	7 March 1982	7 March 1982	3.198	1.167	0.618
	D2	12 March 1986	1 March 1986	4.197	1.532	0.812
	D4	1 March 1985	1 March 1985	3.839	1.401	0.742
	D5	7 March 1978	7 March 1978	3.709	1.354	0.717
	R1	17 March 1984	17 March 1984	3.121	1.139	0.603
	R3	1 March 1980	1 March 1980	**4.368**	**1.595**	**0.845**
	R4	5 March 1984	5 March 1984	3.110	1.135	0.601
Pond	D4	1 March 1985		**0.162**		
	D5	7 March 1978		**0.162**		
	R1	17 March 1984		**0.162**		

Aminobifenox acid

FOCUS STEP 1 aminobifenox acid on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	0 h	2.4834		0.1720	
	24 h	2.4716	2.4775	0.2472	0.2096
	2 d	2.4699	2.4742	0.2470	0.2283
	4 d	2.4665	2.4712	0.2467	0.2376
	7 d	2.4614	2.4681	0.2461	0.2414
	14 d	2.4495	2.4618	0.2449	0.2434
	21 d	2.4376	2.4557	0.2438	0.2438
	28 d	2.4258	2.4497	0.2426	0.2436
	42 d	2.4024	2.4378	0.2402	0.2429
	50 d	2.3891	2.4311	0.2389	0.2423
	100 d	2.3077	2.3896	0.2308	0.2386

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

FOCUS STEP 2 aminobifenox acid on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
Northern EU	0 h	0.8099		0.0806	
	24 h	0.8060	0.8079	0.0805	0.0806
	2 d	0.8054	0.8068	0.0805	0.0805
	4 d	0.8043	0.8059	0.0804	0.0805
	7 d	0.8027	0.8048	0.0802	0.0804
	14 d	0.7988	0.8028	0.0798	0.0802
	21 d	0.7949	0.8008	0.0794	0.0800
	28 d	0.7911	0.7988	0.0791	0.0798
	42 d	0.7834	0.7950	0.0783	0.0794
	50 d	0.7791	0.7928	0.0779	0.0792
	100 d	0.7525	0.7793	0.0752	0.0779
Southern EU	0 h	0.8652		0.0861	
	24 h	0.8613	0.8632	0.0861	0.0861
	2 d	0.8607	0.8621	0.0860	0.0861
	4 d	0.8595	0.8611	0.0859	0.0860
	7 d	0.8577	0.8600	0.0857	0.0859
	14 d	0.8535	0.8578	0.0853	0.0857
	21 d	0.8494	0.8557	0.0849	0.0855
	28 d	0.8453	0.8536	0.0845	0.0853
	42 d	0.8371	0.8495	0.0837	0.0849
	50 d	0.8325	0.8471	0.0832	0.0846
	100 d	0.8041	0.8327	0.0804	0.0832

Bifenox acid

FOCUS STEP 1 bifenox acid on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	0h	159.65		227.56	
	24h	159.45	159.55	228.02	227.79
	2d	159.34	159.48	227.86	227.87
	4d	159.12	159.35	227.55	227.78

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

FOCUS STEP 1 bifenox acid on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	7d	158.79	159.18	227.07	227.58
	14d	158.02	158.80	225.97	227.05
	21d	157.26	158.41	224.88	226.51
	28d	156.50	158.03	223.79	225.97
	42d	154.99	157.27	221.63	224.88
	50 d	154.13	156.83	220.41	224.26
	100 d	148.88	154.16	212.90	220.45

FOCUS STEP 2 bifenox acid on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
Northern EU	0 h	24.26			
	24 h	24.22	24.24	34.61	34.62
	2 d	24.20	24.23	34.59	34.61
	4 d	24.17	24.21	34.54	34.59
	7 d	24.12	24.18	34.47	34.55
	14 d	24.00	24.12	34.30	34.47
	21 d	23.89	24.06	34.13	34.38
	28 d	23.77	24.00	33.97	34.30
	42 d	23.54	23.89	33.64	34.13
	50 d	23.41	23.82	33.45	34.04
	100 d	22.61	23.42	32.31	33.46
Southern EU	0 h	48.06		68.65	
	24 h	48.01	48.04	68.60	68.63
	2 d	47.97	48.01	68.55	68.60
	4 d	47.91	47.98	68.46	68.55
	7 d	47.81	47.93	68.32	68.48
	14 d	47.58	47.81	67.99	68.32
	21 d	47.35	47.69	67.66	68.15
	28 d	47.12	47.58	67.33	67.99
	42 d	46.66	47.35	66.68	67.66
	50 d	46.40	47.22	66.31	67.47
	100 d	44.82	46.41	64.05	66.32

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

2,4-Dichlorophenol

FOCUS STEP 1 2,4-Dichlorophenol on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	0h	0.171		0.000	
	24h	0.158	0.164	0.016	0.008
	2d	0.148	0.159	0.015	0.012
	4d	0.129	0.148	0.013	0.013
	7d	0.106	0.135	0.011	0.012
	14d	0.066	0.110	0.007	0.010
	21d	0.042	0.091	0.004	0.009
	28d	0.026	0.076	0.003	0.007
	42d	0.010	0.057	0.001	0.006
	50 d	0.006	0.049	0.001	0.005
	100 d	0.000	0.025	0.000	0.002

FOCUS STEP 2 2,4-Dichlorophenol on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
Northern and Southern EU	0 h	0.171		0.012	
	24 h	0.159	0.165	0.011	0.012
	2 d	0.148	0.159	0.011	0.011
	4 d	0.130	0.149	0.009	0.011
	7 d	0.106	0.135	0.008	0.010
	14 d	0.066	0.110	0.005	0.008
	21 d	0.042	0.091	0.003	0.007
	28 d	0.026	0.077	0.002	0.006
	42 d	0.010	0.057	0.001	0.004
	50 d	0.006	0.049	0.000	0.004
	100 d	0.000	0.025	0.000	0.002

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Aminobifenox

FOCUS STEP 1 Aminobifenox on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	0h	4.9519		17.5657	
	24h	1.0372	2.9945	46.0916	31.8286
	2d	1.0213	2.0119	45.3886	38.7839
	4d	0.9904	1.5088	44.0147	41.7410
	7d	0.9458	1.2770	42.0313	42.2872
	14d	0.8493	1.0869	37.7442	41.0683
	21d	0.7627	0.9930	33.8943	39.3071
	28d	0.6849	0.9255	30.4372	37.5140
	42d	0.5523	0.8224	24.5447	34.1378
	50 d	0.4884	0.7740	21.7050	32.3711
	100 d	0.2265	0.5574	10.0652	23.7590

FOCUS STEP 2 Aminobifenox on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
Northern EU	0 h	4.5566		28.6857	
	24 h	1.9277	3.2421	28.2482	28.4669
	2 d	1.1794	2.3978	27.8173	28.2498
	4 d	0.9250	1.7019	26.9753	27.8223
	7 d	0.6260	1.2663	25.7598	27.1970
	14 d	0.5621	0.9299	23.1323	25.8100
	21 d	0.5048	0.7976	20.7728	24.5173
	28 d	0.4533	0.7178	18.6540	23.3117
	42 d	0.3655	0.6145	15.0427	21.1358
	50 d	0.3232	0.5712	13.3024	20.0189
	100 d	0.1499	0.3984	6.1687	14.6511
Southern EU	0 h	4.5566		30.2944	
	24 h	1.9277	3.2421	29.8323	30.0634
	2 d	1.1794	2.3978	29.3774	29.8341
	4 d	0.9617	1.7065	28.4881	29.3826
	7 d	0.6611	1.2843	27.2044	28.7223
	14 d	0.5936	0.9555	24.4296	27.2574

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

FOCUS STEP 2 Aminobifenox on winter cereals	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg dry sediment)	
		Actual	TWA	Actual	TWA
	21 d	0.5331	0.8246	21.9378	25.8922
	28 d	0.4787	0.7448	19.7002	24.6190
	42 d	0.3860	0.6401	15.8863	22.3211
	50 d	0.3414	0.5958	14.0484	21.1415
	100 d	0.1583	0.4170	6.5146	15.4727

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

Method of calculation and type of study (e.g. modelling, field leaching, lysimeter)	Model(s) used: FOCUSPEARL 2.2.2 Scenarios: Châteaudun, Hamburg, Jokioinen, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla, Thiva Crop: winter cereals **Bifenox:** geomean DT_{50lab} of 8.3 d (adjusted to soil moisture at field capacity) mean Koc of 7143 mL/mg with a mean 1/n of 0.96. **Bifenox acid:** geomean DT_{50lab} of 56.3 d (adjusted to soil moisture at field capacity) mean Koc of 143.3 mL/mg with a mean 1/n of 0.84. kinetic formation fraction of 1
Application rate	Application rate: 750 g/ha. No. of applications: 1 Time of application: March 15th Crop interception: 25%

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m)

	Scenario	Bifenox (µg/L)	Metabolites (µg/L)		
			Bifenox acid	2	3
FOCUSPEARL/winter cereals	Chateaudun	0.000	0.001		
	Hamburg	0.000	0.087		
	Jokioinen	0.000	0.000		
	Kremsmünster	0.000	0.066		
	Okehampton	0.000	0.113		
	Piacenza	0.000	0.290		
	Porto	0.000	0.000		
	Sevilla	0.000	0.000		
	Thiva	0.000	0.001		

$PEC_{(gw)}$ From lysimeter / field studies

Parent/metabolite	1st year	2nd year	3rd year
Not available			

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

Direct photolysis in air ‡	Not required
Quantum yield of direct phototransformation	Not required
Photochemical oxidative degradation in air ‡	Estimated half life in atmosphere = 12 hr or 1 d (assuming an atmospheric hydroxyl radical concentration of $5x10^5$ radicals cm^{-3})
Volatilisation ‡	From plant surfaces (BBA guideline): <1.3% after 24 hours
	from soil surfaces (BBA guideline): <1% after 24 hours
Metabolites	No metabolite was volatilised after 24 hours

PEC (air)

Method of calculation	Not required

$PEC_{(a)}$

Maximum concentration	Not required

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Residues requiring further assessment

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) and or requiring consideration for groundwater exposure.	Soil: bifenox, bifenox acid Surface Water: bifenox, aminobifenox acid, bifenox acid (from soil) 2,4-dichlorophenol (from mesocosm). Sediment: bifenox, aminobifenox Ground water: bifenox, bifenox acid Air: bifenox

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

Soil (indicate location and type of study)	No data provided - none requested
Surface water (indicate location and type of study)	No data provided
Ground water (indicate location and type of study)	No data provided
Air (indicate location and type of study)	No data provided

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Candidate for R53

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.6: Effects on non-target Species

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

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Colinius virginianus	bifenox	Acute	LD_{50} > 2000	-
Colinus virginianus	bifenox	Acute	LD_{50} > 2150	-
Anas platyrhynchos	bifenox	Acute	LD_{50} > 4640	-
Colinus virginianus	Milan	Acute	LD_{50} > 2000 mg Milan/kg bw (850 mg a.s./kg bw)	-
Colinus virginianus	bifenox	Short-term	LC_{50} > 677	> 5000
Colinus virginianus	bifenox	Short-term	LC_{50} > 2515	> 10000
Anas platyrhynchos mallard ducklings	bifenox	Short-term	LC_{50} > 1190	> 5000
Anas platyrhynchos	bifenox	Short-term	LC_{50} > 1581	> 10000
Coturnix coturnix japonica	bifenox	Long-term	NOEC = 290	1400
Mammals ‡				
Rat	bifenox	Acute	LD_{50} = 1600	-
Rat	bifenox	Long-term	NOAEL = 16	-
Additional higher tier studies ‡				
Not required.				

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

winter cereals, 1 x 0.750 kg a.s./ha

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)				
Large herbivorous bird early crop stage	Acute	46.9	> 45.8	10
	Short-term	25.1	> 27.0	10
	Long-term	13.3	21.8	5
Insectivorous bird early/late crop stage	Acute	40.6	> 53.0	10
	Short-term	22.6	> 30.0	10
	Long-term	22.6	12.8	5
Earthworm-eating bird	Long-term	0.18	1611	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Fish-eating bird	Long-term	0.23	1261	5
Higher tier refinement (Birds)				
Not required				
Tier 1 (Mammals)				
Small herbivorous mammal early crop stage	Acute	148	10.8	10
	Long-term	42	0.4	5
Insectivorous mammal late crop stage	Acute	6.6	242	10
	Long-term	2.4	6.6	5
Earthworm-eating mammal	Long-term	0.22	72.7	5
Fish-eating mammal	Long-term	0.14	114	5
Higher tier refinement (Mammals)				
Small herbivorous mammal early crop stage	Long-term	7.01 (residues, f_{twa}, PD)	2.28	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 (Test type)	End point	Toxicity (mg/L)
Laboratory tests ‡				
Fish				
Oncorhynchus mykiss	bifenox	96 h (flow-through)	Mortality, LC_{50}	0.67 mg a.s./L (nom)
Lepomis macrochirus	bifenox	96 h (flow-through)	Mortality, LC_{50}	> 0.27 mg a.s./L (mm)
Oncorhynchus mykiss	bifenox	21 d (flow-through)	Growth NOEC	0.0091 mg a.s./L (mm)
Lepomis macrochirus	bifenox	14 d (flow-through)	Growth NOEC	0.13 mg a.s./L (mm)
Oncorhynchus mykiss	Milan	96 h (semi-static)	Mortality, LC_{50}	> 60 mg form/L (26 mg a.s./L) (nom)
Oncorhynchus mykiss	RPA 30535H	96 h (static)	Mortality, LC_{50}	35.07 mg form/L (6.85 mg a.s./L) (nom)
Oncorhynchus mykiss	Modown 4 Flowable	96 h (semi-static)	Mortality, LC_{50}	11 mg form/L (4.4 mg a.s./L) (mm)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Lepomis macrochirus	Modown 4 Flowable	96 h (semi-static)	Mortality, LC_{50}	14 mg form/L (5.6 mg a.s./L) (mm)
Cyprinodon variegatus	Modown 4 Flowable	96 h (semi-static)	Mortality, LC_{50}	44 mg form/L (17.6 mg a.s./L) (mm)
Oncorhynchus mykiss	RPA 03681H	28 d (semi-static)	Growth NOEC	1.0 mg form/L (0.42 mg a.s./L) (nom)
Oncorhynchus mykiss	RPA 30535H	21 d (semi-static)	Growth NOEC	0.43 mg form/L (0.084 mg a.s./L) (nom)
Oncorhynchus mykiss	Fox	28 d (static) w/s system	Growth NOEC	0.320 mg a.s./L (nom)
Oncorhynchus mykiss	aminobifenox acid	96 h (semi-static)	Mortality, LC_{50}	3.12 mg/L (mm)
Oncorhynchus mykiss	bifenox acid	96 h (static)	Mortality, LC_{50}	> 100 mg/L (nom)
Aquatic invertebrate				
Daphnia magna	bifenox	48 h (flow-through)	Mortality, EC_{50}	**0.66 mg a.s./L (mm)**
Daphnia magna	bifenox	3 d exposure, 18 d recove-ry, (static)	Reproduction, NOEC	0.01025 mg a.s./L (mm)
Daphnia magna	bifenox	21 d (semi-static)	Reproduction, NOEC	**0.00015 mg a.s./L (mm)**
Daphnia magna	Milan	48 h (semi-static)	Mortality, EC_{50}	> 15 mg form/L (6.51 mg a.s./L) (nom)
Daphnia magna	RPA 30535H	48 h (semi-static)	Mortality, EC_{50}	16.50 mg form/L (3.17 mg a.s./L)
Daphnia magna	Modown 4 Flowable	48 h (semi-static)	Mortality, EC_{50}	61 mg form/L (24.4 mg a.s./L) (mm)
Daphnia magna	Milan	3 d exposure, 18 d recove-ry, (static)	Reproduction, NOEC	< 0.0059 mg form/L (0.0025 mg a.s./L) (nom)
Daphnia magna	RPA 03681H	21 d (semi-static)	Reproduction, NOEC	0.28 mg form/L (0.12 mg a.s./L) (mm)
Daphnia magna	RPA 30535H	21 d (semi-static)	Reproduction, NOEC	0.00067 mg form/L (0.00013 mg a.s./L) (nom)
Daphnia magna	aminobifenox acid	48 h (semi-static)	Mortality, EC_{50}	3.38 mg/L (mm)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Sediment dwelling organisms				
Chironomus riparius	bifenox	28 d (static), w/s system	NOEC	**0.015 mg a.s./L (nom)**
Chironomus riparius	aminobifenox	28 d (static), w/s system	NOEC	0.1 mg/L (nom)
Algae				
Desmodesmus subspicatus	bifenox	96 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.000175 mg a.s./L 0.000190 mg a.s./L (nom)
Desmodesmus subspicatus	bifenox	96 h (static) w/s system	Biomass: E_bC_{50} Growth rate: E_rC_{50}	> 0.001 mg a.s./L > 0.001 mg a.s./L (nom)
Navicula pelliculosa	bifenox	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.0049 mg a.s./L 0.038 mg a.s./L (mm)
Desmodesmus subspicatus	Milan	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.00048 mg form/L (0.00021 mg a.s./L) 0.00068 mg form/L (0.00030 mg a.s./L) (nom)
Navicula pelliculosa	Milan	3 d exposure, 6 d recovery, (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.02 mg form/L (0.0087 mg a.s./L) 0.084 mg form/L (0.036 mg a.s./L) (mm)
Pseudokirchneriella subcapitata	Milan	3 d exposure, 4 d recovery, (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	(72h) 0.00184 mg form/L (0.00080 mg a.s./L) (24h) 0.00324 mg form/L (0.0014 mg a.s./L) (nom)
Desmodesmus subspicatus	Milan	72 h (static) w/s system	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.00579 mg form/L (0.0025 mg a.s./L) 0.00607 mg form/L (0.0026 mg a.s./L) (nom)
Desmodesmus subspicatus	Fox	96 h (static) 3 d recovery w/s system	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.0038 mg form/L (0.0015 mg a.s./L) 0.0088 mg form/L (0.0036 mg a.s./L) (nom)
Desmodesmus subspicatus	Foxtril super	96 h (static) w/s system	NOEC	0.0051 mg form/L (0.0010 mg a.s./L) (nom)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Desmodesmus subspicatus	Foxtril super	96 h (static) w/s system	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.0065 mg form/L (0.0013 mg a.s./L) 0.0083 – 0.0125 mg form/L (0.0016 – 0.0025 mg a.s./L) (nom)
Desmodesmus subspicatus	aminobifenox acid	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	11 mg/L (initial) 19 mg/L (initial)
Desmodesmus subspicatus	bifenox acid	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	2.22 mg/L 2.88 mg/L (nom)
Higher plant				
Lemna gibba	bifenox	14 d (static)	Fronds, EC_{50}	0.0021 mg a.s./L (mm)
Lemna gibba	Foxtril super	14 d (semi-static)	Fronds, EC_{50}	0.028 mg form/L (0.0055 mg a.s./L (nom)
Lemna gibba	bifenox acid	7 d (static)	Fronds, E_bC_{50} Fronds, E_rC_{50}	3.90 mg/L 3.76 mg/L (nom)
Microcosm or mesocosm tests				
87 d static aquatic outdoor mesocosm study: NOAEC agreed in the experts` meeting (PRAPeR 18 in March 2007) = 0.004 mg bifenox/L (nom) (based on effects on the algae, macrophyte and invertebrate communities)				

[1] indicate whether based on nominal (nom) or mean measured concentrations (mm). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

Milan: SC formulation containing 519 g/L bifenox and 9.57 g/L pyraflufen-ethyl (batch n°: OP951099)
SC formulation containing 510 g/L bifenox and 8.47 g/L pyraflufen-ethyl (batch n°: OP970616)
SC formulation containing 504 g/L bifenox and 8.91 g/L pyraflufen-ethyl (batch n°: OP980922)
Fox (FSG 03681H): SC formulation containing 480.3 g/L bifenox (batch n°: V10592001)
formulation containing 466.5 g/L bifenox (batch n°: 05028021)
RPA 30535H: formulation containing 250.0 g/L bifenox, 76.6 g/L ioxynil, 292.0 g/L MCPP-D (batch n°: 900043)
formulation containing 246 g/L bifenox, 79.2 g/L ioxynil, 290 g/L MCCP-D (batch n°: OP910738)
Modown 4 Flowable: formulation containing 40 % bifenox (batch n°: B04155103)
Foxtril super (EXP 30535A): SC formulation containing 255 g/L bifenox, 75.2 g/L ioxynil, 293 g/L mecoprop-P (batch n°: OP980213)
SC formulation containing 237.3 g/L bifenox, 75.0 g/L ioxynil, 297.0 g/L mecoprop-P (batch n°: V464001244)
RPA 03681H: formulation containing 495 g/L bifenox (batch n°: OP910666)
w/s: water sediment system

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 1 /FOCUS Step 2

No acceptable aquatic risk assessment based on FOCUS step 1 and step 2 calculations.

FOCUS Step 3

Only the worst case scenario's are presented in the Listing of Endpoints.

Winter cereals, 1 x 0.750 kg a.s./ha

Test substance	Scenario	Water body type	Test organism	Time scale	Toxicity end point (mg/L)	Max PEC_{SW} (µg a.s./L)	TER	Annex VI trigger
bifenox	D 2	ditch	*Lepomis macrochirus*	96 h flow-through	> 0.27	4.781	56.5	100
bifenox	D 2	ditch	*Oncorhynchus mykiss*	21 d flow-through	0.0091	4.781	1.90	10
bifenox	D 2	ditch	*Daphnia magna*	48 h flow-through	0.66	4.781	138	100
bifenox	D 2	ditch	*Daphnia magna*	21 d semi-static	0.00015	4.781	0.031	10
bifenox	D 2	ditch	*Desmodes-mus sub-spicatus*	96 h static	0.000175	4.781	0.037	10
bifenox	D 2	ditch	*Chironomus riparius*	28 d static	0.015	4.781	3.14	10
bifenox	D 2	ditch	*Lemna gibba*	14 d semi-static	0.0021	4.781	0.44	10
Foxtril super	D 2	ditch	Mesocosm (algae, macrophyte and invertebrate communities)	87 d static	0.004	4.781	0.84	3

The RMS proposes a trigger value of 3 for the outdoor mesocosm study since the study is well performed (long duration, NOAEC based on recovery observed during the study, extended species distribution).

FOCUS Step 4

Only the worst case scenario's are presented in the Listing of Endpoints.

Winter cereals, 1 x 0.750 kg a.s./ha

Scenario	Water body type	Test organism	Time scale	Toxicity end point	Buffer zone distance	Max PEC_{SW} (µg a.s./L)	TER	Annex VI trigger
R 3	stream	*Lepomis macrochirus*	96 h flow-through	> 0.27	5 m	1.595	169	100
					10 m	0.845	320	100

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Scenario	Water body type	Test organism	Time scale	Toxicity end point	Buffer zone distance	Max PEC_{SW} (µg a.s./L)	TER	Annex VI trigger
R 3	stream	*Oncorhyn-chus mykiss*	21 d flow-through	0.0091	5 m	1.595	5.71	10
					10 m	0.845	10.8	10
R 3	stream	*Daphnia magna*	48 h flow-through	0.66	5 m	1.595	414	100
					10 m	0.845	781	100
R 3	stream	*Daphnia magna*	21 d semi-static	0.00015	5 m	1.595	0.094	10
					10 m	0.845	0.18	10
R 3	stream	*Desmodesmus subspicatus*	96 h static	0.000175	5 m	1.595	0.11	10
					10 m	0.845	0.21	10
R 3	stream	*Chironomus riparius*	28 d static	0.015	5 m	1.595	9.40	10
					10 m	0.845	17.8	10
R 3	stream	*Lemna gibba*	14 d semi-static	0.0021	5 m	1.595	1.32	10
					10 m	0.845	2.49	10
R 3	stream	Mesocosm (algae, macrophyte and invertebrate communities)	87 d static	0.004	5 m	1.595	2.5	3
					10 m	0.845	4.73	3

The RMS proposes a trigger value of 3 for the outdoor mesocosm study since the study is well performed (long duration, NOAEC based on recovery observed during the study, extended species distribution).

Bioconcentration				
	Active substance	Metab. 1	Metab. 2	Metab. 3
$logP_{O/W}$	3.64	-	-	-
Bioconcentration factor (BCF) ‡	1500 (whole fish)*	-	-	-
Annex VI Trigger for the bioconcentration factor	100	-	-	-
Clearance time (days) (CT_{50})	1.4 (whole fish)	-	-	-
(CT_{90})	-	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	2 % of total ^{14}C in whole fish			

* based on total ^{14}C

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
bifenox ‡	(72 h) > 200 µg a.s./bee	(48 h) > 200 µg a.s./bee
Milan	(72 h) > 190 µg form/bee (82.5 µg a.s./bee)	(72 h) > 200 µg form/bee (86.9 µg a.s./bee)
Field or semi-field tests		
Not required. The hazard quotients for oral and contact toxicity are below 50, so no higher tier testing is necessary.		

Milan: SC formulation containing 519 g/L bifenox and 9.57 g/L pyraflufen-ethyl (batch n°: OP951099)

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

Winter cereals, 1 x 0.750 kg a.s./ha

Test substance	Route	Hazard quotient	Annex VI Trigger
bifenox	Contact	< 3.8	50
	oral	< 3.8	50
Milan	Contact	< 7.5	50
	oral	< 7.9	50

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

Laboratory tests with standard sensitive species

Not submitted

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)	End point	% effect	Trigger value
Typhlodromus pyri	proto-nymphs	EXP 03681, glass plates, 7 d	720 g a.s./ha, initial	Corrected mortality	100 %	50 %
Poecilus cupreus	adults	RPA 03681 H, sand, 14 d	1440 g a.s/ha, initial	Corrected mortality Food consumption	0 % + 22 %	50 %
Aleochara bilineata	imagines	RPA 03681 H, sand, 63 d	720 g a.s./ha, initial	Parasitisation	+ 0.5 %	50 %
Typhlodromus pyri	proto-nymphs	Milan, glass plates, 14 d	690 g a.s./ha, initial	Corrected mortality Reproduction	100 % 0 %	50 %

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)	End point	% effect	Trigger value
Typhlodromus pyri	proto-nymphs	Milan, glass plates, 14 d	37.8 g a.s./ha, initial	Corrected mortality Reproduction	42.7 % + 12.2 %	50 %
Coccinella septempunc-tata	larvae	Milan, glass plates, 7 weeks	690 g a.s./ha, initial	Corrected mortality Reproduction	2.27 % - 25.1 %	50 %
Poecilus cupreus	adults	Milan, sand, 14 d	690 g a.s./ha, initial	Corrected mortality Food consumption	3.3 % + 5.9 %	50 %
Pardosa	adults	Milan, sand, 14 d	756 g a.s./ha, initial	Corrected mortality Food consumption	0 % + 6.6 % (m) - 12.2 % (f)	50 %
Aphidius rhopalosiphi	adults	Milan, barley plants, 48 h + 11 d	690 g a.s./ha, initial	Corrected mortality Reproduction	0 % - 2.1 %	50 %
Extended laboratory studies						
Aphidius rhopalosiphi	adults	EXP 03681, barley plants, 48 h + 11 d	720 g a.s./ha, initial	Corrected mortality Reproduction	0 % + 4.8 %	50 %
Hypoaspis aculeifer	juveniles	Milan, soil, 14 d + 14 d	31.8 g a.s./ha, initial	Corrected mortality Reproduction	2 % - 25.3 %	50 %
Chrysoperla carnea	larvae	Milan, barley plants, 20 d + 34 d	786 g a.s./ha, initial	Corrected mortality Reproduction	12.5 % - 6.4 %	50 %
Typhlodromus pyri	proto-nymphs	Milan, bean leaves, 7 d + 7 d	734 g a.s./ha, initial	LR_{50} = 24 g a.s./ha No effect on reproduction at 30 g a.s./ha Off-field PEC = 10.4 g a.s./ha		

EXP 03681: SC formulation containing 480 g/L bifenox (batch n°: OP990197)
RPA 03681H: SC formulation containing 480 g/L bifenox (batch n°: OP880662)
Milan: SC formulation containing 519 g/L bifenox and 9.57 g/L pyraflufen-ethyl (batch n°: OP951099)
SC formulation containing 504 g/L bifenox and 8.91 g/L pyraflufen-ethyl (batch n°: OP980922)
SC formulation containing 489 g/L bifenox and 8.75 g/L pyraflufen-ethyl (batch n°: OP980682)
SC formulation containing 500 g/L bifenox and 9 g/L pyraflufen-ethyl (batch n°: 00103202)

Corrected mortality: positive values: adverse effects
Food consumption: negative values: adverse effects; positive values: no adverse effects
Parasitation: negative values: adverse effects; positive values: no adverse effects
Reproduction: negative values: adverse effects; positive values: no adverse effects

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Field or semi-field tests
Not required. Laboratory and extended laboratory tests are available and no higher tier testing is required.

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
Eisenia foetida	bifenox ‡	acute 14 days	LC_{50} > 1000 mg a.s./kg soil d.w. $LC_{50\ corr}$ > 500 mg a.s./kg soil d.w.
Eisenia foetida	Milan	acute 14 days	LC_{50} > 1000 mg form/kg soil d.w. $LC_{50\ corr}$ > 500 mg form/kg soil d.w. $LC_{50\ corr}$ > 217 mg a.s./kg soil d.w.
Eisenia foetida	EXP 30535	long-term 8 weeks	NOEC = 15 L form/ha = 5.1 mg a.s./kg soil $NOEC_{corr}$ = 2.55 mg a.s./kg soil
Eisenia foetida	bifenox acid	acute 14 days	LC_{50} > 1000 mg/kg soil d.w. $LC_{50\ corr}$ > 500 mg/kg soil d.w.
Other soil macro-organisms			
Not required. The field DT_{90} values of bifenox were in the range of 27.7 – 106.6 days, with a mean value of 57.6 days.			
Collembola			
Not required. The field DT_{90} values of bifenox were in the range of 27.7 – 106.6 days, with a mean value of 57.6 days.			
Soil micro-organisms			
Nitrogen mineralisation	bifenox ‡	28 days	- 21.94 % effect at day 28 at 3.1 mg a.s./kg soil d.w. (low organic matter) - 9.43 % effect at day 28 at 3.1 mg a.s./kg soil d.w. (high organic matter)
	Milan	28 days	+ 4.45 % effect at day 28 at 0.9 mg a.s./kg soil d.w.(sandy loamy silt soil) - 0.82 % effect at day 28 at 4.5 mg a.s./kg soil d.w. (sandy loamy silt soil) + 5.60 % effect at day 28 at 0.9 mg a.s./kg soil d.w. (loamy sand soil) - 2.57 % effect at day 28 at 4.5 mg a.s./kg soil d.w. (loamy sand soil)
	bifenox acid	28 days	+ 3 % effect at day 28 at 0.959 mg/kg soil d.w. + 7 % effect at day 28 at 4.793 mg/kg soil d.w.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Test organism	Test substance	Time scale	End point
Carbon mineralisation	bifenox ‡	28 days	- 3.05 % effect at day 28 at 3.1 mg a.s./kg soil d.w. (low organic matter) - 5.81 % effect at day 28 at 3.1 mg a.s./kg soil d.w. (high organic matter)
	Milan	28 days	- 5.49 % effect at day 28 at 0.9 mg a.s./kg soil d.w. (sandy loamy silt soil) - 6.59 % effect at day 28 at 4.5 mg a.s./kg soil d.w. (sandy loamy silt soil) + 8.82 % effect at day 28 at 0.9 mg a.s./kg soil d.w. (loamy sand soil) + 11.76 % effect at day 28 at 4.5 mg a.s./kg soil d.w. (loamy sand soil)
	bifenox acid	28 days	+ 11 % effect at day 28 at 0.959 mg/kg soil d.w. + 8 % effect at day 28 at 4.793 mg/kg soil d.w.
Field studies			
Litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies			

Milan: SC formulation containing 519 g/L bifenox and 9.57 g/L pyraflufen-ethyl (batch n°: OP951099)
EXP 30535: formulation containing 255 g/L bifenox, 75.2 g/L ioxynil, 293 g/L mecoprop-P (batch n°: OP980213)

Toxicity/exposure ratios for soil organisms

Winter cereals, 1 x 0.750 kg a.s./ha

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Earthworms					
Eisenia foetida	bifenox ‡	acute	PEC_{soil} initial = 0.75 mg a.s./kg d.w. soil	> 667	10
Eisenia foetida	Milan	acute	PEC_{soil} initial = 0.75 mg a.s./kg d.w. soil	> 289	10
Eisenia foetida	EXP 30535	long-term	PEC_{soil} initial = 0.75 mg a.s./kg soil	3.4	5
Eisenia foetida	bifenox acid	acute	PEC_{soil} initial = 0.57 mg/kg d.w. soil	> 877	10

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

Preliminary screening data

Not provided

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Laboratory dose response tests

Type of test	Formu-lation	Application rate	2.77 % of the application rate	Most sensitive species	ED_{50}	TER	Annex VI trigger
Vegetative vigour	Fox	1.5 L/ha	41.6 mL/ha	all tested plant species	> 1.5 L/ha	36.1	5
	Milan	1.5 L/ha	41.6 mL/ha	sugar beet	0.214 L/ha (shoot fresh weight)	5.14	5
Seedling emergence	Fox	1.5 L/ha	41.6 mL/ha	onion	1.16 L/ha (shoot fresh weight)	27.9	5
	Milan	1.5 L/ha	41.6 mL/ha	onion	0.46 L/ha (shoot fresh weight)	11.1	5

Fox: SC formulation containing 476.5 g/L bifenox (batch n°: V20212005)
Milan: SC formulation containing 492.8 g/L bifenox and 9.2 g/L pyraflufen-ethyl (batch n°: 00103202)

Additional studies (e.g. semi-field or field studies)

Not provided

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	Endpoint
Activated sludge	EC_{50} (3 h) > 1000 mg a.s./L
Pseudomonas sp	-

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	bifenox, bifenox acid
water	bifenox, aminobifenox acid, 2,4-dichlorophenol
sediment	bifenox, aminobifenox
groundwater	bifenox, bifenox acid

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal	
Active substance	N, R50	harmful Highly toxic to aquatic organisms

	RMS/peer review proposal	
Preparation (Milan)	N, R50	harmful Highly toxic to aquatic organisms

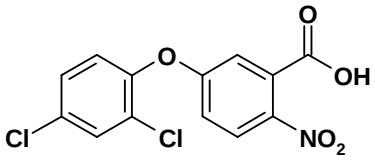
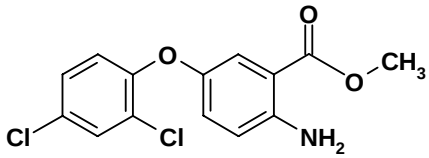
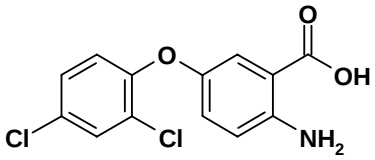
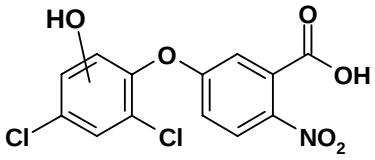
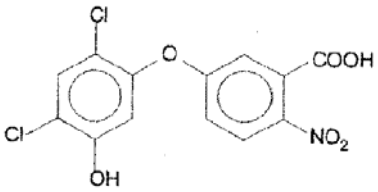
‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry

LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
bifenox acid	5-(2,4-dichlorophenoxy)-2-nitrobenzoic acid	
aminobifenox	5-(2,4-dichlorophenoxy)-2-aminobenzoic acid methyl ester	
aminobifenox acid	5-(2,4-dichlorophenoxy)-2-anthranilate acid	
hydroxybifenox acid LS-825055	5-(2,4-dichloro-?-hydroxy-phenoxy)-2-nitrobenzoic acid	
5-hydroxybifenox acid	5-(2,4-dichloro-5-hydroxy-phenoxy)-2-nitrobenzoic acid	
-	2,4-dichlorophenol