CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

bifenox (ISO); methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate

EC Number: **255-894-7**

CAS Number: **42576-02-3**

Index Number: **-**

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Polish Competent Authority

Bureau for Chemical Substances

Version number: 02 **Date: 2020**

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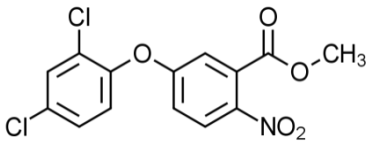
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	bifenox (ISO); methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate;
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	bifenox
EC number (if available and appropriate)	255-894-7
EC name (if available and appropriate)	methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate
CAS number (if available)	42576-02-3
Other identity code (if available)	CIPAC number 413
Molecular formula	$C_{14}H_9Cl_2NO_5$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	342.14 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not relevant
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
bifenox	**> 97%**	**None**	**Aquatic Acute 1; H400** **Aquatic Chronic 1; H410**

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
None				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
None					

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
None				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	**None**										
Dossier submitters proposal		bifenox (ISO);methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate;	255-894-7	42576-02-3	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410	-	M = 1000 M = 1000	
Resulting Annex VI entry if agreed by RAC and COM		methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate; bifenox	255-894-7	42576-02-3	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410	-	M = 1000 M = 1000	

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Conclusive but not sufficient for classification	No
Oxidising gases	Conclusive but not sufficient for classification	No
Gases under pressure	Conclusive but not sufficient for classification	No
Flammable liquids	Conclusive but not sufficient for classification	No
Flammable solids	Conclusive but not sufficient for classification	Yes
Self-reactive substances	Conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Conclusive but not sufficient for classification	No
Pyrophoric solids	Conclusive but not sufficient for classification	Yes
Self-heating substances	Conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Conclusive but not sufficient for classification	Yes
Oxidising liquids	Conclusive but not sufficient for classification	No
Oxidising solids	Conclusive but not sufficient for classification	Yes
Organic peroxides	Conclusive but not sufficient for classification	Yes
Corrosive to metals	Conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Conclusive but not sufficient for classification	Yes
Respiratory sensitisation	Conclusive but not sufficient for classification	No
Skin sensitisation	Conclusive but not sufficient for classification	Yes

Hazard class	Reason for no classification	Within the scope of public consultation
Germ cell mutagenicity	Conclusive but not sufficient for classification	Yes
Carcinogenicity	Conclusive but not sufficient for classification	Yes
Reproductive toxicity	Conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Conclusive but not sufficient for classification	Yes
Aspiration hazard	Conclusive but not sufficient for classification	No
Hazardous to the aquatic environment	harmonised classification proposed H400, M = 1 000 H410, M = 1 000	Yes
Hazardous to the ozone layer	Conclusive but not sufficient for classification	Yes

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

No classification according to Dangerous Product Regulations incl. EC guidelines (67/548/EEC and 1999/45/EC). A harmonised classification for methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate (bifenox) is not available in Annex VI of the Regulation (EC) No 1272/2008.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Bifenox is an active substance in the meaning of Directive 91/414/EEC and Regulation 1107/2009. In accordance with article 36(2) of the CLP Regulation, bifenox shall be subjected to harmonised classification and labelling.

There is no requirement for justification that action is needed at Community level.

5 IDENTIFIED USES

Bifenox was included in Annex I of Council Directive 91/414/EEC (Commission Directive 2008/66/EC of 30 June 2008). This active substance is an approved active substance under Regulation (EC) 1107/2009 (repealing Commission Directive 91/414/EEC) as specified in Commission Implementing Regulation (EU) 540/2011 of 25 May 2011 and Commission Implementation Regulation No. 1124/2013 amending Commission Implementation Regulation No 540/2011.

Bifenox, also in the form of potassium or ammonium salts, is an active substance (herbicide) in many plant protection products against dicotyledonus weeds and other plants as Lamium spp., Viola arvensis, Veronica serpyllifolia, Matricaria spp.. Bifenox is used for great deal of various crops, spring and winter cereals like barley, wheat, oats, spelt, triticale and also grasses, grassland, decorative lawn and turf.

6 DATA SOURCES

Data submitted with the dossier supporting the application for renewal of the regulatory approval of bifenox under Commission Implementing Regulation (EU) 844/2012 of 18 September 2012 submitted to the RMS Poland are used in this CLH report.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Pale yellow crystalline solid with no characteristic odour		
Melting/freezing point	Bifenox purified active substance melts in the range 86.0°C – 87.7°C.	Anonymous (2000)	Measured
	Bifenox technical active substance melts in the range 86.2°C – 87.3°C.		
Boiling point	Bifenox purified active substance does not boil. It decomposes from 398.6°C.	Anonymous (2000)	Measured
	Bifenox technical active substance does not boil. It decomposes from 392.8°C.		
Relative density	The relative density (D_4^{20}) of Bifenox purified active substance is 1.541.	Anonymous (2000)	Measured
	The relative density (D_4^{20}) of Bifenox technical active substance is 1.498.		
Vapour pressure	at 20°C, 4.74×10^{-8} Pa at 25°C, 1.85×10^{-7} Pa	Anonymous (2001a)	Measured
	$< 10^{-7}$ torr (25°C) corresponds to $< 1.33 \times 10^{-5}$ Pa (25°C)	Anonymous (1986)	Measured
	Henry's law constant: $K > 1.62 \times 10^{-4}$ Pa m^3 mol^{-1} at 20°C	Anonymous (2001a)	Calculated

Property	Value	Reference	Comment (e.g. measured or estimated)
	Henry's law constant: $K > 1.13 \times 10^{-7}$ atm m^3 $g.mol^{-1}$ at 25°C	Anonymous (1988)	Calculated
Surface tension	Surface tension of 90% technical Bifenox solubility in water was found to be 72.5 mN/m at 20°C. The substance can be regarded as not surface active.	Anonymous (1998)	Measured
Water solubility	< 0.1 mg/L at 20°C (pH 4 - 9)	Anonymous (2001b)	Measured
Solubility in organic solvents	at 20°C Acetone: 580 ± 14 g/L Acetonitrile: 330 ± 5.8 g/L Dichloromethane: > 1000 g/L Ethyl acetate: 440 ± 29 g/L n- Heptane: 3.1 ± 0.28 g/L Methanol: 23 ± 1.0 g/L n-Octanol: 10 ± 0.33 g/L Toluene: 320 ± 49 g/L	Anonymous (2001b)	Measured
Partition coefficient n-octanol/water	log P_{ow}: 3.64 (within a 95% confidence range of 3.55 to 3.73) Guideline EC method A.8 OECD 117	Anonymous (2000c)	Measured
	Bifenox acid: Log P_{ow}: 2.64 (pH 7; at 20°C ± 1°C) (Mean log P_{OW} of two runs; the result within a range of ± 0.1 log units (absolute deviation)). Guideline EC method A.8 OECD 117	Anonymous (2016a)	Measured

Property	Value	Reference	Comment (e.g. measured or estimated)
	Aminobifenox: Log P_{ow}: 4.86 (pH at 20°C ± 1°C) (Mean log P_{OW} of two runs; the result within a range of ± 0.1 log units (absolute deviation)). Guideline EC method A.8 OECD 117	Anonymous (2016b)	Measured
	Aminobifenox acid: Log P_{ow}: 2.75 (pH 7; at 20°C ± 1°C) (Mean log P_{OW} of two runs; the result within a range of ± 0.1 log units (absolute deviation)). Guideline EC method A.8 OECD 117	Anonymous (2016c)	Measured
	Log P_{ow}: 1.54 (pH 4; at 20°C) Log P_{ow}: -0.82 (pH 7; at 20°C) Log P_{ow}: -1.07 (pH 10; at 20°C) Guideline EC method A.8 OECD 107 OPPTS 830.7550	Document MII, Section 1 by European Union 2,4-D Task Force 2012 dated 27 February 2012- For further information please refer to Document-B.	Measured
	The results not available Guideline EC method A.8 OECD 107 OPPTS 830.7550	Anonymous (2016)	Measured
Flash point	Not relevant to be measured since the substance melts. No auto-ignition occurred before the melting point of ca 89°C was reached.	Anonymous (1998)	Estimated
Flammability	Bifenox is not highly flammable (substance melts, no flame is observed, flash point >100°C)	Anonymous (2000)	Estimated
Explosive properties	Bifenox technical does not have shock sensibility and thermal sensibility to explosion.	Anonymous (1998)	Estimated

Property	Value	Reference	Comment (e.g. measured or estimated)
Self-ignition temperature	No auto ignition occurred since the substance melts (self-ignition temperature >400°C).	Anonymous (1998)	Measured
Oxidising properties	Bifenox technical active substance has no oxidising properties.	Anonymous (1998)	Measured
	Bifenox technical active substance has no oxidising properties.	Anonymous (2006)	Measured
Granulometry			Not available
Stability in organic solvents and identity of relevant degradation products			
Dissociation constant	Bifenox is neither an acid with pKa < 2 nor a base with pKa > 2. The substance does not dissociate	Anonymous (2001b)	Not available
Viscosity	-	-	Not available

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 9: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Guideline: EEC A.14	Bifenox technical does not have shock sensibility, friction sensibility and thermal sensibility to explosion.	Estimated	Anonymous (1998)

8.1.1 Short summary and overall relevance of the information provided on explosive properties

Bifenox technical does not have shock sensibility and thermal sensibility to explosion.

8.1.2 Comparison with the CLP criteria

Bifenox does not meet the criteria.

8.1.3 Conclusion on classification and labelling for explosive properties

Bifenox does not require classification and labelling with regard to explosive properties according to Annex I part 2 of the CLP regulation.

8.2 Flammable gases (including chemically unstable gases)

Not relevant

8.3 Oxidising gases

Not relevant

8.4 Gases under pressure

Not relevant

8.5 Flammable liquids

Not relevant

8.6 Flammable solids

Table 10: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
Guideline: EEC A.10	Bifenox is not highly flammable (substance melts, no flame is observed, flash point >100°C)	Estimated - numerical results are inaccessible	Anonymous (2000)

8.6.1 Short summary and overall relevance of the provided information on flammable solids

Bifenox is not highly flammable.

8.6.2 Comparison with the CLP criteria

Bifenox does not meet the criteria.

8.6.3 Conclusion on classification and labelling for flammable solids

Bifenox does not require classification and labelling with regard to flammability.

8.7 Self-reactive substances

Table 11: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
Guideline: EEC A.16	No auto ignition occurred since the substance melts.	Measured	Anonymous (1998)

8.7.1 Short summary and overall relevance of the provided information on self-reactive substances

No auto ignition occurred since the substance melts.

8.7.2 Comparison with the CLP criteria

Bifenox does not meet the criteria.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Bifenox does not require classification and labelling with regard to self-reactive substances.

8.8 Pyrophoric liquids

Not relevant.

8.9 Pyrophoric solids

Not relevant.

8.10 Self-heating substances

Not relevant.

8.11 Substances which in contact with water emit flammable gases

Not relevant.

8.12 Oxidising liquids

Not relevant.

8.13 Oxidising solids

Table 12: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
Guideline: EEC A.21	Bifenox technical active substance has no oxidising properties.	Measured	Anonymous (1998)
Guideline: EEC A.17	Bifenox technical active substance has no oxidising properties.	Measured	Anonymous (2006)

8.13.1 Short summary and overall relevance of the provided information on oxidising solids

Bifenox technical active substance has no oxidising properties.

8.13.2 Comparison with the CLP criteria

Bifenox does not meet the criteria.

8.13.3 Conclusion on classification and labelling for oxidising solids

Bifenox does not require classification and labelling with regard to oxidising properties.

8.14 Organic peroxides

Not relevant.

8.15 Corrosive to metals

Not relevant.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Absorption, distribution, metabolism and excretion by oral exposure

The rate and extension of absorption, distribution, metabolism and excretion after oral exposure of Bifenox has been evaluated from a study conducted in rats. This study already had been submitted in the context of the inclusion of the active substance Bifenox in Annex I of the Council Directive 91/414/EEC.

Metabolism pattern of Bifenox has been investigated with radiolabelled [^{14}C]-Bifenox on the dichlorophenyl ring. Cleavage of the ether bond and then breaking of the molecule into 2 ring moieties was not expected to occur during the metabolism process. Therefore, only one ring was uniformly labelled. This assumption was confirmed by the *in vivo* metabolism study (Anonymous, 1986), which is summarized below. In this study, more than 95% of the radioactivity recovered was associated with Bifenox or identified metabolites containing the two rings.

As addressed under Regulation (EU) 283/2013, a study comparing *in vitro* metabolism has been investigated to verify rat metabolism as a suitable model. The study compares human and rat metabolism of uniformly ring labelled [^{14}C]-Bifenox *in vitro* in liver microsomes. The results from the *in vitro* study are summarized under Anonymous, 2015.

Evaluation of this study lead to the conclusion, that the metabolism of Bifenox in human and rats is comparable, based on similar metabolites. Therefore, results from the ADME study (Anonymous 1986) may be considered to be toxicologically relevant for humans. This study has been re-evaluated, in order to examine ADME endpoints after oral exposure of Bifenox. The endpoints from the rat metabolism study are summarized as follows:

Rate and extent of absorption:	25% (based on urinary excretion within 48 h)
Distribution:	Highest levels 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
Metabolism in animals:	Nitro-reduction and O-demethylation leading to Bifenox acid and Aminobifenox
Toxicologically significant compounds:	Bifenox

Oral absorption occurred within 48 hours after a single oral gavage and was sex and dose dependent. Bioavailability reached 29% and 53% in male and female rats. An increased dose was followed by a reduced urinary excretion, suggesting saturation of absorption. Based these results, oral absorption is estimated to be 25%. The only tissues showing signs of accumulation after seven days were the kidneys and liver. No evidence of retention in tissues was observed. Bifenox will be found almost metabolized in faeces, but completely metabolized in urine. Metabolism occurred by nitro-reduction and O-demethylation leading to the metabolites Aminobifenox (in faeces) and Bifenox acid (in urine).

Table 13: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
GLP / Guidelines not applicable	Transformations of [^{14}C]-Bifenox in the test system were dominated by protein reactivity and/or ester hydrolysing enzymes. NADPH dependent	*In vitro*, liver microsomes	Anonymous, 2015

Method	Results	Remarks	Reference
	metabolism could not be observed. Reactions in rat and human liver microsomes were similar, no unique human metabolite was observed.		
GLP / OECD 417	Based on urinary excretion, the extent of bioavailability reaches 29% and 53% in male and female rats. Bifenox undergoes a nitro-reduction and O-demethylation leading to formation of Bifenox acid and Aminobifenox.	*In vivo*, rat	Anonymous, 1986

9.2 Absorption, distribution, metabolism and excretion by other routes

Executive Summary

The absorption and excretion of radio-labelled [^{14}C]-Bifenox after single oral doses to bile duct-cannulated male and female Sprague Dawley CD rats at 90 mg/kg bw and 900 mg/kg bw were investigated in this toxicokinetics study.

After single oral doses of [^{14}C]-Bifenox to bile duct-cannulated rats, excretion of radioactivity was rapid with more than 85% of the dose excreted within the first 24 hours post dosing. Biliary excretion accounted for ≤ 18% of the dose at the 90 mg/kg dose level and ≤ 8.0% of the dose at the 900 mg/kg dose level.

Excretion of radioactivity was predominantly via the faeces and accounted for 42.8 – 72.9% dose during 0 – 48 hours at the 90 mg/kg dose level and 89.7 – 96.5% dose at the 900 mg/kg dose level. Urinary excretion during 0 – 48 hours accounted for 13.9 – 32.0% dose at the 90 mg/kg dose level and 4.8 – 9.1% dose at the 900 mg/kg dose level. A sex difference was noted in the routes of excretion at the 90 mg/kg dose level as a higher proportion of radioactivity was eliminated in the urine in females, whilst a greater proportion of radioactivity was eliminated in the faeces of males.

The extent of absorption was assessed as the sum of total radioactivity measured in bile, urine, liver and carcass. On this basis it was estimated that the extent of absorption was 30.3% and 50.3% of the dose for males and females, respectively at the 90 mg/kg dose level and 16.2 % and 12.9% dose for males and females at the 900 mg/kg dose level. At 48 hours, retention of radioactivity in residual carcass and tissues was low, accounting for 0.5 – 0.8% dose at the 90 mg/kg dose level and 0.1 – 0.9% at the 900 mg/kg dose level.

This metabolism study in the Sprague Dawley CD rats is acceptable and satisfies the guideline requirement for a toxicokinetic study OECD 417 and US EPA OPPTS 870.7485 in Sprague Dawley CD rats.

Method	Results	Remarks	Reference
GLP / OECD 417	Oral absorption 90 mg/kg bw: 30.3% male - 50.3% female Oral absorption 900 mg/kg bw: **12.9% male - 16.2% female**	In vivo, rat	Anonymous, 2016

During the course of the study, all animals were routinely observed for behavioural changes, ill health or reactions to treatment. On the day of dosing, all animals were observed immediately after dosing,

again within 2 hours after dosing and on at least one other occasion during the working day. On all other days after dosing, all animals were observed on at least one occasion.

After single oral doses of [14C]-Bifenox to bile duct-cannulated rats at dose levels of 90 and 900 mg/kg bw, excretion of radioactivity was rapid with more than 85% of the dose excreted within the first 24 hours post dose. Biliary excretion accounted for ≤ 17.8% dose at the 90 mg/kg dose level and ≤ 8.0% dose at the 900 mg/kg dose level.

Excretion of radioactivity was predominantly via the faeces and accounted for 42.8 – 72.9% dose during 0 48 hours at the 90 mg/kg dose level and 89.7 – 96.5% dose at the 900 mg/kg dose level. Urinary excretion during 0 – 48 hours accounted for 13.9 – 32.0% dose at the 90 mg/kg dose level and 4.8 – 9.1% dose at the 900 mg/kg dose level. A sex difference was noted in the routes of excretion at the 90 mg/kg dose level as a higher proportion of radioactivity was eliminated in the urine in females, whilst a greater proportion of radioactivity was eliminated in the faeces of males.

At 48 hours, retention of radioactivity in residual carcass and tissues was low, accounting for 0.5 – 0.8% dose at the 90 mg/kg dose level and 0.1 – 0.9% at the 900 mg/kg dose level.

The extent of absorption was assessed as the sum of total radioactivity measured in bile, urine, liver and carcass. On this basis, it was estimated that the extent of absorption was 30.3% and 50.3% dose for males and females respectively at the 90 mg/kg dose level and 16.2 % and 12.9% dose for males and females respectively at the 900 mg/kg dose level.

9.3 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Toxicokinetic data for Bifenox have no impact on classification.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 14: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
GLP, EPA 81-1 870.1100	Rat	Bifenox Lot no. 3123142017 Purity: 97%	at a level of 5000 mg/kg bw. Signs of toxicity and body weights were recorded up to 14 days after dosing.	LD_{50} > 5000 mg/kg bw (male and female)	Anonymous, 1985a
Not confirming GLP or Guidelines, data gaps for endpoints. The study was considered to be not valid.	Mouse	Bifenox Batch #. MCTR-126-78 Purity not stated	between at 0, 316, 1000, 3160, 10000 mg/kg bw Animals were observed for clinical signs	LD_{50} > 1540 mg/kg bw (male), LD_{50} > 1780 mg/kg bw (female)	Anonymous, 1978

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
			of toxicity up to 14 days after dosing.		

10.1.1 Study 1

The first study does not provide a statement of GLP but the study report claims GLP compliance. The study has been performed in accordance with EPA Guideline 81-1 870.1100 and an internal quality assurance statement is provided. Furthermore, the study was accepted in the DAR (2006). In order to assess the current reliability of this study, the ToxRTool (Toxicological data reliability Assessment Tool) has been used for evaluation. Consequently, this study is categorized into Klimisch category 1: reliable without restriction. Therefore, it is concluded that this study is valid, even without a statement of GLP and is considered for classification.

Bifenox (lot no. 3123142017, purity 97%) was administered orally by gavage, to five male and five female Sprague-Dawley rats, at a level of 5000 mg/kg bw. Signs of toxicity and body weights were recorded up to 14 days after dosing. Gross pathological examinations were performed on all main study animals.

No mortality was recorded during the study. The majority of the animals showed expected body weight gain throughout the study. Clinical signs included faecal staining, soft stool and hypoactivity (1-2 animals) 24 hours after dosing. 2 days after oral administration, some animals showed alopecia of abdomen, chest and/or hind leg. Reduced food consumption was observed in some cases. At necropsy, some animals showed red foci and discoloration of lungs.

The results on bodyweight gain and mortality are summarized in Table 15.

Table 15 Summary of body weight gains and mortalities at 5000 mg/kg Bifenox

Animal No.	Body weight gain [g]					Mortality (day)
	Pre-test	Day 7	Change*	Day 14	Change*	
Males						
2066	256	285	29	327	71	14**
2072	264	307	43	365	101	14**
2076	262	263	1	329	67	14**
2081	255	265	10	346	91	14**
2096	250	250	0	316	66	14**
Females						
2108	242	260	18	270	28	14**
2115	230	246	16	261	31	14**
2119	242	270	28	290	48	14**
2126	235	259	24	280	45	14**
2130	236	250	14	275	39	14**

* Change from pre-fasted weight
** At terminal sacrifice – not substance related

The acute oral median lethal dose (LD50) of Bifenox in rats was greater than 5000 mg/kg body weight. Based on the acute oral LD50 value, Bifenox does not require classification and labelling according to Regulation (EC) 1272/2008.

10.1.1 Study 2

The second study does not provide a statement of GLP, not even a statement on internal quality control. Reporting is very brief and no information on test item purity is given. Furthermore, this study was not performed in accordance with any guidelines and it was not accepted in the DAR (2006).

In order to assess the current reliability of this study, the ToxRTool (Toxicological data reliability Assessment Tool) has been used for evaluation. Consequently, this study is categorized into Klimisch category 3: not reliable. Therefore, this study is judged not to be valid and is not considered for classification.

This study does not fully confirm to the directive EEC 92/69 method B1 or GLP and it provides only incomplete data for body weight, clinical signs and necropsy findings. Based on these data gaps and the statement in the DAR (2006), the study is considered not to be valid and the results will not be included for classification according to Regulation (EC) 1272/2008.

Bifenox was suspended in corn oil and administered orally by gavage, to mice (5 per dose-group and sex). The dose groups were between at 0, 316, 1000, 3160, 10000 mg/kg bw. Animals were observed for clinical signs of toxicity up to 14 days after dosing. Body weights were recorded at the beginning and at the end of the study. Gross pathological examinations were performed at the end of the observation period.

On day two, mortality was observed at 1000 mg/kg bw in 1/5 males. At a dose level of 3160 mg/kg bw, 3/5 males and 3/5 females died on day 1, 2/5 males and 2/5 females died on day 2. At a dose level of 10000 mg/kg bw 3/5 males and 4/5 females died on day 1, 1/5 males and 1/5 females on day 2. There was no significant change in body weight gain compared to normal. Clinical signs included inactivity, unsteady gait and shivering. During necropsy, no gross lesions were observed. The results on mortality are summarised in Table 3.1.1-2.

Table 16 Mortalities in the acute oral toxicity study in mice

Group	Dose (mg/kg)	Mortalities in males	Mortalities in females
1	0	0/5	0/5
2	316	0/5	0/5
3	1000	1/5	0/5
4	3160	5/5	5/5
5	10000	4/5	5/5

Based on deaths occurring in the 14 days of treatment and using a modification of the method of Horn (Biometrics. 12. p. 311, 1956), LD50 values of 1540 mg/kg (95% confidence limits: 833-2850) and 1780 mg/kg (95% confidence limits: not determined due to steep response slope) were calculated for male and female mice, respectively.

Signs of toxicity judged to be related to treatment included inactivity, unsteady gait and shivering.

Necropsy findings among the surviving animals showed no gross lessions. Among mice that died, gas in the stomach and intestines was noted.

Following the oral administration of graded doses of the test compound to fasted young mice, LD50 values of 1540 mg/kg and 1780 mg/kg were calculated for males and females, respectively. The gastrointenstinal tract may be a possible site of toxicity.

There are no human data on acute oral toxicity of bifenox.

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Based on the study no 1 (rat) confirm to the directive EEC 92/69 method B1. bifenox is of low (no mortal cases) toxicity by the oral route in rats (LD_{50} > 5000 mg/kg bw).

The study no 2 (mouse) does not fully confirm to the directive EEC 92/69 method B1. The purity of the tested substance was not determined in this study. The test material (bifenox) was suspended in corn oil. There are incomplete raw data for body weight, clinical signs and necropsy findings. Additionaly the lack of information about the solvent and purity of the test substance in the test no 2 (mouse) comparing to test 1 (rat).

However, based on the LD_{50} found in mice the classification *Xn (Harmful), R22 – Harmful if swallowed* has been attributed to the substance in EFSA Scientific Report (2007)[1].

According to DAR (2006)[2] it has been assuming that the diference in the test results is propably related to the solvent used in this study as suggested by absence of toxic effects seen in the micronucleus test performed in mice (Anonymous, 2003) with bifenox suspended in hydroxypropyl-cellulose (aqueous suspension).

Considering all test results of studies number 1 and 2 in oral way and arguments presented above the test on mice could have been omitted for classification.

Taking into account all data bifenox is not classified in acute toxicity by the oral way.

10.1.2 Comparison with the CLP criteria

CLP Criteria (oral route):
Category 1: $0 < ATE \leq 5$
Category 2: $5 < ATE \leq 50$
Category 3: $50 < ATE \leq 300$
Category 4: $300 < ATE \leq 2\ 000$

Bifenox does not meet the CLP criteria classified in acute toxicity (oral).

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Bifenox does not require classification and labelling with regard to acute oral toxicity.

10.2 Acute toxicity - dermal route

Table 15: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
GLP, EPA 81-2 870.1200	Rabbit	Bifenox Lot no.	dose level of 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	Anonymous, 1985b (DAR,

[1] EFSA Scientific Report (2007) 119, 1-84, Conclusion on the peer review of bifenox
[2] DAR – Draft Assessment Report (Belgium, February 2006)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
		3123142017 Purity: 97%	Animals were observed for clinical signs for at least 14 days after treatment		2006)

There are no human data on acute dermal toxicity of bifenox.

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

There was no mortality. Most of the animals were free of significant signs although a single occurrence of ocular discharge was seen, as were occasional observations of nasal discharge and food consumption decrease. No abnormalities were seen at the majority of animals during necropsy.

The acute dermal median lethal dose (LD_{50}) of Bifenox in rabbits was greater than 2000 mg/kg body weight. Based on the acute dermal LD_{50} value, Bifenox does not require classification and labelling according to Regulation (EC) 1272/2008.

Bifenox is of low toxicity by the oral route in rats (LD_{50} > 2000 mg/kg bw).

10.2.2 Comparison with the CLP criteria

CLP Criteria (skin route):

Category 1: $0 < ATE \leq 50$

Category 2: $50 < ATE \leq 200$

Category 3: $200 < ATE \leq 1\,000$

Category 4: $1\,000 < ATE \leq 2\,000$

Based on the acute dermal LD_{50} value, Bifenox does not meet the criteria and does not require classification and labelling according to Regulation (EC) 1272/2008. .

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Bifenox does not require classification and labelling with regard to acute dermal toxicity.

10.3 Acute toxicity - inhalation route

Table 16: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
GLP, EPA 81-3, EC Directive 92/69/EEC, 93/21/EEC B.2 and OECD 403	Rat	Bifenox Lot no. 3123142017 Purity: 97%	dust atmosphere concentration was at 0.91 mg/L, which was the maximum attainable exposure concentration with a MMAD of 2.7 µm and a SGD of 1.6	LC_{50} > 0.91 mg/L (maximal attainable concentration)	Anonymous, 1985

There are no human data on acute inhalation toxicity of bifenox.

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

No mortality was observed throughout study performance. Clinical signs included activity and white material on fur, were exhibited during exposure. Upon removal from the chamber and during the 2-hour post-exposure observation period, increased secretory response, moist rales, yellow/brown ano-genital staining and soft stool were exhibited by the test animals. During the first days of test week 1, rats exhibited yellow ano-genial staining and slightly increased secretory responses. There were no significant changes in body weight gain. During necropsy, no compound related findings were observed.

The acute (4-hour) inhalation LC_{50} for rats exposed to Bifenox was greater than 0.91 mg/L (LD_{50} of 245 mg/kg bw). Based on the acute inhalation LC_{50} value, Bifenox does not require classification and labelling according to Regulation (EC) 1272/2008.

Bifenox is of low toxicity by the inhalation route in rats ($LC_{50\ (4h)}$ > 0.91 mg/L). There were no mortalities at the maximum attainable concentration of 0.91 mg/L air.

10.3.2 Comparison with the CLP criteria

CLP criteria for inhalation route (dusts and mists)
Category 1: $0 < ATE \leq 0.05$
Category 2: $0.05 < ATE \leq 0.5$
Category 3: $0.5 < ATE \leq 1.0$
Category 4: $1.0 < ATE \leq 5.0$

The dust atmosphere concentration was at 0.91 mg/L, which was the maximum attainable exposure concentration No mortality was observed throughout study performance.

The acute (4-hour) inhalation LC50 for rats exposed to Bifenox was greater than 0.91 mg/L (LD50 of 245 mg/kg bw).

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the acute inhalation LC50 value, Bifenox does not require classification and labelling according to Regulation (EC) 1272/2008.

Bifenox does not require classification and labelling with regard to acute inhalation toxicity.

10.4 Skin corrosion/irritation

Table 17: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
GLP, EPA 81-5 870.2500	Rabbit	Bifenox lot no. 3123142017, purity 97%	0.5 g dermal dose The area was examined at 1, 24, 48 and 72 hours after the removal of the patch and scored according to Draize (1959)	The only irritation noted was very slight erythema in one animal at 0.5 h. Not irritating	Anonymous 1985c

There are no human data on skin corrosion/irritation of Bifenox.

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

The potential of Bifenox to irritate skin was tested in New Zealand White albino rabbits. The animals were exposed for 4 h to 0.5 g of the test material. Bifenox was not irritating to the skin of rabbits.

Table 18: Dermal irritation responses in rabbits according to the Draize scheme

Animal	Erythema score						Oedema score					
No. Sex	1 m	2 m	3 m	4 f	5 f	6 f	1 m	2 m	3 m	4 f	5 f	6 f
after 30 min.	0	0	0	0	0	1	0	0	0	0	0	0
24 h	0	0	0	0	0	0	0	0	0	0	0	0
48 h	0	0	0	0	0	0	0	0	0	0	0	0
72 h	0	0	0	0	0	0	0	0	0	0	0	0
Irritation Index*	0						0					

* (Mean scores 24 – 72 h)

Based on mean skin irritation scores 24 to 72 hours after removal of test substance, Bifenox is not a skin irritant and will not require classification and labelling.

10.4.2 Comparison with the CLP criteria

CLP criteria for skin irritation category:

(1) Mean score of ≥ 2,3 and ≤ 4,0 for erythema/ eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

(2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling reactions; or

(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

Bifenox was essentially non-irritating to the skin of rabbits. The only irritation noted was very slight erythema in one animal at 0.5 h.

Bifenox does not meet the criteria and does not require classification and labelling according to CLP Regulation.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Bifenox does not require classification and labelling with regard to skin irritation.

10.5 Serious eye damage/eye irritation

Table 19: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
GLP, EPA 81-4 870.2400	Rabbit	Bifenox lot no. 3123142017, purity 97%	dose of 29.7 mg (equivalent to 0.1 mL) The treated eyes of the rabbits were observed and scored for ocular irritation approx. 1, 24, 48, and 72 hours and 7 days after instillation of the test material.	Slight conjunctival irritation (redness, chemosis, discharge) and iridial changes Slightly irritating	Anonymous, 1985d

Slight conjunctival irritation (redness, chemosis, discharge) and iridial changes were noted in all treated eyes at one hour. No corneal opacity or ulceration was observed. All nine animals were free of ocular irritation within 24 h to 7 days after instillation of the test article. Comparable results were obtained for washed and unwashed eyes.

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

The potential of Bifenox to irritate eyes was tested in New Zealand White albino rabbits. The animals were exposed to 0.1 mL (equivalent to 29.7 mg) of the test material. Bifenox produced only mild and reversible ocular irritation**.**

Table 20: Eye irritation mean scores (24-72 h) in rabbits according to the Draize scheme

	Mean scores (24 - 72 h) – Animal number								
	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8	# 9
Corneal opacity	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Iritis	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Chemosis conjunctivae	0.3	0.3	0.0	0.3	0.3	0.3	0.0	0.3	0.0
Redness conjunctivae	0.7	0.7	0.0	1.3	0.3	0.3	0.0	1.0	0.0
Reversibility (day)	3	3	0	7	2	3	0	7	0

Based on mean eye irritation scores 24 to 72 hours after removal of test substance, bifenox is not an eye irritant and does not require classification and labelling. All effects reverses within an observation period.

10.5.2 Comparison with the CLP criteria

CLP criteria for Category for reversible eye effects:
at least in 2 of 3 tested animals, a positive response of:
(1) corneal opacity ≥ 1 and/or
(2) iritis ≥ 1, and/or
(3) conjunctival redness ≥ 2 and/or
(4) conjunctival oedema (chemosis) ≥ 2
— calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

Instillation of Bifenox technical into the eyes of New Zealand white rabbits produced mild and reversible ocular irritation. Bifenox does not meet the criteria classification.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Bifenox does not require classification and labelling with regard to eye irritation.

10.6 Respiratory sensitisation

There are no experimental data and no observations or indications for respiratory sensitisation.

10.7 Skin sensitisation

Table 21: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
GLP, OECD 406	Guinea pig	Bifenox batch # 0546/7, purity 98.2%	0.1 mL of a 5% mixture of Bifenox the skin reaction results from the first stage were evaluated at 25 and 48 hours, of the second stage at 49 and 72 hours after begin of exposure.	No skin irritations were noted after challenge Non-sensitizing (M&K)	Anonymous, 2001
Not confirming GLP, OECD 406, EC B.06 Dir. 67/548/EEC	Guinea pig	bifenox lot no. 353-12-1, purity 98%	0.5 mL test article (50% w/v in acetone) Cutaneous reactions were	No skin-sensitizing properties Non-sensitizing (Buehler)	Anonymous, 1985

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
V			evaluated 24, 48 and 72 hours after challenge application		

In order to assess the current reliability of the first study (Anonymous, 2001), the ToxRTool (Toxicological data reliability Assessment Tool) has been used for evaluation. Consequently, this study is categorized into Klimisch category 1: reliable without restriction.

Intracutaneous injections of 0.1 mL of a 5% mixture of Bifenox in sesame oil resulted in discrete or patchy erythema in all treated animals after 25 and 48 hours. Topical application of 2 mL of a 30% mixture of Bifenox in sesame oil result in discrete or patchy erythema or moderate and confluent erythema in all treated animals after 49 and 72 hours. No skin irritations were noted after challenge with the 5% mixture of Bifenox in sesame oil. At no time were adverse reactions noted at the vehicle control sites in test animals or at any sites of control animals.

Under the conditions of the Magnusson Kligman test, Bifenox did not exhibit skin-sensitizing properties in guinea pigs and was considered to be non-sensitizing.

According to the criteria laid down in Regulation (EC) 1272/2008, the test substance Bifenox does not require classification for skin sensitizing properties.

The second study does not provide a statement of GLP but the study report claims GLP compliance. However, the study has been performed in accordance with OECD Guideline 406 and an internal quality assurance statement is provided. Furthermore, the study was accepted in the DAR (2006).

Under the conditions of the Buehler test, Bifenox did not exhibit skin-sensitizing properties in guinea pigs and was considered to be non-sensitizing.

According to the criteria laid down in Regulation (EC) 1272/2008 the test substance Bifenox does not require classification for skin sensitizing properties.

There are no observations or indications for skin sensitisation in humans. No incidences of allergic reaction reported.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

The dermal sensitisation of Bifenox was evaluated by means of the Magnusson and Kligman maximisation test (Anonymous, 2001) in 15 female Dunkin-Hartley guinea pigs (10 test and 5 control animals). Concentrations used were determined from a series of "sighting tests" to determine the highest concentrations for the relevant endpoints which were 5% for intra dermal application, 30% for topical induction and 5% for topical challenge. Following challenge with the test material no skin responses were noted. At no time any adverse reactions were noted at the vehicle control sites in test animals or at any sites of control animals. Under the conditions of this assay, Bifenox did not exhibit sensitizing properties.

The use of 10 animals and 5 controls is the minimum in the Guinea-Pig Maximisation Test (GPMT), but then it is not possible to claim that the substance is a sensitizer. In this case, according to the test method it is recommended to use additional animals to test 20 animals with 10 controls.

Another sensitization assay was performed according to the Buehler method (Saeber, 1985). A group of 10 female Hartley guinea pigs were exposed to Bifenox, 10 animals were used as control group. The animals received once weekly during a 3-week induction period an application of 0.5 mL test article to the clipped skin on the left shoulder region for 6 hours. Thereafter, the dressing was removed. The resulting dermal reactions were assessed 24 hours later for erythema and oedema according to the Draize scale. Control animals were treated similarly without test substance. Following a rest of 2 weeks, a challenge cutaneous application of 0.5 mL test article to the clipped skin of the right flank for 6 hours. At no time any adverse reactions were noted at the vehicle control sites in test animals or at any sites of control animals. Under the conditions of the Buehler test, Bifenox did not exhibit skin-sensitizing properties in guinea pigs and was considered to be non-sensitizing.

10.7.2 Comparison with the CLP criteria

Under the conditions of the Magnusson Kligman test and the Buehler method, Bifenox did not exhibit skin-sensitizing properties in guinea pigs and was considered to be non-sensitizing.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Bifenox does not require any hazard classification for skin sensitizing properties

10.8 Germ cell mutagenicity

Table 22: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial mutagenicity GLP / OECD 471, EC 440/2008 B. 13/14, EPA, OPPTS 870.5100, 712-C-98-247	Bifenox D-20140741 Purity: 98%	*S. typhimurium* (TA100, TA1535, TA98, TA1537 and TA1538), *E. coli* WP2 uvrA **Conditions:** Plate incorporation assay, with and without S9 mix 3.16-5000 µg/plate	Bifenox technical did not cause gene mutations by base pair changes or frameshifts in the genome of the tester strains used. Negative	Anonymous, 2015
Mammalian cell gene mutation GLP / OECD 476, EC 440/2008 B. 17, EPA, OPPTS 870.5300, 712-C-98-221	Bifenox Batch no. D-20140741 Purity: 98%	*V79 Chinese Hamster cells* HPRT locus assay **Conditions:** 0.25 - 250 µg/mL without S9 mix; 0.5 - 250 µg/mL with S9 mix	Bifenox technical did not cause gene mutations in the genome of V79 Chines Hamster cells. Negative	Anonymous, 2016
Chromosomal aberration GLP / OECD 473, EC 440/2008 B. 10, EPA, OPPTS 870.5375, 712-	Bifenox D-20140741 Purity: 98%	*V79 Chinese Hamster cells* **Conditions:** Two experiments (4 and 21 h), 5-500 µg/mL with	Bifenox technical did not induce structural chromosomal aberrations in the	Anonymous, 2016 (amended 2017)

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
C-98-223		and without S9 mix	V79 Chinese hamster cell line Negative	
Bacterial mutagenicity GLP / OECD 471	Bifenox Batch no. 10830 Purity: 99.1%	*S. typhimurium* (strain TA100, TA1535, TA98, TA1537, TA1538 and TA102) **Conditions:** Plate incorporation assay and a preincubation method at 3.16 to 316 µg/plate	Bifenox did not induce gene mutation towards *S. Typhimurium under the experimental condition* Negative	Anonymous, 2005a
Bacterial mutagenicity No GLP statement / assay was conducted according to standard procedures (Ames et al, 1975) on which OECD 471 is based / test is judged to be valid	Bifenox Batch no. not stated Purity: 99.5%	*S. typhimurium* (TA100, TA1535, TA98, TA1537 and TA1538), *E. coli* WP2 uvrA **Conditions:** Plate incorporation assay, with and without S9 mix 10-5000 µg/plate	Bifenox did not increase the reversion rate in the different *S. Typhimurium under the experimental condition* Negative	Anonymous, 1982
Chromosomal aberration No GLP statement / assay was conducted according to standard procedures on which OECD 473 is based / test is judged to be valid	Bifenox Lot no. 3123142024 Purity: 97%	CHO cells **Conditions:** 25 - 2510 µg/mL With and without S9 mix	Bifenox was tested at 25, 75, 250 and 750 µg/ml without S9mix for 8 hr. None of the concentrations induced aberration frequencies different from the negative control. Mitomycin induced a significant increase in aberration frequency. After 18 hr exposure, negative results were seen. With S9mix, bifenox was tested at 125, 250, 400, 1260 and 2510 µg/ml for 2 hr + 8 hr (growth period). Very low mitotic index was reported at 1260 µg/ml. No chromosomal aberrations were observed. When the growth period	Anonymous, 1985

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
			was 17 hr, mitotic indexes at concentrations > 400 µg/ml were extremely low. No chromosomal aberrations were observed. Cyclophosphamide induced a significant increase in aberration frequencies. Negative	
Mammalian cell gene mutation GLP / OECD 476	Bifenox Batch no. 10830 Purity: 99.1%	Mouse lymphoma L5178Y cells ($tk^{+/-}$ system) **Conditions:** 19.53 to 312.5 µg/mL with and w/o S9 mix; in the second experiment w/o S9 mix concentrations ranging from 9.77 to 156.25 µg/mL were used.	bifenox was negative with respect to the mutant frequency in the LK5178Y TK+/- mammalian cell mutagenicity test Negative	Anonymous, 2005b
Mammalian cell gene mutation No GLP statement / assay was conducted according to standard procedures on which OECD 476 is based / test is judged to be valid	Bifenox MCTR-12-79 (MRI #248) Purity not stated	Mouse lymphoma L5178Y cells ($tk^{+/-}$ system) **Conditions:** w/o S9 mix: 133-1000 µg/mL, with S9 mix: 18 - 133 µg/mL	Bifenox did not induce mutation in the TK locus of L5178Y TK+/- cells when tested in the presence and absence of metabolic activation system Negative	Anonymous, 1979
Mammalian cell gene mutation GLP/assay was conducted according to standard procedures on which OECD 476 is based/test is judged to be valid	Bifenox Batch no. and purity not stated	CHO-cells (HGPRT system) **Conditions:** 50 - 500 µg/mL with S9 mix, 30 – 250 µg/mL without S9 mix	Bifenox were negative in the CHO/HGPRT mammalian cell forward gene mutation test Negative	Anonymous, 1983
UDS assay GLP/assay was conducted according to standard procedures on which OECD 482 is based / test is judged to	Bifenox Lot no. 16230 Purity not stated	Rat hepatocytes **Conditions:** 8 doses from 100 µg/mL to 0.5 µg/mL	Bifenox was considered to be inactive in the primary rat hepatocytes UDS assay	Anonymous, 1981

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
be valid			Negative	

Table 23: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mouse micronucleus GLP / OECD 474	Bifenox Batch no. 20010903 Purity: 97.3%	Mouse bone marrow **Route of administration:** Oral gavage **Dose range tested** 500, 1000, 2000 mg/kg bw	No signs of systemic toxicity tested up to the highest reasonable dose of 2000 mg/kg bw showed no mutagenic properties Negative	Anonymous, 2003
Metaphase analysis No GLP statement / assay was conducted according to standard procedures on which OECD 475 is based / test is judged to be valid	Bifenox Lot no 16230 Purity 93.8%	Rat bone marrow **Route of administration:** Oral gavage, 5 days **Dose range tested** 500, 1000, 1500 mg/kg bw	Bifenox did not induce any remarkable pharmacological effects. Cytotoxicity was not observed although bifenox was detected in blood. No clastogenic activity was seen with bifenox. Severe cytotoxicity was observed with cyclophosphamide, which was clastogenic. Negative	Anonymous, 1981

There are no human data on mutagenicity.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Bifenox is structurally related to the genotoxic carcinogen nitrofen. The genotoxic activity of nitrofen is believed to be mediated by enzymatic reduction and activation of its nitro group to highly reactive electrophilic intermediates, which can react with DNA-bases to form DNA adducts. However, it was shown that bifenox is not genotoxic although sharingmost of its structural features with nitrofen. 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 active the N hydroxylamine intermediate to highly reactive O-conjugates. Similar to bifenox, 3-

nitro-2-naphtoic acid is not mutagenic, whereas its isomer 8-nitro-1-naphtoic acid or 2-nitronaphtalene is mutagenic.

A number of studies had been investigated in order to evaluate genotoxic effects of Bifenox in vitro or in vivo in somatic cells. There was no evidence or signs of genotoxic effects from the active substance, an in vivo study in germ cells has therefore been concluded not to be relevant in accordance with Regulation (EU) No. 283/2013.

Bifenox was concluded to be non-genotoxic.

10.8.2 Comparison with the CLP criteria

Category 1

There is no evidence or indication that Bifenox induces heritable mutations in germ cells of humans.

There are no epidemiological studies indicating that Bifenox induces heritable mutations in germ cells of humans.

There are no positive results from *in vivo* heritable cell mutagenicity tests or *in vivo* somatic cell mutagenicity tests in mammals. In fact these tests gave negative results.

Category 2

There is no concern for humans. Bifenox is not considered to induce heritable mutations in humans because:

No positive evidence was obtained from experiments in mammals.

No positive results were obtained from *in vitro* mammalian mutagenicity assays.

In fact, the negative *in vivo* results confirm the negative *in vitro* results. There is no evidence that Bifenox may cause genotoxic effects.

Under the conditions of the *in vivo* and *in vitro* assays that were conducted with Bifenox, no genotoxic potential from the substance was revealed. Bifenox is concluded to be non-genotoxic

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Bifenox does not require labelling as mutagenic.

10.9 Carcinogenicity

Table 24: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Oral toxicity/ carcinogenicity, 104 weeks, Rat	Bifenox Batch, # 353-12-1 purity	No significant adverse effects Not carcinogenic	Anonymous, 1987

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
GLP / not fully compliant to OECD 453 (MTD not reached)	98% 50 Charles River Sprague Dawley CD 500, 1580, 5000 ppm corresponding to Males: 18.9, 59, 188 mg/kg bw/d Females 24.6, 77, 252 mg/kg bw/d	NOEL: 252 mg/kg bw/day (top dose tested)	
Carcinogenicity, 24 months, Mice GLP / not fully compliant to OECD 451 (MTD not reached)	Bifenox Batch # 16230, purity 98.3%, Males: 7, 30, 147 mg/kg bw/d Females: 9, 35, 179 mg/kg bw/d	Small effects on haematological parameters at highest dose level Not carcinogenic NOEL: 30 mg/kg bw/day	Anonymous, 1982

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In order to identify adverse parameters after chronic exposure towards the active substance Bifenox on target organs or dose-response relationships, long-term studies conducted in rats or mice were re-evaluated. Those studies already were submitted in the context of the inclusion of the active substance Bifenox in Annex I of the Council Directive 91/414/EEC.

Long-term exposure in rats or mice did not reveal significant substance related effects up to the top dose levels of 252 mg/kg bw/day for rats. For mice, the NOAEL was set at 30 mg/kg bw/day, based on small effects on haematological parameters.

The endpoints were discussed in the conclusion on the peer review of Bifenox by the EFSA and were corrected to original study results. Effects that were seen in rats at 252 mg/kg bw/day were considered not to be relevant. Initially the NOAEL was determined to be 59 mg/kg bw/day, based on reduced body weight gain in 6% of male and female rats. However, this effect was statistically not significant.

Target/critical effect: Reduced platelets and reticulocytes at terminal sacrifice (mice). Reduced body weight gain and decreased food consumption (rat).

Lowest relevant NOAEL: 30 mg/kg bw/day, 2-year mice, 252 mg/kg bw/day, 2-year rats

Carcinogenicity: Not carcinogenic in rat or mice up to the highest dose tested

Bifenox is not carcinogenic. This conclusion is supported by the absence of genotoxic activity of Bifenox, *tested in vivo* and *in vitro*. The results of the long-term toxicity studies are summarized in Table 24.

Rats

In a 104 weeks study in rats, reduced body weight gain and decreased food consumptions was noted, however, those effects were not significant. Islet cell adenoma and/or adenocarcinoma of the pancreas were observed for male rats at the low and intermediate dose reaching statistical significance when compared with control. However, there was no evidence of a trend across the treatment groups. The low dose for females was found to have significantly more tumours than the controls, but again no trend across the treatment groups was apparent. Comparison with data from open literature indicates that for this common type of tumour, the marginally significant increase at low and intermediate dose in male rats results probably from a random occurrence of a low concurrent control rate.

Tumours of the pancreas were not directly responsible for animal deaths. Islet cell adenoma and/or adenocarcinoma of the pancreas were observed for male rats at the low and intermediate dose reaching statistical significance when compared with control. However, there was no evidence of a trend across the treatment groups. The low dose for females was found to have significantly more tumours than the controls, but again no trend across the treatment groups was apparent.

No statistical significance was found in the incidence of malignant islet cell tumours in any group of male or female rats when compared to control, nor was there any significant trend in malignant islet cell tumour incidence with increasing dosage. A statistical significance was found in a pair wise comparison for combined benign and malignant islet cell in male ($p = 0.05$) and female ($p = 0.03$) rats receiving 500 ppm and in male rats ($p = 0.04$) receiving 1580 ppm, but the dose response trend between control and exposure groups indicated a lack of statistical significance.

When comparing the combined incidence of tumours in the study with the historical control data based on adenoma and adenocarcinoma incidences provided by the laboratory (background data from the study report), the results at 500 and 1580 ppm are outside the concurrent historical control data. However, according to the open literature the incidence of islet cell adenomas is within 1.67-25.71% and 1.43-14.29% for male rats and female rats (CD Sprague Dawley rats). For carcinoma the incidence is 0.77-14% and 0.77-4.29% for male and female rats respectively. Islet cell tumours subclassified as adenoma and adenocarcinomas, increase in incidence with age and are more frequently observed in males than in females.

Background data from the study report on islet cell tumours in CD Sprague Dawley rats was evaluated as demonstrated in Table 24.1.

Table 24.1 Incidence of islet cell tumors in background data from CD Sprague Dawley rats

Study number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of islet cell tumors	Male	12	14	10	2	13	7	19	7
	Female	5	4	5	4	3	3	7	3
Number of pancreas examined	Male	100	100	50	49	100	50	100	50
	Female	100	99	50	50	100	50	100	50

Table 24.2: Further details for the incidence of islet cell tumors in background data from CD Sprague Dawley rats reported in Anonymous(1987) for the same test laboratory and strain from 1980 to 1982. See table below for data relating 1982 to 1984

Study number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Study start	Feb-80	Apr-80	Sep-80	Jun-80	Apr-81	Feb-81	Jul-81	Jan-82			
Animal supplier	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa		**% range**	
Study duration	115	115	105	108	104	104	105	104	**mean**	**Min**	**Max**
	Males										
Number of animals	100	100	50	50	100	50	100	50			
Number examined	100	96	50	49	100	50	97	50			
Islet cell tumours incidence	12	14	10	2	13	7	19	7			
%	12.0	14.6	20.0	4.1	13.0	14.0	19.6	14.0	**14.19**	**4.1**	**20.0**
	Females										
Number of animals	100	100	50	50	100	50	100	50			
Number examined	100	99	50	50	100	50	100	50			
Islet cell tumours incidence	5	4	5	4	3	2	7	3			
%	5.0	4.0	10.0	8.0	3.0	4.0	7.0	6.0	**5.51**	**3.0**	**10.0**

crusa = Charles River USA

Table 24.3: Incidence of islet cell tumors in background data from CD Sprague Dawley rats for the same test laboratory and strain for the period 1982 to 1984

Study number	**8**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**			
Code number	cdr8201	cdr8203	cdr8207	cdr8207b	cdr8210a	cdr8210b	cdr8301	cdr8304	cdr8305	cdr8307	cdr8311	cdr8312	cdr8406	cdr8409	cdr8409	cdr8410a	cdr8410b			
Study start	Jan-82	Mar-82	Jul-82	Jul-82	Oct-82	Oct-82	Jan-83	Apr-83	May-83	Jul-83	Nov-83	Dec-83	Jun-84	Sep-84	Sep-84	Oct-84	Oct-84			
Animal supplier	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa	crusa		**% range**	
Study duration	104	111	104	104	110	106	105	105	110	106	106	106	106	106	106	106	106	**Mean**	**Min**	**Max**
	Males																			
Number of animals	50	105	60	50	50	50	50	55	50	50	50	55	100	50	50	50	55			
Number examined	50	104	60	50	50	50	49	55	50	49	50	55	100	50	50	50	55			
Islet cell tumours incidence	7	17	9	8	7	6	6	10	10	9	8	11	22	7	15	15	12			
%	14.0	16.3	15.0	16.0	14.0	12.0	12.2	18.2	20.0	18.4	16.0	20.0	22.0	14.0	30.0	30.0	21.8	**18.2**	**12**	**30**
	Females																			
Number of animals	50	105	61	50	50	50	50	55	50	50	50	55	100	50	50	50	55			
Number examined	50	105	61	50	50	49	50	55	50	50	50	55	100	50	50	50	55			
Islet cell tumours incidence	3	7	5	4	2	1	5	1	11	4	5	13	7	6	5	8	1			
%	6.0	6.7	8.2	8.0	4.0	2.0	10.0	1.8	22.0	8.0	10.0	23.6	7.0	12.0	10.0	16.0	1.8	**16**	**1.8**	**23.6**

crusa = Charles River USA

Data from open literature

Data from open literature examined for spontaneous pancreas tumour occurrence in rats

Islet cell tumours (endocrine tumours), subclassified as adenoma and adenocarcinomas, increase in incidence with age and are more frequently observed in males than females. The incidence of spontaneous tumours has been reported by different authors. The reported incidence of Islet cell tumours of rats has ranged from 0 to 17.6% in two small series of 71 male Sprague Dawley Hap and 108 females Sprague Dawley CD rats. The histological type of tumours of the Islet cell of the pancreas in rats is similar from that in humans, but in rats, the spontaneous incidence of Islet cell tumours is higher than that of exocrine tumours (Longnecker and Millar, 1990).

A survey of the incidence of spontaneous pancreatic tumours in CD rats from two-year carcinogenicity studies over a 15-year period was carried out. The survey revealed Islet cell adenomas to be the most common of pancreatic tumours with a higher incidence in untreated males (11.7% in comparison to females 5.5%) (Majeed, 1997).

A more recent compilation of spontaneous neoplastic lesions in Crl:CD (SD) BR rats from control groups (Charles River laboratories), in a total number of 1531 pancreases from male rats, 106 has Islet cell adenoma and 47 had carcinoma. In 1729 pancreases of female rats, 59 had Islet cell adenoma and 19 carcinoma. In this study minimum and maximum percent found were 1.67-25.71% and 1.43-14.29% for Islet cell adenoma in male and female rats, and 0.77-14% and 0.77-4.29% for carcinoma in male and female rats respectively (Giknis and Clifford, 2001).

In 2001, a study compared the effects of ad libitum (AL) overfeeding and moderate or marked dietary restriction (DR) on age related degenerative and proliferative changes of the endocrine pancreas in Sprague Dawley rats. In AL-fed rats, early changes in the islet morphology occurred, which resulted in a high incidence of islet fibrosis, focal hyperplasia and adenomas by two years. Compared to AL-fed rats, DR-fed rats had smaller pancreas, smaller pancreatic islets, smaller insulin secreting cell volumes, a lower degree of Islet fibrosis and a lower Islet cell BrdU labelling index, which correlated with a lower incidence of Islet adenoma and carcinoma at study termination. Moderate and marked degrees of DR delayed the onset and severity of Islet hyperplasia and fibrosis in a temporal and dose related manner (Molon-Noblot et al, 2001).

Table 24.4: Incidence of islet cell tumors in CD Sprague Dawley rats from open literature

Reference		**Gikins and Clifford, 2001[3]**	**Majeed, 1997[4]**	**Longnecker and Millar, 1990[5]**
Species / Strain		Crl:CD Sprague Dawley	CD Sprague Dawley	CD Sprague Dawley
Incidence Islet tumours	Male	Adenocarcinoma: 0.8-14% Adenoma: 1.7-25.7%	11.7%	0-17%
	Females	Adenocarcinoma: 0.8-4.3% Adenoma: 1.4-14.3%	5.5%	

[3] Gikins, M.L.A., Clifford, C.B., (2001) Compilation of Spontaneous Neoplastic Lesions And Survival in Crl:CD (SD) BR Rats From Control Groups, Charles River Laboratories

[4] Majeed, S.K., (1997) Studies of the incidence of spontaneous pancreatic tumors in ageing CD rats, Arzeneimittel-Forschung, 47 (7), 879-884

[5] Longnecker, D.S. and Millar, P.M., (1990) Pathology of tumours in laboratory animals. Vol I. Tumors of the rat, IARC scientific publications (99)

Table 24.5: Elaboration of the public domain historical control data cited in connection with Ruckman et al., 1987.

Reference		**Lang, 1992** elaborated on instead of Gifkins and Clifford, (2001)*	**Majeed, 1997**	**Longnecker and Millar, 1990**
Strain		Crl:CD Sprague Dawley, bred at Portland Michig Source Charles River Breeding Laboratories, Portage, Michigan, USA.	CD Sprague Dawley, (Charles River UK Ltd., Margate, Kent, UK)	CD Sprague Dawley ***Crl: COBS(r) CR(r) SD.*** These rats have been produced continuously at the Charles River Breeding Laboratories (CRBL) Wilmington, Massachusetts since 1955
Incidence Islet tumours	Male	Adenocarcinoma: 1.6-8.2% Adenoma: 2.9 -24.0%	11.7%	The reported incidence of islet cell tumours of rat has ranged from 0 to 17.6% in two small series of 71 male Sprague-Dawley Hap and 108 female
	Females	Adenocarcinoma: 1.4-8.2% Adenoma: 1.4-8.6%	5.5%	
Reference		Lang PL (1992) Spontaneous Neoplastic Lesions and Selected Non-neoplastic Lesions in the Crl:CD®BR Rat Published by Charles River Laboratories (February 1992)	Majeed, S. K. (1997). Studies of the incidence of spontaneous pancreatic tumours in ageing CD rats. Arzneimittel-forschung, 47(7), 879-884	Longnecker DS and Millar PM. (1994). Pathology of Tumours in Laboratory Animals. Vol. I. Tumours of the Rat. pp241-257 IARC Sci. Publ. No. 99, Publ. Lyon 1990 citing Anver MR, Cohen BJ, Lattuada CP, Foster SJ (1982) Age associated lesion in barrier-reared male Sprague-Dawley rate: A comparison between Hap:(SD) and Crl: COBS(r) CR(r) SD stocks. Exp. Agric. Res., 8(1), 3-22
Period covered		Studies with Start dates ranging from Dec 1985 to Feb 1989	1970 - 1995	Assumed to be 1980-1982.

***Although Gifkins and Clifford, (2001) was cited, Lang, 1992 also published by Charles River Laboratories, is more temporally relevant.**

For this common type of tumour, the marginally significant increases at 500 and 1580 ppm in male rats results from a random occurrence of a low concurrent control rats.

For mammary adenocarcinoma, there was no significant trend in tumour incidence with increasing dose. The intermediate dose group however, showed a slight increase from the controls, but this difference did not attain statistical significance ($p = 0.08$). No significant treatment effects were found when the combined category of any mammary tumour was considered.

A NOAEL of 5000 ppm = 252 mg/kg bw/day in rats was set, because the effects were statistically not significant or lacked dose response.

Table 24.6 Data from Lang, P. L. (1992). Spontaneous neoplastic lesions and selected non-neoplastic lesions in the Crl: CD® BR rat. *Charles River Laboratories.*[6]

TABLE 5a (Continued)
NEOPLASMS
24 MONTH STUDIES
MALE CD® RATS

LOCATION & TUMOR	# groups in which organ examined	total if lesions	percent of total	# groups using this diagnosis	minimum % found	maximum % found
LIVER	19					
nodular hepatocellular proliferation		9	0.72	2	8.0	10.2
hepatocellular adenoma		53	4.21	18	1.3	18.2
hepatocellular carcinoma		33	2.62	12	1.1	9.1
cholangioma		1	0.08	1	-	1.4
cholangiocellular carcinoma		2	0.16	2	1.0	2.0
carcinosarcoma		1	0.08	1	-	2.0
PANCREAS (EXOCRINE)	19					
acinar cell adenoma		7	0.56	7	1.3	2.0
sarcoma (NOS)		1	0.08	1	-	1.8
URINARY SYSTEM						
KIDNEY	19					
renal cell adenoma		3	0.24	3	1.4	2.1
renal adenocarcinoma		4	0.32	4	1.0	2.0
transitional cell carcinoma		2	0.16	2	1.4	2.0
hemangiosarcoma		1	0.08	1	-	2.1
lipoma		1	0.08	1	-	1.3
liposarcoma		1	0.08	1	-	2.1
lipomatous tumour (M)		1	0.08	1	-	1.0
mixed cell tumor (M)		3	0.24	2	2.0	3.0
mixed mesenchymal tumor (NOS)		1	0.08	1	-	1.4
URINARY BLADDER	19					
transitional cell papilloma		1	0.08	1	-	1.0
transitional cell carcinoma		3	0.24	3	1.4	1.5
mesothelioma		1	0.08	1	-	1.0
REPRODUCTIVE SYSTEM						
TESTIS	19					
interstitial (leydig) cell tumor (B)		59	4.68	18	1.4	10.0
interstitial cell tumor (M)		1	0.08	1	-	1.4
mesothelioma (M)		2	0.16	2	1.0	1.4
PROSTATE	19					
carcinoma (M)		3	0.24	3	1.0	1.8
lipoma		1	0.08	1	-	1.4
mesothelioma (M)		1	0.08	1	-	1.0
ENDOCRINE SYSTEM						
PANCREAS (ENDOCRINE)	19					
islet cell adenoma		103	8.29	17	2.9	24.0
islet cell carcinoma		25	2.01	10	1.6	8.2
mesothelioma		1	0.08	1	-	1.0
PITUITARY GLAND	19					
adenoma, pars intermedia		4	0.32	2	1.0	4.9
adenoma, pars distalis		750	60.68	19	37.1	81.3
carcinoma, pars distalis		79	6.39	10	1.0	33.3
craniopharyngioma		1	0.08	1	-	1.9
hemangioma		1	0.08	1	-	1.9

TABLE 5b (Continued)
NEOPLASMS
24 MONTH STUDIES
FEMALE CD® RATS

LOCATION & TUMOR	# groups in which tissue examined	total X lesions	percent of total	k groups using this diagnosis	minimum % found	maximum % found
URINARY BLADDER	19					
polyp		1	0.08	1	--	1.4
transitional cell papilloma		1	0.08	1	--	1.4
transitional cell carcinoma		1	0.08	1	--	1.4
REPRODUCTIVE SYSTEM						
UTERUS/CERVIX	19					
adenocarcinoma (M)		4	0.32	4	1.0	1.4
endometrial stromal polyp		51	4.05	15	1.1	10.0
fibroma		1	0.08	1	--	1.4
leiomyoma		3	0.24	1	--	5.5
endometrial stromal sarcoma		3	0.24	3	1.4	1.6
leiomyosarcoma		2	0.16	1	--	3.6
hemangiosarcoma		1	0.08	1	--	1.4
sarcoma (NOS)		1	0.08	1	--	1.4
fibroma, cervix		1	0.08	1	--	1.4
leiomyosarcoma, cervix		1	0.08	1	-	1.4
squamous cell carcinoma, vagina/cervix		2	0.16	2	1.4	1.6
squamous cell carcinoma, vagina		4	0.32	3	1.4	2.9
stromal polyp, vagina		3	0.24	3	1.4	1.6
fibroma, vagina		4	0.32	4	1.4	2.0
hemangioma, vagina		1	0.08	1	--	1.4
OVARY	19					
granulosa/theca cell tumor		13	1.04	9	1.4	3.2
papillary adenoma		1	0.08	1	1.4	1.4
tubular adenoma		1	0.08	1	1.0	1.0
sex cord stromal tumor (B)		3	0.24	3	1.0	2.0
ENDOCRINE SYSTEM						
PANCREAS (ENDOCRINE)	19					
islet cell adenoma		48	3.82	17	1.4	8.6
islet cell carcinoma		18	1.43	8	1.4	8.2
PITUITARY GLAND	19					
microadenoma, pars intermedia		1	0.08	1	--	1.0
adenoma, pars distalis		902	72.10	19	31.4	88.8
carcinoma, pars distalis		131	10.47	14	1.3	57.1
THYROID GLAND	19					
follicular cell adenoma		32	2.58	15	1.0	14.5
follicular cell carcinoma		13	1.05	9	1.0	5.8
C-cell adenoma		91	7.33	19	1.0	17.1
medullary carcinoma		42	3.38	11	2.1	13.1
PARATHYROID GLAND	19					
adenoma (B)		6	0.53	5	1.6	4.0

6 https://www.criver.com/sites/default/files/Technical%20Resources/Spontaneous%20Neoplastic%20Lesions%20and%20Selected%20Non-neoplastic%20Lesions%20in%20the%20Crl-CD%20BR%20Rat%20-%20February%201992.pdf

Data from Majeed, S. K. (1997). Studies of the incidence of spontaneous pancreatic tumours in ageing CD rats. Arzneimittel-forschung, 47(7), 879-884.

The Majeed (1997) paper included data from 33618 Sprague-Dawley CD rats (soured from Charles River UK Ltd., Margate, Kent, UK) from studies of up to 104 weeks duration. All rats in this survey were fed similar diet and kept under similar housing conditions. Among these were 4655 untreated males and 4385 untreated females. In addition, data from 15709 rats from 13 week studies, 7627 rats from 26 week studies, 2899 rats from 52 week studies and 1533 rats from 78 week studies were also included. All studies were performed during the period 1970-1995. The data from untreated and treated animals are included for comparative purposes as none of the studies included showed any evidence of a treatment effect on the pancreas. Sections of visceral organs, bone marrow, brain, spinal cord and peripheral nerve were routinely prepared from all rats and stained with haematoxylin end eosin. A small proportion of islet cell tumours were also stained with strept-Avidin Biotin Complex, as anti-insulin stain for beta cells.

Table 24.7: Incidence of pancreatic tumours in <u>untreated</u> CD rats up to 78 weeks of age:

Type of tumour	Male	Female
Islet cell adenoma	8 (3%)	-
Islet cell carcinoma	-	-
Exocrine adenoma	:	-
Exocrine carcinoma	-	
Mixed Islet-acinar cell adenoma	-	-
Multiple Islet cell adenoma	-	-
Number of rats examined	277	283

Table 24.8: Incidence of pancreatic tumours in <u>treated</u> CD rats up to 78 weeks of age:

Type of tumour	Male	Female
Islet cell adenoma	-	4 (1%)
Islet cell carcinoma	3 (0.6%)	-
Exocrine adenoma	2 (0.4%)	-
Exocrine carcinoma	1 (0.2%)	-
Mixed Islet-acinar cell adenoma	-	-
Multiple Islet cell adenoma	-	-
Number of rats examined	489	488

Table 24.9: Incidence of pancreatic tumours in <u>untreated</u> CD rats up to 104 weeks of age:

Type of tumour	Male	Female
Islet cell adenoma	543 (11.66%)	239 (5.45%)
Islet cell carcinoma	112 (2.40%)	46 (1.040%)
Exocrine adenoma	94 (2%)	20 (0.45%)
Exocrine carcinoma	4 (0.08%)	1 (0.02%)
Mixed Islet-acinar cell adenoma	4 (0.08%)	2 (0.04%)

Multiple Islet cell adenoma	20 (0.4%)	-
Number of rats examined	4655	4385

Table 24.10: Incidence of pancreatic tumours in <u>treated</u> CD rats up to 104 weeks of age:

Type of tumour	Male	Female
Islet cell adenoma	1457 (11.45%)	442 (3.71%)
Islet cell carcinoma	293 (2.30%)	141 (1.18%)
Exocrine adenoma	275 (2.15%)	42 (0.35%)
Exocrine carcinoma	53 (0.41%)	11 (0.09%)
Mixed Islet-acinar cell adenoma	22 (0.2%)	6 (0.05%)
Multiple Islet cell adenoma	4 (0.03%)	16 (0.09%)
Number of rats examined	12718	11860

Table 24.11: Data from Anonymous (1982) Age associated lesion in barrier-reared male Sprague-Dawley rate: A comparison between Hap:(SD) and Crl: COBS(r) CR(r) SD stocks. *Exp. Agric. Res.*, 8(1), 3-22

AGE-ASSOCIATED LESIONS IN RATS 7

Table 1 Continued

	Age (Months)										
	6-11	12-17		18-23		24-29			30-38	Incidence	
Type of Neoplasm	HAP	CD	HAP	CD	HAP	CD	HAP	Sig.	CD	CD	HAP
ALIMENTARY SYSTEM											
Liver:											
Neoplastic nodule	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	2/27 (7.4)	0/34 (0)	–	2/45 (4.4)	4/104 (3.8)	0/70 (0)
Hepatocellular carcinoma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	2/27 (7.4)	1/34 (2.9)	–	1/45 (2.2)	3/104 (2.9)	1/70 (1.4)
Hemangioma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	1/45 (2.2)	1/104 (1.0)	1/70 (1.4)
Capillary hemangiosarcoma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	1/70 (1.4)
Pancreas:											
Islet cell tumor	0/13 (0)	1/21 (4.8)	0/13 (0)	0/12 (0)	0/11 (0)	9/32 (28.1)	0/34 (0)	**	9/43 (20.9)	19/108 (17.6)	0/71 (0)
Mouth:											

Mice

In a 24 months study in mice, the MTD was not reached. No clear toxic effects were demonstrated on mortality, clinical signs, body weight, food consumption or haematology through the course of the study. Slight changes on haematological parameters (Leucocyte and RBC count) and slightly increased liver and kidney weight were observed at the top dose level.

Long-term oral exposure of Bifenox did not reveal any statistically significant substance related effects. Based on small effects on haematological parameters in mice at terminal sacrifice, the lowest relevant NOAEL was determined to be 30 mg/kg bw/day.

Islet cell adenoma or carcinoma were observed in the pancreas of male rats (Anonymous, 1987) at lower dose levels. Comparing these results to historical data of data from open literature, it was concluded that statistical significant results were due to a random occurrence of a low concurrent control group and related to the treatment with Bifenox.

There was no evidence of carcinogenic potential from Bifenox. Therefore, Bifenox is considered not to be carcinogenic. This conclusion is supported by the absence of genotoxic activity of Bifenox, tested *in vivo* and *in vitro*.

Based on the data derived from these studies, Bifenox is not carcinogenic.

Hepatic neoplasms were diagnosed as carcinoma and adenomas and were encountered more frequently at 24 months in top dose group male mice (combined hepatocellular adenoma and carcinoma 31.57%), but this incidence was not unusually high for mice of this age and strain. Statistical analyses were performed which examined incidence of hepatocellular carcinoma, adenoma and carcinoma or adenoma in each sex separately. Of the tests employed, none indicated statistical significance at the $p < 0.05$ levels in males. In females the trend test was weakly positive when hepatocellular carcinomas alone were examined or when carcinomas were combined with adenomas ($p = 0.45$ and $p = 0.41$). Because of the small numbers of tumours involved, this finding is considered to represent a statistical aberration rather than evidence for oncogenicity. Anonymous (1990) reported a mean incidence of 42.2% for male B6C3F1 control mice spontaneous liver tumours. Anonymous (1981) report a mean incidence for five independent laboratories for spontaneous liver tumours in mal B6C3F1 mice of 32.1%.

Malignant lymphomas occurred more frequently in exposed than in unexposed females. In several instances, the line between hyperplasia and neoplasia was not clear. In no sex or dose group was the incidence of this class of tumour unusual for this age and strain of mouse.

Lung tumours were fairly frequent occurrences. The incidence of hepatic neoplasms in the males and malignant lymphomas in females as not unusual for this age and strain of mouse, statistical analysis provided no substantive evidence for oncogenicity

Haematology at 12 months was without significant observations. At terminal sacrifice reduced platelet counts were noted in males only which reached significance at the highest dose level. In females this parameter was unaffected or increased. Also at the highest dose level significantly reduced reticulocyte counts were noted in females while in males a non-significant reduction was noted.

In both rat and mice, no clear toxic effects were demonstrated on mortality, clinical signs, body weight, food consumption or haematology through the course of two long-term studies.

10.9.2 Comparison with the CLP criteria

Application of the classification criteria of Annex I to Regulation (EC) 1272/2008 to the available body of genotoxicity and carcinogenicity data for Bifenox indicate that a classification into category 1A can be ruled out because the substance is not known to cause cancer in humans.

For classification into category 1B (presumed human carcinogen) requires animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity.

For classification into category 2 (suspected human carcinogen) requires animal experiments for which there is limited evidence to demonstrate animal carcinogenicity.

Based on the available studies there were no substance related carcinogenic effects from Bifenox evidenced in rats or mice.

Based on the criteria laid down in Regulation (EC) 1272/2008, Bifenox is not carcinogenic.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Bifenox is not carcinogenic in rats or mice. This conclusion is supported by the absence of genotoxic activity of Bifenox and published data on background tumour incidences.

Bifenox does not require classification for carcinogenicity.

10.10 Reproductive toxicity

10.10.1Adverse effects on sexual function and fertility

Table 25: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Rat, 2-generation reproduction and chronic toxicity GLP / not fully compliant to OECD 416 28 Sprague Dawley rats of Charles River CD; 24 male and female F1 weanlings were selected for rearing to maturity and mating to produce F2 generation.	Bifenox Batch # 9401021 Purity: 99% Dose levels: 125, 750, 4500 ppm Concentrations were within ± 10% of nominal concentration at all dose levels	4500 ppm Parental (systemic): decreased body weight gain Reproductive: decreased pup and litter weight at weanling in F1 and F2 generation NOAEL: Chronic toxicity: 44.5 mg/kg bw/day Reproduction: 148 mg/kg bw/day	Anonymous, 1995

There are no observations in humans regarding reproductive toxicity of Bifenox.

Parental toxicity was evidenced either by reduced body weight gain and/or reduced food utilisation efficiency (food conversion to bodyweight) at the top dose in the premating and/or gestational phases. As a result maternal body weights at the top dose were lower than all other groups at the start of lactation. During lactation bodyweight gain in top dose dams was increased over control as was food efficiency. As result top dose dams at least partially recouped the weight differential to controls, seemingly at the expense of lactational bodyweight gain in the pups. Hence reduced body weight gain in pups was more likely due to dams recouping reduced bodyweight gains up to the beginning of lactation, rather than direct toxicity of the milk to pups. i.e. results in pups due to maternal toxicity.

Maternal body weight data, fertility and developmental parameters are provided as far as they were available in the report, in the three tables below. With respect to providing corrected maternal body weights, there were no gravid uterine weights provided in the 2 generation study report, however body weight gains for various periods have been presented as a % proportion of the starting bodyweights for the period in question (highlighted rows).

Historical control data: No historical control data was cited against findings from this study in the evaluation that would require further elaboration.

Table 25.1: Parameters of maternal toxicity in the two-generation rat study with bifenox. Anonymous (1995): maternal toxicity. Blank cell = zero incidence

Generation	Dose Level	0 ppm	125 ppm	750 ppm	4500 ppm

		Mortality			
F0		1			
F1				1	
		Clinical observations and Necropsy findings			
F0	Hair Loss / scabbing	3	6		2
	Red liquid evident from Vagina				1
	Ear torn/black/encrusted				1
	Mass (no further info provided)				1
	Uterus:dilated	2	2		
	Vagina:mass	1			
	Cervix: enlarged		1		1
	Lungs: dark				1
F1	Scabbing/staining/coat scruffy	1		2	1
	Lump/mass	1		1	
	Hair loss	4	1		2
	Pale/breathing difficulty			1	
	Eyelid encrusted/lacrimation		1	3	
	Red liquid from vagina/nervous/ agitated/piloerection			1	
	Incisors short/chipped				1
	Hind limbs swollen/purple/red	1			
	Uterus dilated	1		1	
	Red staining around mouth and nose/lungs dark/blood in thoracic cavity			1	
		Maternal body weight, body weight gain and food consumption			
F0 premating	Body weight (g±SD) Week 0	142±14	140±12	145±13	140±14
	Weight gain (g) Week 0-9	126	132 (+5%)	132 (+5%)	117 (-7%)
	Weight gain, Week 0-9, corrected for maternal body weight by expression as a percentage of starting body weight (%change versus control)	88.7%	94.3% (+6.3%)	91.0% (+2.6%)	81.4% (-8.2%)
	Total Food consumption Week 0-9 (total g/animal)	1119	1348	1343	1295
	Food conversion to body weight (% w/w)	11.3	9.8	9.8	9.0
F1 premating	Body weight (g±SD) Week 3	69±15	67±16	75±16	56±10
	Weight gain (g) Week 3-15 (%change vs control)	227	238 (+5%)	236 (+4%)	220 (-3%)
	Weight gain, Week 3-15, corrected for maternal body weight by expression as a percentage of starting body weight (%change versus control)	329.0%	355.2% (+8.0%)	314.7% (-4.4%)	392.9% (+19.4%)
	Total Food consumption Week 3-15 (total g/animal)	1782	1811	1816	1716

	Food conversion to body weight (% w/w)	12.7	13.1	13.0	12.8
F0 gestation	Body weight (g±SD) D0	305±30	318±34	319±30	298±30
	Weight gain (g) D 0-20	156	154 (-1%)	147 (-6%)	137 (-12%)
	Weight gain, D 0-20, corrected for maternal body weight by expression as a percentage of starting body weight (%change versus control)	51.1%	48.4% (-5.3%)	46.1% (-9.9%)	46.0% (-10%)
	Total Food consumption D 0-20 (total g/animal)	613	653	630	620
	Food conversion to body weight (% w/w)	2.0	2.1	2.0	2.1
F1 gestation	Body weight (g±SD) D0	297±28	299±25	301±30	275±30
	Weight gain (g) D 0-20	157	157	147 (-5%)	147 (-6%)
	Weight gain, D 0-20, corrected for maternal body weight by expression as a percentage of starting body weight (%change versus control)	52.9%	52.5% (-0.7%)	48.8% (-7.6%)	53.5% (+1.1%)
	Total Food consumption D 0-20 (total g/animal)	629	650	608	638
	Food conversion to body weight (% w/w)	25.0	24.2	24.2	23.0
F0 lactation	Body weight (g±SD) D 0	337±38	344±39	346±32	329±39
	Body weight gain (g) D 0-21	10	16	11	18 (+5%)
	Weight gain, D 0-21, corrected for maternal body weight by expression as a percentage of starting body weight (% change versus control)	3.0%	4.7% (56.7%)	3.2% (7%)	5.5% (84.4%)
	Total Food consumption D 0-21 (total g/animal)	1534	1544	1583	1455
	Food conversion to body weight (% w/w)	0.65	1.04	0.69	1.24
F1 lactation	Body weight (g±SD) D 0	332±37	339±34	336±40	325±40
	Body weight gain (g) D 0-21	9	7	20	14
	Weight gain, D 0-21, corrected for maternal body weight by expression as a percentage of starting body weight (%change versus control)	2.7%	2.1% (-23.8%)	6.0% (+119.6%	4.3% (+58.9%)
	Total Food consumption D 0-21 (total g/animal)	1461	1517	1525	1454
	Food conversion to body weight (% w/w)	0.6	0.5	1.3	1.0

Table 25.2: Fertility, gestational and birth indices and pup bodyweight parameters

Dose Level	**0 ppm**	**125 ppm**	**750 ppm**	**4500 ppm**
	F0 Dams Fertility, gestational and birth indices and pup bodyweight parameters			

Median number of nights to positive mating sign	2	2.5	2.5	2
Number passing one oestrus	0	0	1	1
Male fertility Index (%)[a]	68	75	79	86
Female fertility index (%)[a]	71	82	82	86
Duration of gestation				
21 days	2	5	3	5
22 days	17	16	16	19
23 days	1	2	4	0
Mean duration gestation	22.0	21.9	22.0	21.8
Gestation index[b] % dams producing live litters (N)	100 (20)	100 (23)	100 (23)	100 (24)
Mean implant sites±SD	17.2±3.3	17.3±1.4	17.5±1.3	16.1±2.6
Mean pups born/litter ±SD	15.5±3.4	15.8±1.7	15.4±2.6	14.8±2.5
	Mean live pups ±SD			
Day 0 lactation	15.4±3.4	15.6±1.8	15.1±2.8	14.6±2.4
Day 4 lactation	13.8±3.3	14.4±2.9	14.7±2.7	14.4±2.5
Day 21 lactation	13.6±3.3	13.3±3.1	13.8±2.8	13.0±3.4
	F1 pup indices			
	Birth index[c]			
Mean litter index (%)	90	90	88	92
Number losing >2 pups	3	6	6	4
Number of litters	20	23	23	24
	Live Birth index[d]			
Mean litter index (%)	99	99	97	99
Number losing >1 pups	0	1	2	1
Number of litters	20	23	23	24
	Viability index Day 0-4[e]			
Mean litter index (%)	91	86	89	92
Number losing >3 pups	4	4	4	2
Number of litters	20	23	23	24
	Lactation index Days 4-21[f]			
Mean litter index (%)	98	94	99	98
Number losing >1 pups	1	2	1	2
Number of litters	20	23	22	24
	Overall survival index Birth to Day 21[g]			
Mean litter index (%)	89	81	86	88
Number losing >4 pups	3	4	4	2
Number of litters	20	23	23	24
	Group mean litter weight (g±SD)			
Lactation Day 1	97±20	93±17	97±17	92±15
Lactation Day 21	621±118	604±104	635±108	478±96***
	Mean litter pup weight (g±SD)			
Lactation Day 1 males	6.7±0.9	6.6±0.7	6.8±0.7	6.5±1.0
Lactation Day 21 males	48.6±9.2	48.2±9.7	47.6±6.5	38.9±6.4***
Lactation Day 1 females	6.3±0.9	6.3±0.7	6.5±0.6	6.2±0.7
Lactation Day 21 females	46.0±9.0	46.2±9.2	46.3±5.4	36.9±5.9***
	F1 Dams Fertility, gestational and birth indices and pup bodyweight parameters			

Median number of nights to positive mating sign	3	3	3	2.5
Number passing one oestrus	0	0	0	3
Male fertility Index (%)[a]	92	88	83	88
Female fertility index (%)[a]	92	92	92	92
Duration of gestation				
21 days	5	5	4	11
22 days	17	16	16	10
23 days	0	0	2	1
Mean duration gestation	21.8	21.8	21.9	21.5
Gestation index[b] % dams producing live litters (N)	100 (22)	100 (22)	100 (22)	100 (22)
Mean implant sites±SD	15.8±2.8	15.8±2.6	16.3±2.7	15.1±2.1
Mean pups born/litter ±SD	14.3±2.9	14.7±2.6	14.3±2.7	13.2±2.0
	Mean live pups ±SD			
Day 0 lactation	14.3±2.9	14.5±2.6	14.1±2.5	13.2±2.1
Day 4 lactation	13.6±2.9	13.2±3.3	13.6±2.5	12.9±2.3
Day 21 lactation	13.3±2.8	12.9±3.2	13.4±2.6	12.4±2.2
	F2 pup indices			
	Birth index[c]			
Mean litter index (%)	91	93	89	89
Number losing >2 pups	6	3	6	4
Number of litters	22	22	21	22
	Live Birth index[d]			
Mean litter index (%)	100	99	99	99
Number losing >1 pups	0	0	1	0
Number of litters	22	22	21	22
	Viability index Days 0-4[e]			
Mean litter index (%)	91	92	89	84
Number losing >3 pups	0	3	2	3
Number of litters	22	22	22	22
	Lactation index Days 4-21[f]			
Mean litter index (%)	98	98	98	96
Number losing >1 pups	0	1	1	2
Number of litters	21	21	19	19
	Overall survival index Birth to Day 21[g]			
Mean litter index (%)	89	89	81	80
Number losing >4 pups	0	3	1	3
Number of litters	22	21	20	22
	Group mean litter weight (g±SD)			
Lactation Day 1	90±16	94±15	94±15	86±16
Lactation Day 21	604±100	599±113	628±78	470±65***
	Mean litter pup weight (g±SD)			
Lactation Day 1 males	6.7±0.7	6.8±0.8	7.0±0.8	6.7±0.5
Lactation Day 21 males	47.7±7.6	48.9±8.0	48.9±7.9	39.3±5.1***
Lactation Day 1 females	6.3±0.7	6.7±1.7	6.6±0.7	6.4±0.5
Lactation Day 21 females	45.3±7.2	46.5±7.7	46.9±7.5	37.5±4.9***

*** Statistically significantly different from controls (P<0.001)

a = Number of pregnant females or siring males / number paired

b = Number bearing live pups / number pregnant
c = Total number of pups born (live and dead) / Number of implantation scars
d = Number of pups live on Day 0 of lactation / Total number born
e = Number of pups live on Day 4 of lactation / Number live on Day 0
f = Number of pups live on day 21 of lactation / Number live on Day 4
g = Number of pups live on Day 21 of lactation / Total number of pups born (live and dead)

Table 25.3: Developmental toxicity and other findings in pups

Dose Level	0 ppm	125 ppm	750 ppm	4500 ppm
	F1 pups			
Litters (pups) with malformations	0	1 (2)[a]	0	1(1)[d]
Litters (pups) with other findings (but no malformations)	1(1)[c]	0	1 (1)[b]	1(2)[e]
	F2 pups			
Litters (pups) with malformations	0	0	0	0
Litters (pups) with other findings (but no malformations)	0	0	0	2(2)[f,g]

[a]Two pups in F0parent-F1Litter 152 (125 p.p.m. Bifenox), died shortly after birth, with multiple abnormalities including misshapen cranium, shortened lower jaw, open eyes, cleft palate, fused digits and subcutaneous oedema.
[b]One pup in F0parent-F1Litter 180 (750 p.p.m. Bifenox) with a small kidney at necropsy.
[c]One pup in F0parent-F1Litter 139 (Control), killed Day 19, with body tremors, piloerection, encrusted eyes and apparent hind limb weakness/ataxia.
[d]One pup in F0parent-F1Litter 212 (4500 p.p.m. Bifenox), killed Day 23, with ataxia, hydrocephalus and one eye apparently absent.
[e]One pup in F0parent-F1Litter 223 (4500 p.p.m. Bifenox), died Day 19, with piloerection prior to death. Second pup with piloerection and swollen abdomen Day 21.
[f]One pup in F1parent-F2Litter 479 (4500 p.p.m. Bifenox), killed Day 16, with a firm, lobular mass on the lower lip.
[g]One pup in F1parent-F2Litter 496 (4500 p.p.m. Bifenox), small with brown fluid in one kidney at necropsy.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In a 2-generation rat study, the MTD was not reached. Two rats died during the course of the study, without association to treatment. Clinical signs and necropsy findings did not indicate any association with treatment.

Mating performance, fertility and duration of gestation were not considered to be affected by treatment. Litter size, pup survival and mean number of implantation was slightly reduced at 4500 ppm in both generations. The differences did not reach statistical significance and were considered incidental.

During the lactation period, the mean body weight gain of litter and pups was lower at top dose and on day 21 weights were approximately 80% of control. The reduction in litter and pup weights at 4500 ppm were statistically significant lower than controls but were accompanied by (slight) parental toxicity (evidenced by reduced body weight gain at top dose). Based on this, these effects were not considered to be relevant for a classification with regard to reproduction toxicity. Fertility parameters were not affected. In the parental generation females reveal slight reduction of body

weight gain even in the mid dose during gestation (up to 12%) and especially a significant reduction of body weight gain during lactation from Day 1 to Day 14 (up to 42%).

The NOAEL is based on statistically significant reduction of litter/pup weight at top dose, clearly evident at slight parental toxicity and was also not considered to be relevant for a classification in view of the accompanying parental toxicity. Abnormalities among pups did not suggest any association with treatment.

A reproductive NOAEL = 750 ppm (148 mg/kg bw/day) was based on decreased pup and litter weight in F_1 and F_2 generation at 4500 ppm. The reproductive effects occurred in the presence of slight parental (systemic) toxicity as suggested by the decreased body weight gain seen at 4500 ppm. NOAEL parental toxicity = 750 ppm (44.5 mg/kg bw/day).

10.10.3 Comparison with the CLP criteria

Bifenox was thoroughly evaluated for fertility and reproductive toxic potential in one rat two-generation study. The NOAEL is based on statistically significant reduction of litter/pup weight at top dose, clearly evident at slight parental toxicity and was also not considered to be relevant for a classification in view of the accompanying parental toxicity. Abnormalities among pups did not suggest any association with treatment. According to CLP criteria adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals. The reduction in litter and pup weights at the highest dose level (4500 ppm) were statistically significant lower than controls although but were accompanied by (slight) parental toxicity (evidenced by reduced body weight gain at top dose). A significant toxic effect in the offspring, e.g. irreversible effects, was not noted. In conclusion, Bifenox did not adversely affect fertility and general reproductive performance in the two-generation rat study at the reproductive NOAEL of 148 mg/kg bw/day.

Therefore, it can be concluded that from the discussed rat study, no evidence of a reproductive toxic effect of Bifenox can be derived and there is no classification required for fertility or reproductive toxicity.

10.10.4 Adverse effects on development

Table 26: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Rat, developmental toxicity GLP / not fully compliant to OECD 414	Bifenox Batch # 353-12-1 Purity: 98% Dose levels: 225, 900, 3600 mg/kg bw/day	NOAEL 3600 mg/kg bw/d (top dose tested) Maternal: mortality and clinical signs marginally higher incidence of foetuses/litters with a large fontanel at the top dose, but size not consistent and hence not considered treatment related. The top dose was also 3.6 x the normal limit dose, again casting doubt on the usefulness of the finding as a relevant hazard indicator. NOEL maternal + developmental: 900	Anonymous. 1987

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		mg/kg bw/day	
Rabbit, developmental toxicity GLP / not fully compliant to OECD 414	Bifenox Batch # 312165 Purity: 98% Dose levels: 2, 20, 200 mg/kg bw/day	200 mg/kg bw/d Maternal: mortality, clinical signs, reduced body weight gain and food consumption Developmental: slightly increased incidence of hyoid alae angulated, but well within the historical control range, and made prominent by an abnormally low concurrent control incidence. Not reproduced in the subsequent study. NOEL maternal + developmental: 20 mg/kg bw/day	Anonymous, 1986
Rabbit developmental toxicity GLP / OECD 414	Bifenox Batch # 3123142024 Purity: 97% Dose levels: 5, 50, 160, 500, 1000 mg/kg bw/day	160 mg/kg bw/d Maternal: clinical signs, very slight body weight decrease (NS) reduced food consumption Developmental: No adverse effects NOEL maternal + developmental: 50 mg/kg bw/day	Anonymous, 1986

There are no observations in humans regarding reproductive toxicity of Bifenox.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

At the top dose severe maternal toxicity might be characterized by at least 2 treatment related maternal deaths and clinical signs of salivation, staining of mouth, patchy hair loss. The patchy hair loss might indicate poor general condition. It is noteworthy that the top dose was 3.6 fold greater than todays permitted limit dose, hence the relevance of results from this group to hazard assessment is questionable.

Data available in the report pertaining to maternal toxicity is provided in the table below.

The extra details on the historical control data presented were requested from current incarnation of the test laboratory. The laboratory could not provide exact study details to the data cited, but did state that: “The HCD presented in the report would have been matched to the study for species, strain, supplier and performing laboratory.”

Table 26.1: Maternal toxicity findings and key fetal findings including those for which historical control data was cited in the report, for the developmental rat toxicity study by Anonymous (1987)

Endpoint/dose (mg/kg bw/d)	**0**	**225**	**900**	**3600**
N° mated females	25	25	25	25
Mortality	0	0	0	5
Not pregnant	7	5	3	5
Clinical signs	none	none	none	Salivation, staining mouth, patchy hair loss
	Water consumption (g/animal/day)			
D 13	27	35	33	38
D 14-16	32	37	37	42
D 17-19	33	39	40	38
Avg D 13-19 (% change vs control)	27.9	37.6 (+35%)	37.7 (+35%	39.7 (+42%)
	Food consumption (g/animal/day)			
D 6-9	21	20	20	19
D 10-13	24	25	25	23
D 14-16	25	26	26	25
D 17-19	25	26	26	27
Avg D 6-19	23.6	24.1	24.2	23.4
Body weight (g)				
D 6	228.9	231.5	230.2	235.7
D 20	345.8	348.0	343.0	351.3
Body weight gain (g) D 6-20	116.9	116.5	112.8	115.6
Maternal Reproductive performance				
Total resorptions			1	
N° females with live young	17	20	21	15
N° corpora lutea	13.1	13.4	13.6	13.5
N° implants	12.3	12.3	12.2	12.8
N° dead implants	0.9	0.5	1.1	1.1
Pre implantation loss %	6.1	10	9.1	4.8
Post implantation loss %	7.8	3.7	11.4	8.5
Mean litter weight (g)	39.19	40.43	38.29	40.64
Mean fetal weight (g)	3.45	3.41	3.5	3.46

Fœtal examination:				
N fetuses (litters) examined	98 (17)	119 (20)	115 (21)	88 (15)
	Skeletal evaluation: % fetal incidence (N litters affected)			
Number of ribs				
12/12	-	-	-	1.1 (1)
13/13	98.0 (17)	98.8 (20)	95.6 (21)	92.2 (15)
13/14	-	0.6 (1)	0.8 (1)	5.3 (3)
14/14	1.0 (1)	1.6 (2)	-	1.1 (1)
Historical control data extra 14th rib:	10 studies performed in 1985: mean fetal incidence: 2.9% with a range of 0.9-7.1%			
Small fontanelles	2.0 (1)	2.1 (2)	3.6 (3)	1.1 (1)
Medium fontanelles	96 (17)	95.3 (20)	94.4 (21)	88.8 (15)
Large fontanelles	2 (2)	2.6 (3)	2 (3)	10.1 (6)
Frontonasal suture enlarged	1.0 (1)	5.4 (4)	2.6 (3)	1.3 (1)
Incomplete ossification of frontal/parietal/squamosal/jugal/nasal bone (s)	1.0 (1)	3.3 (4)	1.0 (1)	3.2 (3)
Incomplete ossification of interparietal bone	5.1 (5)	16.7 (12)	12.4 (7)	12.1 (5)
Incomplete ossification of supraoccipital bone	8.0 (6)	11.5 (11)	6.2 (7)	7.2 (5)
Patchy/incomplete ossification of one or more cranial bones	1.0 (1)	0.7 (1)	-	-
Incomplete ossification/absence of hyoid bone	7.0 (6)	14.0 (12)	12.2 (11)	14.4 (8)

The results reported in the table are not statistically significant.

Developmental toxicity studies have been investigated in order to assess effects on embryonic and foetal development, maternal toxicity and to establish dose-response relationships in dams and offspring in rats and rabbits,

Bifenox was thoroughly evaluated for a developmental toxic potential in one rat and two rabbit studies. The study directors concluded in all these studies that there is no evidence of a developmental toxic potential of Bifenox.

In this evaluation a few parameters which showed some degree of variability (see table below) are discussed with regard to their possible interference with the overall conclusion.

In the rat study, the extra 14th rib incidences were within the historical data range given in the report (up to 7.1 %) so that they are due to variability and not to treatment. Furthermore, the other findings of extra 13th and combined 13th and 14th ribs were not dose-related and thus most likely due to variation which supports an absence of an effect of Bifenox on the rib development.

The litter incidences of small, medium and large fontanelles appear to show a slight increase in "large fontanelles" at the highest dose. However, the size definitions are not explained and may only be subjective, and in the absence of any other head bone variations, this increase is of doubtful relevance.

Furthermore a size reduction might rather be expected at this maternal-toxic dose and not an enlargement. However, the incidence of small size fontanelles was not increased by treatment. In addition this apparent increase also occurred at 3.6 x the limit dose, at which strong maternal toxicity was also observed (salivation, staining of mouth, patchy hair loss), hence usefulness of this parameter as an indicator of a pertinent developmental hazard is doubtful.

The incidences of the finding incomplete ossification/absence of hyoid bone did not show a dose-response relationship, since the incidence in the low dose was as high as that of the highest dose, whereas the incidence in the 900 mg/kg bw group was lower again despite a 4-fold higher dose compared to the low dose.

Overall, therefore, the findings from the rat developmental toxicity study are not sufficient evidence of a developmental toxicity hazard by bifenox.

Table 26.2: Selected findings in the rat developmental toxicity study

	Finding in % fetal incidence (number of litters affected)			
Dose (mg/kg bw/day)	**0**	**225**	**900**	**3600**
Number of fetuses (litters) examined	95 (17)	118 (20)	118 (21)	88 (15)
Size of fontanelle				
small	2.0 (1)	2.1 (2)	3.6 (3)	1.1 (1)
medium	96.1 (17)	95.3 (20)	94.4 (21)	88.8 (15)
large	2.0 (2)	2.6 (3)	2.0 (3)	10.1 (6)
Incomplete ossification/absence of hyoid bone	7.0 (6)	14.0 (12)	12.2 (11)	14.4 (8)
Number of ribs				
12/12	-	-	-	1.1 (1)
13/13	98.0 (17)	98.8 (20)	95.6 (21)	92.2 (15)
13/14	2.0 (2)	0.6 (1)	3.6 (3)	1.3 (1)
14/14	-	0.6 (1)	0.8 (1)	5.3 (3)
Historical incidence 14th rib (min – max)	0.9 - 7.1 %			

In the rabbit studies (Anonymous, 1986) at the top dose there were maternal deaths, gastric ulcerations, perturbations to the condition of the faeces, and resorptions and abortions indicating that this dose produced severe toxicity.

Data available in the report pertaining to maternal toxicity is provided in the two tables below (Table 26.3 and Table 26.4).

The extra details on the historical control data are presented in the Table 26.5.

Table 26.3: Maternal toxicity findings and key fetal findings including those for which historical control data was cited in the report for the developmental rabbit toxicity study by Anonymous (1986).

Endpoints/ dose	**0**	**2**	**20**	**200 mg/kg bw/d**
	Mortality and clinical signs			
Mortality				3[a]
Dried feces	2/13	0/0	2/11	8**/41**
No feces present	1/2	0/0	1/1	2/9**
Soft or liquid feces	1/1	3/8c	8**/18**	1/3
Alopecia	3/18	4/19	8/52**	3/21
	Necropsy observations			

Aborted	0	0	0	3
Gastric ulceration[b]	0	0	0	6
Kidneys light brown in colour	0	0	0	1
Kidney cortex light brown in colour	0	0	0	1
Liver pale brown in colour	0	0	0	1
Urine red brown in colour	0	0	0	1
Left uterine horn filled with dark red fluid	0	0	0	1
	Bodyweight and bodyweight gain			
Body weight (kg) **Day 29**	4.27±0.46	4.25±0.41	4.38±0.50	4.12±0.52
Body weight gain (kg) **Day 6-29**	0.30±0.18	0.23±0.19	0.30±0.14	0.13±0.38 (↓ Day 6-12)
Food consumption **Day 6-29 (g/animal/day)**	146.1±30	147.1±33.3	147.9±34.8	135.2±39.7
Food conversion to body weight (% w/w)	0.21	0.16	0.20	0.10
	Reproductive data			
N° gravid females	20	20	20	20
Pregnant rabbits (n°)	17	16	20	16
Corpora lutea mean	9.8	11	10.7	9.4
Implantations mean	7.2	7	7.9	7.8
Litter size mean	6.6	6.6	7.5	6.8
N° live/death fetuses	106/0	106/0	143/0	75/0
N°early/late resorption	8/2	5/1	5/2	8/3
Resorptions mean	0.6±1.3	0.4±0.5	0.4±0.8	1±1.4
Live fetal bw/litter	46.06	48.44	46.05	42.75
% Resorbed conceptuses/litter	7.7±16	6.3±9.8	3.5±8	13.5±17.2
N° litters evaluated	16	16	19	11
	Skeletal alterations: litter/fetal incidence n° (%)			
Hyoid, Alae, angulated	1/1 (6.2/0.9%)	2/2 (12.5/1.9)	2/2 (10.5/1.4)	3/3 (27%/4%)
	Historical data from laboratory			
Hyoid, Alae, angulated (See final table below for a breakdown of studies from which it was derived)	Litter incidence 0 – 35% Fetal incidence 0 – 5.3%			

[a]One rabbit was sacrificed moribund on day 18 of gestation prior to sacrifice, this rabbit was observed to have corneal opacity, lacrimation, ataxia, decreased motor activity, increased sensitivity to touch in the abdominal area and a lack of muscular control in the hindlegs.
[b]ulcerations in cardiac, pyloric and/or fundic regions
/ Rabbits / days
** Significantly different from vehicle control value, at P≤0.01.
↓ Statistically significantly different from control at at P≤0.05; () not significantly different from control

Table 26.4: Uterine contents and litter data in individual rabbits which died, were sacrificed moribund, aborted or delivered naturally

Dose Group (mg/kg bw/day animal number)	Day of termination or death	Corpora lutea			Implantations			Embryos or fetuses[a]				Resorptions[b]			
		R	L	T	R	L	T	R	L	A/Del	T	R	L	A/Del	T
0 (vehicle) 10409	Delivered and sacrificed on day 28 of gestation	6	5	11	2	4	6	0	1[c]	2[c]	3[c]	1(LR)	1(LR)	1(LR)	3(LR)
20 10452	Delivered and sacrificed on day 29 of gestation	5	5	10	5	5	10	3[d]	3[d]	4[d]	10[d]	0	0	0	0
200 10461	Aborted and sacrificed on day 26 of gestation	5	6	11	4	5	9	0	0	8[e]	8[e]	0	0	-	-[e]
200 10463	Moribund sacrificed on day 18 of presumed gestation	6	5	11	0	0	0	0	0	-	0	0	0	-	0
200 10464	Aborted and sacrificed on day 24 of gestation	4	7	11	4	5	9	0	0	-[f]	-[f]	0	0	6(LR)[f]	-[f]
200 10469	Aborted and sacrificed on day 24 of gestation	5	5	10	1	0	1	0	0	1[g]	1[g]	0	0	0	0
200 10472	Found dead on day 14 of gestation	5	4	9	5	4	9	0	0	-	0	5	4	-	9
200 10480	Found dead on day 20 of gestation	4	7	11	4	7	11	3	5	-	8[b]	1(LR)	2(LR)	-	3(LR)

R Right; L Left; A Aborted; T Total; LR Late resorption

[a] Live unless noted otherwise

[b] Early unless noted otherwise

[c] Two delivered pups and one late resorption were found in the cage pan. One fetus was found in utero. All conceptuses appeared to have been alive at the time of delivery and normal for their developmental ages.

[d] Four delivered pups and one placenta were found in the cage pan. One delivered pup was observed to have a cannibalized tail. All remaining fetuses and delivered pups appeared to have been alive at the time of delivery and normal for their developmental ages.

[e] Eight aborted fetuses (four with placentas attached) and five placentas were found in the cage pan. Aborted fetuses appeared to have been alive at the time of abortion and normal for their developmental ages. Remaining conceptus was presumed to have been cannibalized.

[f] Six late resorptions were found in the cage pan. Remaining conceptuses were presumed to have been cannibalized.

[g] One aborted fetus was found in the cage pan. Aborted fetus appeared to have been alive at the time of abortion and normal for its developmental age.

[h] Fetuses found in utero appeared to have been alive at the time of maternal death and normal for their developmental ages.

Historical control data for New Zealand White Rabbits sourced from Hazleton Research Animals, Denver, Pennsylvania, USA and used at **Argus Research Laboratories**, Pensylvania, USA

Table 26.5: Data is from studies conducted within 2.5 year of the conduct of Dearlove (1986)

Study Code	**1**	**2**	**6**	**7**	**10**	**12**	**13**	**14**	**16**	**17**	**18**	**23**	**24**	**25**	**26**	**27**			
Study type	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II	Seg II			
Vehicle	Propanol/ water	0.5% CMC	3.0% cornstarch suspension	3.0% cornstarch suspension	0.25% CMC	None - sham	Water	Water	Tween80 and CMC	Water	Water	0.5% CMC	0.5 hydroxypr opyl cellose	Not known	0.5% Tween and 0.7% CMC	Corn oil			
Dose vol (mL/Kg))	2	5	10	10	10/5	None - sham	10	0.75	5	Drinking water	5	5	5	0.83	5	2			
Route	Topical	Oral	Oral	Oral	Oral	Intra uterine implant	Oral	IV	Oral	Drinking water	Oral	Oral	Oral	I.V.	Oral	Oral			
First date of C-section	31/07/1984	31/01/1984	26/06/1984	09/10/1984	07/11/1983	21/05/1984	31/03/1984	21/08/1984	13/09/1983	17/04/1984	15/08/1983	26/02/1985	17/06/1985	22/02/1985	03/12/1984	23/04/1985			
Litters	20	20	12	17	12	15	17	17	16	15	16	15	20	19	18	14			
Fetuses	138	97	98	112	87	90	150	110	96	99	133	105	135	135	111	101			
Hyoid Angulated																	**mean**	**Min**	**Max**
Litters	0	0	0	6	0	2	0	2	0	0	3	3	1	5	3	3			
%	0	0	0	35	0	13	0	12	0	0	19	20	5	26	17	21	**10.6**	**0**	**35**
Fetuses	0	0	0	6	0	2	0	2	0	0	3	3	1	6	3	3			
%	0	0	0	5.3	0	2.2	0	1.8	0	0	2.2	2.8	0.7	4.4	2.6	3	**1.6**	**0**	**5.3**

In the rabbit studies no evidence of a developmental toxic potential was obvious. If were not considered incidental, the frequency of hyoid alae, angulated' was within the litter incidence of historical background data and a treatment relationship is considered unlikely, not least given the ten fold increases between dose levels. Furthermore, the highest dose was severely maternally-toxic (as evidenced by the death and occurrence of moribund animals and gastric ulceration) and this dose, in principle this dose should not be used for evaluation. The finding was also not observed in a second rabbit developmental toxicity study. Overall therefore, a relevance of this finding for human safety is doubtful particularly in absence of any other relevant findings and it's non-repeatability in other rabbit studies.

Table 26.6: Selected findings in the rabbit developmental toxicity study

Dose (mg/kg bw)	**0**	**2**	**20**	**200**
Litters evaluated	16	16	19	11
Fetuses evaluated	106	106	143	75
Hyoid alae, angulated				
Number of litter (%)	1 (6.2)	2 (12.5)	2 (10.5)	3 (27.3)
Number of fetuses (%)	1 (0.9)	2 (1.9)	2 (1.4)	3 (4.0)
Historical control data (HCD)				
Number of litters (%) Number of foetuses (%)	29 (8.63) 32 (1.29)			

Therefore it can be concluded that from the discussed rat and rabbit studies no evidence of an intri developmental toxic effect of Bifenox can be derived and there is no classification required for developmental toxicity. This is also supported by the fact that a published mouse developmental toxicity study with Bifenox did not reveal evidence of a developmental toxic effect.

The overall NOAEL for maternal toxicity was determined to be 50 mg/kg bw/day from a developmental study in rabbits (Anonymous, 1986). The NOAEL for developmental toxicity from the same study was 160 mg/kg bw/day based on the slight increased incidence of hyoid alae angulated at 200 mg/kg bw/day.

Table 26.7: Summary of findings (maternal and fetal) from the rabbit developmental toxicity study (Anonymous, 1986)

Dose level [ppm]	**0**	**5**	**50**	**160**	**500**	**1000**
Mortality	0/16	0/16	1/16	0/16	14/16	16/16
Abortion or signs of imminent abortion	1	3	0	2	1	Group died
	Clinical signs					
Soft faeces:	0	1	0	0	1	
Hypoactive:	0	0	0	4	13	10
Slightly hypoactive:	0	0	0	2	15	14
Thin:	0	0	0	1	5	1
Ashen or pale appearance:	0	0	0	1	9	4
Ataxia:	0	0	0	1	2	3
Tremors:	0	0	0	0	1	6
	Body weight					
Body weight (day 6) [g]	4260±462	4017±358	4139±350	4078±331	4110±375	4063±356
Body weight (day 11) [g]	4273±442	4064±332	4201±357	4141±319	3667±431	3379±374b

Body weight (final) [g]	4401±443	4192±304	4305±414	4144±363	4246a	Group died
Body weight gain [g]	281 ± 248	311 ± 134	284 ± 243	229 ± 282 (-19%)		
Food consumption (G.-days 20-24) [mg]	580 + 347	479 + 239 (-18%)	495 + 260 (-15%)	410 + 321 (-30%)		
	Reproductive indices and fetal paramaters					
Corpora lutea[b] / dam	12	11	13	12	16	
Implantations[b] / dam	6	7	6	8	12	
Implantation efficiency	53.0	71.0	66.3	71.7	75.0	
Mean early resorptions (%)	1 (19.9)	1 (22.3)	1 (10.6)	2 (16.3)	0 (0.0)	
Mean late resorptions (%)	0 (0.0)	0 (0.0)	0 (5.2)	0 (0.7)	0 (0.0)	
Mean total resorptions (%)	1 (19.9)	1 (22.3)	1 (15.8)	2 (17.0)	0 (0.0)	
Mean number dead foetuses (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Mean number live foetuses (%)	5 (80.1)	6 (77.8)	7 (84.2)	7 (83.0)	12 (100.0)	
Mean number of litters with viable foetuses	11	9	13	11	1	
Mean number of male foetuses (%)	3 (56.1)	3 (41.4)	4 (43.7)	4 (46.8)	7 (58.3)	
Mean viable fetal weights (g)	46.7	45.5	41.5	40.6	35.1	
Males	47.8	45.3	42.2	43.1	33.4	
Females	45.0	44.5	41.1	39.5	37.5	
	Malformations and variations					
	Fetal external malformations					
Fetuses evaluated N	59	62	96	82	12	
Live N	59	62	96	82	12	
Dead N	0	0	0	0	0	
Short tail						
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7	0	0	
	Hyperflexion forepaw (both)					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7	0	0	
	Midline closure effect[c]					
Fetal incidence N(%)	0	0	0	1(1.2)	0	
Litter incidence N(%)	0	0	0	1(9.1)	0	
	Fetal visceral variations					
Litters evaluated N	11	9	13	11	1	
Fetuses evaluated (total)[d] N	59	62	96	82	12	
Fetuses evaluated (intact)[d] N	33	35	52	44		
Live N	59	62	96	82	12	
Dead N	0	0	0	0	0	
	Dark area, right side, maxilla, approximately 4 mm in length[d]					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1(7.7)	0	0	
	Left carotid arising from innominate artery					
Fetal incidence N(%)	0	0	1 (1.0)	0	1 (8.3)	

Litter incidence N(%)	0	0	1 (7.7)	0	1 (100.0)	
	Lung – intermediate lobe agenesis					
Fetal incidence N(%)	11 (18.6)	7 (11.3)	6 (6.3)	8 (9.8)	1 (8.3)	
Litter incidence N(%)	3 (27.7)	4 (44.4)	3 (23.1)	4 (36.4)	1 (100.0)	
	Lung – intermediate lobe hypoplastic					
Fetal incidence N(%)	0	1 (1.6)	1 (1.0)	0	0	
Litter incidence N(%)	0	1 (11.1)	1 (7.7)	0	0	
	Fetal visceral malformations					
Litters evaluated N	11	9	13	11	1	
Fetuses evaluated N	59	62	96	82	12	
Live N	59	62	96	82	12	
Dead N	0	0	0	0	0	
	Heart and/or great vessel anomaly[e]					
Fetal incidence N(%)	0	0	2 (2.1)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Midline closure effect[c] (also in external malformations above)					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	Fetal skeletal variations					
Litters evaluated N	11	9	13	11	1	
Fetuses evaluated (total)[d] N	59	62	96	82	12	
Fetuses evaluated (intact)[d] N	33	35	52	44		
Live N	59	62	96	82	12	
Dead N	0	0	0	0	0	
	Skull-accessory bone					
Fetal incidence N(%)	1 (3.0)	0	2 (3.9)	1 (2.3)	0	
Litter incidence N(%)	1(9.1)	0	2 (15.4)	1 (9.1)	0	
	Frontal – incompletely					
Fetal incidence N(%)	0	0	2 (3.9)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Interparietal – incompletely ossified					
Fetal incidence N(%)	0	0	1 (1.9)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Thoracic vertebral centra misaligned					
Fetal incidence N(%)	0	1 (1.6)	0	0	0	
Litter incidence N(%)	0	1 (11.1)	0	0	0	
	Lumbar arches interrupted ossification					
Fetal incidence N(%)	0	0	1 (1.0)	1 (1.2)	0	
Litter incidence N(%)	0	0	1 (7.7)	1 (9.1)	0	
	Caudal vertebrae – misaligned					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	26 presacral vertebra count					
Fetal incidence N(%)	3 (5.1)	6 (9.7)	8 (8.3)	8 (9.8)	0	

Litter incidence N(%)	3 (27.3)	2 (22.2)	6 (46.2)	5 (45.5)	0	
	Centra bipartites					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Sternebra 5th not ossified					
Fetal incidence N(%)	9 (15.3)	13 (21.0)	10 (10.4)	12 (14.6)	1 (8.3)	
Litter incidence N(%)	6 (54.5)	5 (55.6)	6 (46.2)	6 (54.5)	1 (100.0)	
	Sternebra 5th bipartite					
Fetal incidence N(%)	1 (1.7)	0	1 (1.0)	0	0	
Litter incidence N(%)	1 (9.1)	0	1 (7.7)	0	0	
	Sternebra 6th bipartite					
Fetal incidence N(%)	1 (1.7)	0	2 (2.1)	2 (2.4)	0	
Litter incidence N(%)	1 (9.1)	0	2 (15.4)	2 (18.2)	0	
	Sternebra 6th not ossified					
Fetal incidence N(%)	1 (1.7)	1 (1.6)	4 (4.2)	5 (6.1)	0	
Litter incidence N(%)	1 (9.1)	1 (11.1)	3 (23.1)	4 (36.4)	0	
	Sternebra 2nd not ossified					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	Sternebra 2nd bipartite					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	Sternebrae Misaligned					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	13th full rib –unilateral					
Fetal incidence N(%)	9 (15.3)	0	7 (7.3)	8 (9.8)	3 (25.0)	
Litter incidence N(%)	6 (54.5)	0	6 (46.2)	5 (45.5)	1 (100.0)	
	13th Rudimentary rib – unilateral					
Fetal incidence N(%)	12 (20.3)	6 (9.7)	22 (22.9)	11.8(13.4)	1 (8.3)	
Litter incidence N(%)	7 (63.6)	5 (55.6)	9 69.2()	8 (72.7)	1 (100.0)	
	13th full ribs –bilateral					
Fetal incidence N(%)	10 (16.9)	12 (19.4)	29 (30.2)	20 (24.4)	1 (8.3)	
Litter incidence N(%)	7 (63.6)	5 (55.6)	12 (92.3)	8 (72.7)	1 (100.0)	
	Ribs 13th Floating					
Fetal incidence N(%)	3 (5.1)	3 (4.8)	1 (1.0)	5 (6.1)	0	
Litter incidence N(%)	2 (18.2)	2 (22.2)	1 (7.7)	4 (36.4)	0	
	13 Rudimentary ribs - bilateral					
Fetal incidence N(%)	1 (1.7)	1 (1.6)	6 (6.3)	8 (9.8)	1 (8.3)	
Litter incidence N(%)	1 (9.1)	1 (11.1)	5 (38.5)	6 (54.4)	1 (100.0)	
	Ribs - forked					
Fetal incidence N(%)	1 (1.6)	1 (1.0)	1 (1.0)	1 (1.2)	0	
Litter incidence N(%)	1 (11.1)	1 (7.7)	1 (7.7)	1 (9.1)	0	
	Ribs – interrupted ossification					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	Rib(s) – extra					

Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	First thoracic rib(s) small					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Metacarpals and phalanges less than 19 count					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Metacarpals and phalanges misaligned					
Fetal incidence N(%)	0	0	0	0	2 (16.7)	
Litter incidence N(%)	0	0	0	0	1 (100.0)	
	Skeletal malformations					
	Centra fused					
Fetal incidence N(%)	0	0	2 (2.1)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Vertebral anomaly with associated rib anomaly					
Fetal incidence N(%)	0	0	1 (1.0)	0	0	
Litter incidence N(%)	0	0	1 (7.7)	0	0	
	Stenebrae fused					
Fetal incidence N(%)	0	0	0	1 (1.2)	0	
Litter incidence N(%)	0	0	0	1 (9.1)	0	
	Ribs fused					
Fetal incidence N(%)	1 (1.7)	0	0	0	0	
Litter incidence N(%)	1 (9.1)	0	0	0	0	
	Summary of External, visceral and skeletal findings by fetus					
Fetuses evaluated N	59	62	96	82	12	
Fetuses with any malformation N (%)	1 (1.7)	0	6 (6.3)	2 (2.4)	0	
Litters evaluated N	11	9	13	11	1	
Litters with any malformation N	1	0	3	2	0	
Percent with any malformation	9.0	0	23.1	18.2	0	
	Total findings by litter					
	External					
Litters with variants N (%)	0	0	0	0	0	
Litters with malformations N (%)	0	0	2 (15.4)	1 (9.1)	0	
	Visceral					
Litters with variants N (%)	3 (21.3)	4 (44.4)	5 (38.5)	4 (36.4)	1 (100.0)	
Litters with malformations N (%)	0	0	1 (7.7)	1 (9.1)	0	
	Skeletal					
Litters with variants N (%)	11 (100.0)	9 (100.0)	13 (100.0)	11 (100.0)	1 (100.0)	
Litters with malformations N (%)	1 (9.1)	0	1 (7.7)	2 (18.2)	0	

[a] Only one survivor by this point
[b] all animals started losing bodyweight from the beginning of dosing and were lost between day 8 and 24
[c] liver protruding through umbilicus
[d] Fetuses evaluated (Total) includes all foetuses, those without heads and those with heads (foetuses evaluated intact); whereas, foetuses evaluated (intact) include only foetuses with heads.
[e] one dextrocardia, one major heart anomaly.

Mean number of corpora lutea and implantations as well as foetal viability and foetal sex distribution were comparable for all groups. Mean foetal body weights decreased across groups in a dose related, but not statistically significant manner. Foetal skeletal and visceral variations were noted in all groups with foetuses available for examination. The incidence was not dose related. A single malformation was observed in the control group. Six foetuses in three litters at 50 mg/kg bw/day had malformations and two foetuses in two litters at 160 mg/kg bw/day. The single litter available for evaluation at 500 mg/kg bw/day had no malformations.

Signs of slight maternal toxicity were noted at 160 mg/kg bw/day. At 50 mg/kg bw/day, one female was found dead during the treatment period (prior to dosing on Day 15). No other evidence of maternal toxicity was observed. No abortions occurred in this group. Body weights and food consumption were comparable to the control values. Foetal malformations in this group included hyperflexed paws, two heart anomalies (in one litter), and one litter containing foetuses with fused vertebral centra and one foetus with multiple anomalies including the vertebral column.

Marked maternal toxicity resulted from doses at and above 500 mg/kg/day and included increased incidences of death, abortion, and reduced body weight gain and food consumption.

The incidence of spontaneous abortions did not occur in a dose related pattern; therefore, it is not clear whether the three abortions are attributable to treatment with Bifenox technical. Except for these three abortions, females had no observable signs of adult or foetal toxicity or teratogenicity at 160 mg/kg bw/day. Foetal malformation did not occur in a dose related pattern.

No increased incidence of the variation (hyoid alae angulated) noted in the Anonymous (1986) study was noted.

On the basis of these observations, the maternal no-effect level (NOEL) was proposed to be 50 mg/kg/day.

However, without any effects noted on foetuses it is considered that the developmental NOAEL is 160 mg/kg bw/day.

10.10.6 Comparison with the CLP criteria

Category 1 Known or presumed human reproductive toxicants

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Application of the classification criteria of Annex I to Regulation (EC) 1272/2008 to the available body of reproductive toxicity data for Bifenox indicate that a classification into category 1 can be ruled out because the substance is not known to cause reproductive toxicity in humans. Furthermore, there is no evidence that Bifenox adversely affects sexual function and fertility or development in the absence of other toxic effects.

Category 2 Suspected human reproductive toxicants

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.

Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Bifenox did not adversely affect fertility or general reproductive performance. There were no teratogenic effects evidenced in rats or rabbits induced by Bifenox.

10.10.7 Adverse effects on or via lactation

Table 27: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Rat, 2-generation reproduction and chronic toxicity GLP / not fully compliant to OECD 416	Bifenox Batch # 9401021 Purity: 99% Dose levels: 125, 750, 4500 ppm	4500 ppm Parental (systemic): decreased body weight gain Reproductive: decreased pup and litter weight at weanling in F1 and F2 generation NOAEL: Chronic toxicity: 44.5 mg/kg bw/day Reproduction: 148 mg/kg bw/day	Anonymous, 1995

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

In a 2-generation study in the rat during the lactation period, the mean body weight gain of litter and pups was lower at top dose and on day 21 weights were approximately 80% of control. The reduction in litter and pup weights at 4500 ppm were statistically significant lower than controls but were accompanied by (slight) parental toxicity (evidenced by reduced body weight gain at top dose). There was no treatment related incidence of abnormal lactation or pups suckling abnormally, and weight disturbance was considered to be due to systemic toxicity of material passed through the milk. Based on this, these effects were not considered to be relevant for a classification with regard to reproduction toxicity.

10.10.9 Comparison with the CLP criteria

There are no clear evidence of adverce effects in the offspring due to transfer bifenox in the milk nor evidences that bifenox interferes with lactation. Adverse effect on the quality of the milk has not been shown. Absorption, metabolism, distribution and excretion studies have not indicated the likelihood that the substance is present in potentially toxic levels in breast milk and are hence not considered to be relevant for a classification with regard to effects on or via lactation.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Bifenox does not require classification for reproductive toxicity.

10.11 Specific target organ toxicity-single exposure

In acute animal testing bifenox was of minimal oral toxicity. Alopecia was observed in rats after dosing with 5000 mg/kg bw. Gas in the stomach and intestines was noted among mice that died in the acute toxicity test. Other signs noted in mice included inactivity, unsteady gait and shivering. However, from subchronrc animal testing data it is assumed that blood parameters may be affected adversely (i.e. reduced RBCcount) after poisoning. Thus signs of anemia and cyanosis may not be excluded.

No specific data on humans are available.

10.11.1Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

Adverse effects, that were noted in acute toxicity studies in experimental animals included faecal staining, soft stool and hypoactivity. Those clinical findings were related to acute systemic toxicity due to a single exposure at very high dose levels and were fully reversible within the period of the experiment. Neither the adverse effects nor necropsy findings in those acute toxicity studies could be related to a specific target organ toxicity. Bifenox is of low toxicity.

No human data available on specific target organ toxicity of Bifenox. No clinical cases are reporterted. There are no observations in humans indicating any adverse effects upon a single dose of Bifenox. Bifenox is of low toxicity.

10.11.2Comparison with the CLP criteria

Specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed.

No avers effects were noted in acute studies in experimental animals and there are no observations in humans indicating any adverse effects upon a single dose of Bifenox. Bifenox is of low toxicity.

10.11.3Conclusion on classification and labelling for STOT SE

Bifenox does not require classification for specific target organ toxicity – single exposure.

10.12 Specific target organ toxicity-repeated exposure

Table 28: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	Targets/main effects	**Reference**
Oral repeated dose toxicity			
Oral 90-day study in rats GLP / study in accordance with OECD 408	**Dose levels** 0, 300, 900 and 2500	Liver toxicity, slight blood toxicity (at top dose), kidney toxicity **NOAEL** [mg/kg bw/day] 300	Anonymous, 1982
Oral 52 weeks study in dogs GLP / study in accordance with OECD 409	**Dose levels** 20, 145 and 1000	Blood toxicity, liver toxicity, liver fibrosis **NOAEL** [mg/kg bw/day] 145	Anonymous 1986
Dermal repeated dose toxicity			
Percutaneous 28-day study in rats GLP / EC Directive 92/69/EC, OECD 410	**Dose levels** 15, 150 and 1000	Slight bw gain reduction, slight food consumption reduction, liver necrosis **NOAEL** [mg/kg bw/day] 150	Anonymous 2002

There are no observations in humans regarding repeated dose toxicity of Bifenox.

10.12.1Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Animals repeatedly exposed to Bifenox in their diet developed mild signs of porphyria as suggested by small-altered blood parameters, kidney toxicity and some altered clinical chemistry, which could suggest hepatotoxicity Those effects are considered to be treatment related and occurred only at the highest dose levels of 900 mg/kg bw/day in rats (90 days) and 1000 mg/kg bw/day in dogs (90-days) or 47 mg/kg bw/day in mice (2 years).

Dermal repeated exposure revealed minor treatment related effects at the top dose (1000 mg/kg bw/d) that suggested hepatotoxicity are confirmed by systemic effects seen after oral repeated exposure.

Those effects occurred in all studies at the highest dose levels. Administration at lower dose levels did not exhibit any significant adverse effects due to the low toxicity of Bifenox.

10.12.2Comparison with the CLP criteria

The experimentally observed LOAELs exceeded the trigger values for classification regarding STOT RE of 100 mg/kg bw/day upon 90-day oral administration and 600 mg/kg bw/d upon 28-day dermal exposure.

10.12.3Conclusion on classification and labelling for STOT RE

Bifenox does not require classification for specific target organ toxicity upon repeated exposure.

10.13 Aspiration hazard

Not relevant. Substance is a solid at RTP.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 29: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Kinetic evaluation of aerobic degradation in soil (Simmonds and Burr, 1999) FOCUS 2006 & 2014	DT_{50} soil (persistence) at 20°C and 45% MWHC: - chloro phenyl label: Bifenox: 5.65 d (DFOP) Bifenox acid: 64.55 (SFO) - nitro phenyl label: Bifenox: 5.44 d (DFOP) Bifenox acid: 75.22 (SFO) DT_{90} soil (persistence) at 20°C and 45% MWHC: - chloro phenyl label: Bifenox: 111.70 d (DFOP) Bifenox acid: 214.4 (SFO) - nitro phenyl label: Bifenox: 116.90 d (DFOP) Bifenox acid: 249.90 (SFO)	^{14}C-chloro phenyl-Bifenox and ^{14}C-nitro phenyl Bifenox Soil: loam	Anonymous, 2016a
Kinetic evaluation of degradation in soil (Simmonds and Burr, 2000) FOCUS 2006 & 2014	DT_{50} & DT_{90} soil (persistence) at 20°C and 45% MWHC: - sandy loam, high microbial content: Bifenox: DT_{50} soil 14.64 d, DT_{90} soil 84.92 d (FOMC) Bifenox acid: DT_{50} soil 60.0 d, DT_{90} soil 199.30 d (SFO) - clay loam Bifenox: DT_{50} soil 3.96 d, DT_{90} soil 13.17 d (SFO) Bifenox acid: DT_{50} soil 86.47, DT_{90} soil 287.24 (SFO) - sandy loam, low microbial content Bifenox: DT_{50} soil 8.97 d, DT_{90} soil 29.81 d (SFO) Bifenox acid: DT_{50} soil 165.27, DT_{90} soil : 549.01 (SFO)	^{14}C-chloro phenyl-Bifenox and ^{14}C-nitro phenyl Bifenox Soils: sandy loam (high microbial content), clay loam, sandy loam (low microbial content)	Anonymous, 2016b

Method	Results	Remarks	Reference
Kinetic evaluation of degradation in soil (metabolite, Heintze, 2003) FOCUS 2006 & 2014	DT_{50} & DT_{90} soil (persistence) at 20°C and 45% MWHC: Bifenox acid: - 2.2 loamy sand: DT_{50} soil 22.65, DT_{90} soil : 75.26 (SFO) - 2.3 sandy loam: DT_{50} soil 90.52, DT_{90} soil : 300.7 (SFO) - 3A loam: DT_{50} soil 26.53, DT_{90} soil : 88.13 (SFO)	Bifenox acid Purity: 97.5% Soil: 2.2 loamy sand, 2.3 sandy loam and 3A loam	Anonymous, 2016c
Kinetic evaluation of degradation in soil (metabolite, Anonymous, 2005a and b) FOCUS 2006 & 2014	DT_{50} & DT_{90} soil (persistence) at 20°C and 45% MWHC: Aminobifenox - 2.2 loamy sand: DT_{50} soil 5.75, DT_{90} soil : 37.70 (FOMC) - 2.3 sandy loam: DT_{50} soil 4.89, DT_{90} soil : 16.24 (SFO) - 3A loam: DT_{50} soil 6.37, DT_{90} soil : 21.17 (SFO) - Aminobifenox acid - 2.2 loamy sand: DT_{50} soil 1.22, DT_{90} soil : 28.81 (FOMC) - 2.3 sandy loam: DT_{50} soil 1.58, DT_{90} soil : 20.06 (DFOP) - 3A loam: DT_{50} soil 0.55, DT_{90} soil : 10.94 (DFOP)	Aminobifenox and Aminobifenox acid Purity: 97.5% Aminobifenox and 97% Aminobifenox acid Soil: 2.2 loamy sand, 2.3 sandy loam and 3A loam	Anonymous, 2016d
Anaerobic degradation in soil OECD 307 (2002)	DT_{50} in soil (anaerobic): Metabolites: Bifenox acid under initial aerobic conditions. Under anaerobic conditions aminobifenox acid formed in major amounts of 29.3% AR.	[dichlorophenyl ring –U-^{14}C] Bifenox Soil: sandy loam	Anonymous, 2016a
Soil photolysis US EPA 161-3 (1982)	DT_{50}: 41.3 days (irradiated) Metabolite: Bifenox acid 16.5% AR after 30 d (irradiated)	^{14}C-dichloro-Bifenox Purity: > 99% Soil: loam soil	Anonymous, 1999
Field soil dissipation SETAC 1995, EPA OPPTS 835.6100, OECD 217	DT_{50} & DT_{90} soil (persistence), not normalised: Bifenox - N. Germany: DT_{50} soil 51, DT_{90} soil : 282 (DFOP) - N. France: DT_{50} soil 8.8, DT_{90} soil : 99.1 (DFOP) - S. France: DT_{50} soil 34.5, DT_{90} soil : 115 (SFO) - Spain: DT_{50} soil 22.9, DT_{90} soil : 75.9 (SFO) - S. Germany: DT_{50} soil 43.7, DT_{90} soil : 145 (SFO)	Formulated Bifenox, 480 g/L 5 sites: - N Germany (loamy sand) - N France (silt clay loam) - S France (loam) - Spain (clay loam) - S Germany (silt loam)	Anonymous, 2016
Adsorption/ desorption	Strong absorption to soil. K_{fOC} 4477-8070 L/kg	^{14}C-chlorophenyl Bifenox	Anonymous, 1983

Method	Results	Remarks	Reference
OECD 106	1/n 1.055-1.117	Soils: sandy loam, loamy sand and clay loam	
Adsorption/ desorption OECD 106	Strong absorption to soil. K_{fOC} 4400-23000 L/kg (n=3) 1/n 0.77-0.99 (n=3)	^{14}C-nitrophenyl Bifenox Soils: sand, sandy loam, silt loam, sandy clay loam	Anonymous, 1984
Adsorption/ desorption (metabolite) Dutch batch adsorption guidelines	Bifenox acid: moderately absorbed to soil, K_{fOC} 130-155 L/kg, 1/n 0.79-0.89 Aminobifenox: strongly absorbed to soil, K_{fOC} 3697-5024 L/kg, 1/n 0.70-0.77	^{14}C-chlorophenyl Bifenox acid ^{14}C-chlorophenyl Aminobifenox Soils: sand (high humic content), loam, sand soil (low humic content)	Anonymous, 1992
Adsorption/ desorption (metabolite) OECD 106	Aminobifenox acid: moderately to strongly absorbed to soil, K_{fOC} 417-3756 L/kg, 1/n 0.72-1.01	Aminobifenox acid (cold) Soils: fine sand, loam, sandy loam	Anonymous, 2005c
Hydrolysis study US EPA 161-1	Half lives (1st order): -pH 4 buffer; 50ºC: stable -pH 5 buffer; 50ºC stable -pH 7 buffer; 25ºC 265 d -pH 9 buffer; 25ºC 4 d Metabolites: Bifenox acid > 10% (21.6% at pH 7 and 102.1% at pH 9 at end of incubation)	^{14}C-chlorophenyl Bifenox Purity: 99.2%	Anonymous, 2000a
Hydrolysis study OECD 111 (2004)	pH 4, 7 and 9 at 50°C for 5 days: stable	^{14}C-dichlorophenyl bifenox acid Purity: > 98.8%	Anonymous, 2016b
Direct photochemical degradation in water OECD 316 (2008)	Half lives (h): 22.9 to 80.3 in irradiated samples. Main photolysis products: 2,4-dichlorophenol, max. 11.5% AR after 48 hours, max. 6.6% AR at study end (168 h). Methyl-5-hydroxy-2-nitrobenzoate, max. 42.9% AR after 72 hours, max. 22.3% AR at study end (168 h).	^{14}C-chlorophenyl Bifenox Purity: 99.9%	Anonymous, 2016c
Ready biodegradability OECD 301 B	11.8-14.0 % $ThCO_2$ after 28 d. The result of the study showed that Bifenox is not biodegradable within 28 days.	Bifenox, not specified	Anonymous, 1989
Aerobic mineralization in surface water of Bifenox OECD 309 (2004)	The DT_{50} were 4.5 d (lowest test concentration) and 3.7 d (highest test concentration) in water phase. Metabolite: Bifenox acid was identified in relevant amounts (max. 48.0% AR)	^{14}C-dichlorophenyl bifenox Purity: 100%	Anonymous, 2015
Kinetic evaluation of Water/ sediment study (Knoch, 1992)	-DT_{50} system (persistence): 0.02 d (FOMC) and 0.06 d (SFO) - DT_{50} water (persistence) 0.01 d (FOMC) and 0.07 d (SFO)	^{14}C-dichlorophenyl bifenox Purity: > 98.9% Systems: two (silty loam sand and silty loam)	Anonymous, 2016

Method	Results	Remarks	Reference
FOCUS 2006, 2014	- DT_{50} sediment (persistence) 0.02 d (FOMC) and 0.05 d (SFO) Metabolites: Aminobifenox bound to sediment at up to 64% AR and at 6.4% AR in the water phase. - DT_{50} system (persistence): 102.14 and 93.88 d - DT_{50} water (persistence): 0.83 and 3.00 d - DT_{50} sediment (persistence): 38.11 and 25.01 d) Bifenox acid one time > 5% (7.8%) in water. - DT_{50} water (persistence): 2.54 and 0.33 d, SFO Aminobifenox acid > 10% or > 5% for two successive time intervals in water phase.		
Degradation in air BBA Guideline part IV, 6-1 (phase 2)	No significant volatilisation of Bifenox from plant surfaces (up to 0.8 and 1.3% AR). No volatile metabolites found.	[ring-^{14}C] Bifenox System: volatilisation chamber, French beans	Anonymous, 1994a, b
Degradation in air BBA Guideline part IV, 6-1 (phase 2)	No significant volatilisation of Bifenox from soil surfaces (< 1.0%AR). No volatile metabolites found.	[ring-^{14}C] Bifenox System: volatilisation chamber, soil surface (sandy soil)	Anonymous, 1994a, b
Transport via air	Bifenox displays low overall persistence, limited transfer potential and low travel distance (estimated at 89 km)	Bifenox	Anonymous, 2015

11.1.1 Ready biodegradability

The biodegradability of Bifenox was investigated in one ready biodegradability study (28 days). The 10% level was not reached within the 10 days from the beginning of the study. The biodegradation after 28 days was 14.0 and 11.8% for the 10 and 20 mg/L test concentrations, respectively. The result of the study showed that Bifenox is not biodegradable within 28 days, the criterion of 'rapid degradability' is not met.

11.1.2 BOD_5/COD

Please refer to point 11.1.1.

11.1.3 Hydrolysis

In the available hydrolysis study with Bifenox, the preliminary test showed Bifenox was stable at pH 4 and 5 at 50°C. In the main test at 25°C, the corresponding first order hydrolysis rate constant was determined and equivalent to a DT_{50} of 265 days and 4 days at pH 7 and 9, respectively. Bifenox acid was the only metabolite detected and occurred at maximum amounts at end of incubation of 21.6% AR at pH 7 and 102.1% AR at pH 9.

In the aqueous hydrolysis study conducted with the metabolite bifenox acid, the substance was determined to be hydrolytically stable at pH 4, 7 and 9 over a period of 5 days at 50°C and, therefore, no additional testing was required or was performed. The DT_{50} (25°C) is estimated to be > 1 year.

11.1.4 Other convincing scientific evidence

The adsorption and desorption in soil of Bifenox has been evaluated in two batch adsorption studies with ^{14}C-chlorophenyl and ^{14}C-nitrophenyl Bifenox. The studies showed that Bifenox is strongly adsorbed to soil particles. The Freundlich adsorption coefficient K_{fOC} was found to be in the range of 4477 to 8070 L/kg (n=3) in the first study and ranging between 4400 L/kg and 23000 L/kg (n=3) in the second study. Therefore, Bifenox is considered to be immobile in soil.

The adsorption and desorption in soil of the major Bifenox metabolite formed under aerobic conditions, i.e. bifenox acid, and also of aminobifenox (formed in minor amounts under anaerobic conditions) has been evaluated in one study with three soils. It was found that bifenox acid is weakly adsorbed to soil particles. The K_{fOC} values in humic sand, loam and low humic sand were determined to be 145, 155 and 130 L/kg, respectively. Aminobifenox is strongly adsorbed to soil with high K_{fOC} values of 4611, 5024 and 3697 L/kg, respectively. In an additional study the adsorption properties of aminobifenox acid (major metabolite under anaerobic conditions) were determined in a laboratory experiment in three soils. It was found that aminobifenox acid was moderately to strongly adsorbed to the test soils with K_{fOC} values of 3756 L/kg (silty sand), 417 L/kg (sandy loam) and 636 L/kg (loamy sand).

Bifenox has a vapour pressure of 4.74×10^{-8} Pa at 20°C and a Henry law constant of $> 1.62 \times 10^{-4}$ Pa m^3 mol^{-1}. Bifenox may thus be considered as not volatile from soil or plant surfaces. Additionally, metabolism degradation studies in soil, water and water/sediment systems indicated there are no volatile breakdown products of concern from Bifenox. And moreover, the results of volatilisation studies from plant and soil surfaces conducted with Bifenox under controlled conditions showed negligible volatilisation of the substance from either surface.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

In a field soil dissipation study, the residue levels of Bifenox and its metabolite bifenox acid were determined and additionally analysis for Nitrofen was made in five soil trials at sites in northern Europe (N-Germany, S-Germany and N-France) and southern Europe (S-France and Spain). A single autumn application of Fox was applied to bare soil at a nominal application rate of 757.5 g a.s./ha. Immediately after application, the soil surface was covered with a sand layer of 0.5 cm thickness. Soil samples were collected at day 0 (0-30 cm) and 11 additional timings (0-100 cm) over the course of 1 year.

In treated soil samples of all trials, residues of Bifenox were determined between 0.21 mg/kg and 0.52 mg/kg (as wet weight) 0 days after application (DAA) in the 0 to 10 cm layer. In all trials, residue amounts decreased to negligible levels by study end and were seldom found in relevant amounts in lower soil layers throughout the study.

Residues of bifenox acid ranged from < LOD to 0.018 mg/kg at 0 DAA. The residues of bifenox acid increased to a maximum between 0.14 mg/kg (Trial 1 at 90 +/- 3 DAA) to 0.23 mg/kg mg/kg (Trial 5 at 60 +/- 3 DAA) in the 0 to 10 cm layer. In the 10 to 20 cm layer a maximum from 0.035 mg/kg (Trial 2 at 120 +/- 3 DAA) to 0.095 mg/kg (Trial 4 at 60 +/- 3 DAA) was observed. Bifenox acid was not detected in any samples from soil layers below 30 or 40 cm, depending on the trial site. In all trials, no residues of nitrofen were detected (LOD < 0.03 mg/kg).

A kinetic evaluation of the five available trial datasets was performed to derive trigger and modelling endpoints of Bifenox and its metabolite bifenox acid according to the guidance of the FOCUS work group on degradation kinetics and EFSA. The derived DT_{50} / $DegT_{50}$ values (trigger and modelling endpoints – modelling endpoints normalised to 20°C and pF2) for Bifenox ranged from 8.8 (SFO) to 51 days (DFOP) and from 11.2 (SFO) to 23.3 days (SFO), respectively. For the metabolite bifenox acid, the derived DT_{50} / $DegT_{50}$ values (trigger and modelling endpoints – modelling endpoints normalised to 20°C and pF2) were ranging from 60.8 to 110 days (both SFO) and from 24.4 to 43.4 days (both SFO), respectively.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No information available or required. Please refer to point 11.1.1.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

In a water/sediment study with ^{14}C dichlorophenyl Bifenox, two natural systems 'Bickenbach' and 'Unter Widdersheim' were used. Bifenox was applied to the test systems at initial concentration of 0.33 mg/L. Bifenox rapidly disappeared from the two water/sediment systems within the first day.

Aminobifenox, the major metabolite was bound to the sediment in amounts up to 67% AR of the applied parent compound. No other metabolite was detected in the sediment throughout the study. Aminobifenox occurred to 6.4% AR in the water phase. Aminobifenox acid appeared in one system at a maximum of 12.7% AR in water 24 hours after treatment. This level decreased to 5.2% within the following 24 hours and did not reach amounts above 10% thereafter. In the other system, a maximum amount of 10.6% AR was found on day 14 and decreased to 3.1% AR at the consecutive sampling event. However, at day 105 still 5% AR found in the water accounted for this metabolite. Bifenox acid accounted for maximum 7.8% AR in water 48 hours after application and did not exceed 5% at any other sampling time.

Kinetic re-evaluation of the DT values was performed and the half-lives of Bifenox in the total system were 0.02 and 0.06 days in the 'Bickenbach' and 'Unter Widdersheim' system, respectively. For the metabolite bifenox acid, maximum DT_{50} value for the water compartment was 2.54 days (Bickenbach system), and since there was no occurrence in the sediment phase, this endpoint can be extrapolated to the total system as well. For the metabolite aminobifenox acid, for the whole system maximum DT_{50} value was 30.75 days (Bickenbach system). For the metabolite Aminobifenox acid, no appropriate kinetic fitting could be found.

Two studies on the route and rate of degradation of Bifenox were conducted. In the first study with radio-labelled [chloro phenyl-^{14}C] Bifenox and [nitro phenyl-^{14}C] Bifenox, there were no notable differences in the metabolism and rate of degradation of Bifenox between the two labels. Bifenox was moderately quickly degraded in one soil declining from mean 87.01-90.16% AR at day 0 to 9.04-9.59% AR after 120 days. One major metabolite was detected. Bifenox acid was observed accounting for maximum on day 14 of 63.8% AR (chloro phenyl label) and 60.87% AR (nitro phenyl label) and decreased to ca. 27% AR at study end forming bound residues (maximum 46% AR) and CO_2 (maximum ca. 11% AR). As minor metabolites, aminobifenox and aminobifenox acid occurred to a maximum levels of 1.15% AR (day 2) and 0.84% AR (day 90), respectively with no remarkable difference between the labels. In second study in three soils with radio-labelled [chloro phenyl-^{14}C] Bifenox, the active substance was moderately quickly degraded in the soils at 20°C declining from 98.07-95.01% AR at day 0 to 2.00-3.78% AR after 181 days. At 10°C, Bifenox degraded from 95.86% AR at day 0 to 10.80% AR at day 181. One major metabolite was detected. Bifenox acid was observed accounting for maximum on day 10 at 78.71% AR (clay loam) and decreased to 23.11% AR at study end forming bound residues (maximum ca. 52% AR) and CO_2 (maximum ca. 19% AR). As minor metabolites, aminobifenox and aminobifenox acid occurred to a maximum levels of 0.59% AR (day 181) and 2.58% AR (day 120), respectively with no remarkable difference between the soils. Incubation at 10°C resulted in a slower degradation of Bifenox and subsequently lower metabolite amounts formed.

In one study, the rate of degradation of bifenox acid (non-radio-labelled) was investigated. Bifenox acid was moderately to quickly degraded in the soils at 20°C declining from mean of 98.5-107.7% applied at day 0 to 2.84-35.8% applied after 120 days. The results were corrected for recovery of fortified samples at each sampling time.

Kinetic re-evaluation of the DT_{50} values was performed and DT_{50} values (at 20°C, not normalised to pF2) of Bifenox ranged from 3.96 to 14.64 days (n=5) and respective DT_{90} values ranged from 13.17 to 116.90 days.

For Bifenox acid the DT_{50} values (at 20°C, not normalised to pF2) ranged from 22.65 to 165.27 days (n=8) and respective DT_{90} values ranged from 75.26 to 549.01 days. For Aminobifenox the DT_{50} values (at 20°C, not normalised to pF2) ranged from 4.89 to 6.37 days (n=3) and respective DT_{90} values ranged from 16.24

to 37.70 days. For Aminobifenox acid the DT_{50} values (at 20°C, not normalised to pF2) ranged from 0.55 to 1.58 days (n=3) and respective DT_{90} values ranged from 10.94 to 28.81 days.

Soil metabolism in anaerobic (flooded) conditions was evaluated considering the intended uses of Bifenox with application in the autumn to winter cereals and oilseed rape. In a study with radio-labelled [chloro phenyl-^{14}C] Bifenox, incubation of a treated soil for 6 days under aerobic conditions was followed by an anaerobic phase lasting up to 120 days. The amounts of Bifenox decreased quickly under aerobic conditions to 33.9% AR by day 6 after treatment and afterwards, under anaerobic conditions, decreased further and was not detected after 90 d of incubation. Bifenox acid built up during the aerobic incubation phase and increased to a concentration of 49.3% until 6 days after application of Bifenox. Afterwards, under anaerobic conditions, this major aerobic metabolite was further degraded to aminobifenox acid. No bifenox acid was detected any more from day 30 onwards. Beginning from day 14 after application, aminobifenox acid was detected indicating that amination takes place under anaerobic conditions. The amounts of aminobifenox acid increased slowly reaching maximum of 29.3% AR after 90 days of incubation and thereafter decreasing to 24.0% AR at the final sampling at day 120. Aminobifenox was detected in some samples but without a clear temporal trend and not at consecutive samplings with a maximal value of 8.6% AR observed after 30 days. Nitrofen was never detected (LOQ of the method 0.01 mg/kg; LOD: 0.003 mg/kg). Bound radioactive residues increased throughout the incubation, reaching a maximum value of 54.4% AR at the end of incubation (120 d). Only negligible amounts (< 1% AR) of volatile degradation products were found in the trapping solutions.

An additional non-GLP study on anaerobic soil degradation with non-radio labelled Bifenox demonstrated similar results to the above discussed GLP study with radio-labelled material. The initial aerobic phase was 7 days and was followed by a 90-day anaerobic phase. Analysis was made for the metabolites bifenox acid (maximum 49% of applied amount) and aminobifenox acid (maximum 8.9% of applied amount). Additionally, this study included detailed analysis for the metabolite nitrofen which was not found in any of the samples under either initial aerobic or main anaerobic conditions.

11.1.4.4 Photochemical degradation

The aqueous phototransformation of the test item Bifenox was studied under continuous artificial light for up to 168 hours in sterile aqueous media. The direct photolysis rate constant of Bifenox was determined using a single first order (SFO) kinetic model (KinGUI version 1.1). The $DegT_{50}$ values were 63.4, 80.3, 22.9 and 43.9 hours for [dichlorophenol-^{14}C] label (middle rate), [dichlorophenol-^{14}C] label (low rate), [benzoyl-^{14}C] label (middle rate) and [benzoyl-^{14}C] label (low rate), respectively. 2,4-Dichlorophenol as major metabolite of [dichlorophenyl-^{14}C]-labelled reached maximum levels of 11.5% AR and 6.2% AR after 48 h irradiation and decreased to ranges of 6.6% AR and 5.8% AR at the final sampling point at 168 h at middle and low concentration, respectively.

Methyl-5-hydroxy-2-nitrobenzoate as major metabolite of [benzoyl-^{14}C]-labelled-Bifenox reached maximum levels of 37.6% AR after 48 h and 42.9% AR after 72 h irradiation and decreased to ranges of 17.7% AR to 22.3% AR at the final sampling point at 168 h at middle and low concentration, respectively.

The quantum yield was calculated after measuring the spectral photon irradiance of the light source and the molar decadic absorption coefficient and ranged from 7.60×10^{-5} to 2.67×10^{-4}.

Soil photolysis was found not to have any significant contribution to the degradation of Bifenox on soil surfaces. The metabolism observed was similar between irradiated and non-irradiated soils with 16.5 and 28.2% AR recovered as bifenox acid after 30 days. According to first order kinetics, DT_{50} / DT_{90} values of Bifenox determined for irradiated soils were, respectively, 41.3 / 137.2 days.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

11.3 Environmental fate and other relevant information

No further data.

11.4 Bioaccumulation

Table 30: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
ASTM, proposed standard practise for conducting bioconcentration with fish, 1977 - 1979	BCF = 1500 (whole fish) Clearance time CT_{50} = 1.4 days	$^{-14}$C-bifenox by bluegill sunfish (*Lepomis macrochirus)*	Anonymous (1986)

11.4.1 Estimated bioaccumulation

On the base on the experimental study the bioconcentration factor (BCF) was determined to be 1500, a bioconcentration study was conducted with bluegill sunfish (*Lepomis macrochirus*). A rapid elimination of ^{14}C Bifenox related residues from fish was recognized, the DT_{50} for clearance was 1.4 days.

The agreed BCF value in the EFSA Conclusion (2007) from this study was 1500.

11.4.2 Measured partition coefficient and bioaccumulation test data

The water partitioning coefficient value of bifenox (log P_{OW}) 3.64 (range 3.55 to 3.73, 20 – 25 °C, pH unadjusted)[7] is confirmed in the DAR document 2016 (CA 8.2.2.3). Bifenox rapidly degrades in water/sediment systems (DT_{50} = 0.03 days, DT_{90} = 0.44; geometric mean, whole system, n = 2. The values of partition coefficient are less than cut-of value (CLP criteria: $K_{OW} \geq 4$ for chronic categories).

According to CLP using a cut-off value of log K ow ≥ 4 is intended to identify only those substances with a real potential to bioconcentrate. The log P_{OW} value is used to classification if experimentally determined BCF is not available.

Taking into account above-mentioned not rapidly degradability and the experimentally determined BCF value for bifenox, the partition coefficient value (log P_{OW}) can be omitted in the consideration of the bifenox classification.

11.5 Acute aquatic hazard

Table 31: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
OECD 203	Rainbow trout (*Oncorhynchus mykiss*)	Bifenox	LC_{50} (96 h, flow-through) = 0.67 mg/L (nom.)	-	Anonymous (1993)

[7] EFSA Scientific Report (2007) 119, 1-84, Conclusion on the peer review of bifenox (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2008.119r)

US-EPA (1975)	Bluegill sunfish (*Lepomis macrochirus*)	Bifenox	LC_{50} (96 h, flow-through) > 0.27 mg/L (m.m.)	-	Anonymous (1985a)
US-EPA (1975)	*Daphnia magna*	Bifenox	EC_{50} (48 h, flow-through) > 0.66 mg/L (m.m.)	-	Anonymous (1985b)
OECD 201	*Scenedesmus subspicatus*	Bifenox	E_rC_{50} (72 h, static) = 0.00042 mg/L (m.m.)	-	Anonymous (1998a)
OECD 201	*Naviculla pelliculosa*	Bifenox	E_rC_{50} (72 h, static) = 0.0380 mg/L (m.m.)	-	Anonymous (1999)
FIFRA 122-2 and 123-3	*Lemna gibba*	Bifenox	E_rC_{50} (14 d, static) = 0.0028 mg/L (m.m.)	-	Anonymous (1998)
OECD 238	*Myriophyllum spicatum*	Bifenox	E_rC_{50} (14 d, semi-static) = 0.00189 mg/L (m.m.)	-	Anonymous (2016c)
OECD 239	*Myriophyllum spicatum*	Bifenox	E_rC_{50} (14 d, semi-static) = 0.000629 mg/L (m.m.)	Water-sediment	Anonymous (2016h)

11.5.1 Acute (short-term) toxicity to fish

The lowest LC_{50} (96 h) of Bifenox for fish was determined to be 0.67 mg/L from a study with rainbow trout. The LC_{50} (96 h) of Bifenox for bluegill sunfish based on measured concentrations was determined to be > 0.27 mg/L.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

The EC_{50} (48 h) of Bifenox for *Daphnia magna* was calculated to be > 0.66 mg/L.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Effects of Bifenox on algal growth were investigated in several studies submitted during the first EU evaluation for Annex I inclusion of Bifenox. They were conducted according to OECD guideline 201 (1984) and in compliance with Good Laboratory Practice (GLP) regulations; however, not all of the studies fulfil the validity criteria according to the current guideline version (2011). Only studies still considered valid are summarized in Table 31 above. The re-calculated EC_{50} values for Bifenox from a study with *Scenedesmus subspicatus* are 0.000420 mg/L for growth rate and 0.000272 mg/L for yield. This study with *Scenedesmus subspicatus* provides the lowest acute endpoint. A second algal species (*Naviculla pelliculosa)* was tested since Bifenox is an herbicide. The E_rC_{50} of 0.038 mg/L value was considerably higher.

The E_rC_{50} derived from a study with *Lemna gibba* was 0.0028 mg/L, the E_bC_{50} was 0.0021 mg/L. Effects of Bifenox on the dicotyledonous aquatic macrophyte *Myriophyllum* have also been investigated since Bifenox is an herbicide to control dicotyledonous weeds. The E_rC_{50} value was determined to be 0.000488 mg a.s./L and 0.000476 mg/L, respectively. The presence of sediment in the method can effect the reliability of the results especially as bifenox appears to adsorb strongly to soil/sediment. The water-sediment *Myriophyllum spicatum* test method complements the sediment-free *Myriophyllum spicatum* Toxicity Test.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

Further acute toxicity studies are not available and are considered not necessary.

11.6 Long-term aquatic hazard

Table 32: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
OECD 204	Rainbow trout (*Oncorhynchus mykiss*)	Bifenox	NOEC (21 d, flow-through) = 0.0091 mg/L (m.m.)	-	Anonymous (1991)
US-EPA (1975)	Bluegill sunfish (*Lepomis macrochirus*)	Bifenox	NOEC (14 d, flow-through) = 0.13 mg/L (m.m.)	-	Anonymous (1981)
OECD 211	*Daphnia magna*	Bifenox	NOEC (21 d, static) = 0.015 mg/L (m.m.)	3 d exposure, 18 d recovery	Anonymous (1999)
OECD 211	*Daphnia magna*	Bifenox	NOEC (21 d, static) = 0.00033 mg/L (m.m.)	-	Anonymous (1990)
BBA Guideline Proposal (1995)	*Chironomus riparius*	Bifenox	NOEC (28 d, static) = 0.015 mg/L (nom.)	Water-sediment	Anonymous (1996)
OECD 201	*Scenedesmus subspicatus*	Bifenox	NOE_rC (72h, static) < 0.000250 mg/L (m.m.)	-	Anonymous (1998a)
OECD 201	*Naviculla pelliculosa*	Bifenox	NOE_rC (72 h, static) = 0.00016 mg/L (m.m.)	-	Anonymous (1999)
FIFRA 122-2 and 123-3	*Lemna gibba*	Bifenox	NOE_rC (14 d, static) = 0.00045 mg/L (m.m.)	-	Anonymous (1998)
OECD 238	*Myriophyllum spicatum*	Bifenox	NOE_rC (14 d, semi-static) = 0.000058 mg/L (m.m.)	-	Anonymous (2016c)
OECD 239	*Myriophyllum spicatum*	Bifenox	NOE_rC (14 d, semi-static) < 0.000064 mg/L (m.m.)	Water-sediment	Anonymous (2016h)

[1] Indicate if the results are based on the measured or on the nominal concentration

11.6.1 Chronic toxicity to fish

The lowest NOEC (21 d) of 0.0091 mg/L for Bifenox (*Oncorhynchus mykiss)* was determined from a prolonged toxicity study with rainbow trout. Chronic toxicity data from OECD TG 204 is not considered suitable for chronic classification under CLP (Guidance on the Application of CLP Criteria).

The second study results NOEC (14 d, flow-through) of 0.13 mg/L (m.m.) for Bifenox (*Lepomis macrochirus).* The test results do not cover the life stages of the used species. The NOEC value is higher than for rainbow trout therefore it is not considered to classification.

11.6.2 Chronic toxicity to aquatic invertebrates

The lowest NOEC (21 d) for reproduction of 0.00033 mg/L for Bifenox was determined from a chronic study with *Daphnia magna.*

11.6.3 Chronic toxicity to algae or other aquatic plants

Effects of Bifenox on algal growth were investigated in several studies submitted during the first EU evaluation for Annex I inclusion of Bifenox. They were conducted according to OECD guideline 201

(1984) and in compliance with Good Laboratory Practice (GLP) regulations; however, not all of the studies fulfil the validity criteria according to the current guideline version (2011). Only studies still considered valid are summarized in Table 32 above. The lowest NOE_rC for algae of < 0.00025 mg/L for Bifenox was determined from a study with *Scenedesmus subspicatus.* A second algal species (*Naviculla pelliculosa) was tested since Bifenox is an herbicide. The* NOE_rC of 0.00016 mg/L was considerably lower. Results obtained in a water-sediment test system for *Chironomus riparius* due to feasible adsorption of bifenox with demonstrated strong absorption to soil may be tough to interpretation.

The NOE_rC derived from a study with *Lemna gibba* was 0.00045 mg/L. Effects of Bifenox on the dicotyledonous aquatic macrophyte *Myriophyllum* have also been investigated since Bifenox is an herbicide to control dicotyledonous weeds. The lowest definitive NOE_rC for aquatic plants of 0.000058 mg/L for Bifenox was determined from a study with *Myriophyllum spicatum*. This study provides the lowest definitive chronic endpoint to be considered for classification and labelling. Results obtained in a test system only in water phase, without sediment (OECD 238) enable clearer interpretation than in case of the presence of sediment (OECD 239) where for poorly soluble substances adsorption can be confused with degradation. Proceses of bifenox adsorption on sediment can have direct impact on test results and interpretation could be more complicated.

11.6.4 Chronic toxicity to other aquatic organisms

A NOEC (28 d) for reproduction of 0.015 mg/L for Bifenox was determined from a development study with *Chironomus riparius*.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Bifenox is of high acute toxicity (endpoints < 1 mg/L) to fish, invertebrates, algae and macrophytes (lowest E_rC_{50} = 0.000420 mg/L, *Scenedesmus subspicatus)* and fulfils the criteria for the proposed classification as Category Acute 1 (H400 - Very toxic to aquatic life) according to Regulation EC 1272/2008.

The corresponding M factor for an acute endpoint between 0.0001 and 0.001 mg/L to be considered for mixture toxicity is 1000.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Substances that rapidly degrade can be quickly removed from the environment. Bifenox is not rapidly degradable in the environment.

Experimentally determined BCF 1500 for bifenox indicated for its bioaccumulation potential (comparing to CLP criteria: BCF≥500) is clearly above criteria. An octanol-water partition coefficient value (log P_{OW}) is assumed 3.64 (CLP criteria K_{OW} ≥4). According to CLP criteria an experimentally determined BCF value provides a better measure and shall be used in preference if available. BCF 1500 is indicative of the potential to bioconcentrate for classification purposes in chronic aquatic hazarad.

Bifenox is of high chronic toxicity (endpoints < 0.1 mg/L) to fish, invertebrates, algae and macrophytes (lowest NOEC = 0.000058 mg/L, Myriophyllum spicatum) and fulfils the criteria for the proposed classification as Category Chronic 1 (H410 - Very toxic to aquatic life with long lasting effects) according to Regulation EC 1272/2008 for a non-rapidly degradable substance.

The corresponding M factor for a chronic endpoint between 0.00001 and 0.0001 mg/L of a non-rapidly degradable substance to be considered for mixture toxicity is 1000.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Classification according to Regulation (EC) No 1272/2008 [CLP]

Acute aquatic toxicity: Category 1 - H400

Chronic aquatic toxicity: Category 1 - H410

M factor = 1000 (acute) and M factor = 1000 (chronic)

Labelling according to Regulation (EC) No. 1272/2008 [CLP]

GHS Pictogram:

GHS09

Signal word:

Warning

Hazard statements:

H410 - Very toxic to aquatic life with long lasting effects

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Table 33: Summary table of data concerning hazardous properties of the substance for the ozone layer

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Degradation in air BBA Guideline part IV, 6-1 (phase 2)	[ring-^{14}C] Bifenox System: volatilisation chamber, French beans	No significant volatilisation of Bifenox from plant surfaces (up to 0.8 and 1.3% AR). No volatile metabolites found.		Anonymous, 1994a,b
Degradation in air BBA Guideline part IV, 6-1 (phase 2)	[ring-^{14}C] Bifenox System: volatilisation chamber, soil surface (sandy soil)	No significant volatilisation of Bifenox from soil surfaces (< 1.0%AR). No volatile metabolites found.		Anonymous, 1994a,b
Transport via air	Bifenox	Bifenox displays low overall persistence, limited transfer potential and low travel distance (estimated at 89 km)		Anonymous, 2015

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

Bifenox has a vapour pressure of 4.74×10^{-8} Pa at 20°C and a Henry law constant of $> 1.62 \times 10^{-4}$ Pa m^3 mol^{-1}. Bifenox may thus be considered as not volatile from soil or plant surfaces. Additionally, metabolism degradation studies in soil, water and water/sediment systems indicated there are no volatile breakdown products of concern from Bifenox. And moreover, the results of volatilisation studies from plant and soil surfaces conducted with Bifenox under controlled conditions showed negligible volatilisation of the substance from either surface.

The estimated half life in the atmosphere of 10.19 days based on the Atkinson method was calculated wit AOPWIN v 1.92a. However, it was shown via a multimedia model that when other factors are taken into account, overall persistence of Bifenox in air is lower, i.e. 8 days. Of more relevance, the characteristic travel distance estimated at 89 km is quiet low when compared to a theoretical travel distance of 1000 km that is proposed to be represented by the estimated DT_{50} in air of 2 days. In addition, when compared to known POP-like chemicals, the model shows that Bifenox does not share their characteristics but displays instead a low overall persistence, limited transfer potential and low travel distance.

Overall, considering the negligible volatilisation potential from experimental evidence, a contamination of air in amounts that can be considered of relevance to the environment are considered very unlikely. Additionally, the calculation of half-life in the atmosphere based on the Atkinson method only includes reaction with OH radicals and no ozone reaction estimation. When considering also reactions with ozone, the half-life in reality would be expected to be lower.

Therefore, no effects or hazards to the ozone layer from Bifenox are to be expected.

12.1.2 Comparison with the CLP criteria

There is no calculation of the ozone depleting potential of Bifenox available. However, this is considered as not relevant, please refer to point 12.1.1.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Bifenox is not considered as hazardous to the ozone layer. The available evidence concerning its properties and its predicted or observed environmental fate and behaviour indicate that it will not present a danger to the structure and/or the functioning of the stratospheric ozone layer.

13 ADDITIONAL LABELLING

Not relevant.

14 REFERENCES

14.1 Physicochemical Properties

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	2016	Study plan: PARTITION COEFFICIENT OF 5-METHYL- 2-HYDROXY NITROBENZOATE ADAMA Agan Ltd, 90019750 GLP/GEP: yes Published: no	ADM
Anonymous	2001a	Bifenox Henry´s law constant ADAMA Agan Ltd Report-no. ACS/EDRA/BAJ/01023 GLP/GEP: no Published: no	ADM
Anonymous	2001b	Bifenox pH and dissociation constant ADAMA Agan Ltd Report-no. 00-139 GLP: yes Published: no	ADM
Anonymous	1998	Bifenox technical grade active ingredient: Surface tension ADAMA Agan Ltd Report-no. 98-129 GLP: yes Published: no	ADM
Anonymous	2001a	Bifenox: Vapour pressure ADAMA Agan Ltd Report-no. 1905/4-D2141 GLP: yes Published: no	ADM
Anonymous	2001b	Bifenox: Water and solvent solubility ADAMA Agan Ltd Report-no. 448792, 1905/3-D2141 GLP: yes Published: no	ADM
Anonymous	2000c	Bifenox: n-Octanol: Water Partition Coefficient ADAMA Agan Ltd Report-no. 1905/2-D214 GLP: yes Published: no	ADM
Anonymous	2016a	DRAFT REPORT: PARTITION COEFFICIENT OF BIFENOX ACID (HPLC METHOD) ADAMA Agan Ltd Report-no. S16-00565 GLP/GEP: yes Published: no	ADM
Anonymous	2016b	DRAFT REPORT: PARTITION COEFFICIENT OF AMINO-BIFENOX (HPLC METHOD) ADAMA Agan Ltd Report-no. S16-00566 GLP/GEP: yes Published: no	ADM
Anonymous	2016c	DRAFT REPORT: PARTITION COEFFICIENT OF AMINO-BIFENOX ACID (HPLC METHOD) ADAMA Agan Ltd Report-no. S16-00564 GLP/GEP: yes Published: no	ADM

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	2000	Bifenox - Determination of the flammability ADAMA Agan Ltd Report-no. 00-331-SEC GLP: yes Published: no	ADM
Anonymous	1998	Determination of the explosion properties, ability for self heating and oxidizing properties of technical bifenox ADAMA Agan Ltd Report-no. 98-226-SEC, 98-133 GLP: yes Published: no	AMD
Anonymous	2006	Oxidizing Properties A.17. Feinchemie Schwebda GmbH Report-no. 20060054.01 GLP: yes Published: no	ADM
Anonymous	1988	Bifenox - Henry´s Law Constant ADAMA Agan Ltd Report-no. 440111, 793C10 GLP/GEP: no Published: no	ADM
Anonymous	2000	Bifenox: Physical characteristics ADAMA Agan Ltd Report-no. 447998, 1905/1-D2141 GLP: yes Published: no	ADM
Anonymous	1986	Determination of ambient vapour pressure of Bifenox ADAMA Agan Ltd Report-no. 440110, 34611 GLP/GEP: no Published: no	ADM

14.2 Health Hazard

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous.	1985a	ACUTE ORAL TOXICITY STUDY ON RATS ADAMA Agan Ltd, 440124, 5799-85 GLP: yes Published: no	ADM
Anonymous	1985b	ACUTE DERMAL TOXICITY STUDY IN RABBITS ADAMA Agan Ltd, 440126, 5800-85 GLP: yes Published: no	ADM
Anonymous	1985c	PRIMARY DERMAL IRRITATION STUDY IN RABBITS ADAMA Agan Ltd, 440128, 5801-85 GLP: yes Published: no	ADM
Anonymous	1985d	EYE IRRITATION STUDY IN RABBITS - EPA ADAMA Agan Ltd, 440129, 5802-85 GLP: yes Published: no	ADM
Anonymous .	1995	BIFENOX TWO GENERATION REPRODUCTION STUDY IN RATS ADAMA Agan Ltd, 600885, 11324 GLP: yes Published: no	ADM
Anonymous .	1987	EFFECT OF BIFENOX ON PREGNANCY OF THE RAT ADAMA Agan Ltd, 412538, RNP 242/861056 GLP: yes Published: no	ADM
Anonymous	1982	13-WEEK DIETARY TOXICITY STUDY IN RATS MCTR-299-79 ADAMA Agan Ltd, 440132, 450 035 GLP: yes Published: no	ADM
Anonymous .	2015	COMPARATIVE IN VITRO METABOLISM OF [14C]-BIFENOX USING RAT AND HUMAN LIVER MICROSOMES ADAMA Agan Ltd, 20664, 90017812 GLP: yes Published: no	ADM
Anonymous .	1986	DEVELOPMENTAL TOXICITY (EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL) STUDY OF BIFENOX TECHNICAL ADMINISTERED ORALLY (STORMACH TUBE) TO NEW ZEALAND WHITE RABBITS ADAMA Agan Ltd, 218-003 GLP: yes Published: no	ADM
Anonymous	1992	REVIEW OF THE KIDNEY SLIDES FROM STUDY: 24-MONTH CARCINOGENICITY STUDY IN MICE WITH BIFENOX 440135, Report n° R-21063 GLP: Not applicable	
Anonymous .	1983	CHO/HGPRT MAMMALIAN CELL FORWARD GENE MUTATION ASSAY PH 314-DC-001-83 BIFENOX-TECHNICAL ADAMA Agan Ltd, 440140, PH 314-DC-001-83 GLP: yes Published: no	ADM
Anonymous.	1986	BIFENOX ORAL TOXICITY STUDY IN BEAGLE DOGS (REPEATED DAILY DOSAGE FOR 52 WEEKS) ADAMA Agan Ltd, 410810, RNP 218/85998 GLP: yes Published: no	ADM
Anonymous	1979	SALMONELLA/MAMMALIAN-MICROSOME PLATE INCORPORATION MUTAGENESIS ASSAY ADAMA Agan Ltd, 440138, 595-248-1 GLP/GEP: no	ADM

		Published: no	
Anonymous	1982	BIFENOX - MUTAGENICITY STUDY USING BACTERIAL STAINS ADAMA Agan Ltd, 440137, 82-095 GLP/GEP: no Published: no	ADM
Anonymous .	2016	IN VITRO MAMMALIAN CHROMOSOME ABERRATION TEST IN CHINESE HAMSTER V79 CELLS WITH BIFENOX TECHNICAL ADAMA Agan Ltd, 160132, 90019295 GLP: yes Published: no	ADM
Anonymous.	1978	ACUTE TOXICITY STUDY IN MICE BIFENOX (MCTR-126-78) ADAMA Agan Ltd, 440125, 20982 GLP/GEP: no Published: no	ADM
Anonymous.	2002	BIFENOX: TWENTY-EIGHT DAY REPEATED DOSE DERMAL TOXICITY STUDY IN THE RAT ADAMA Agan Ltd, 644/061 GLP: yes Published: no	ADM
Anonymous .	1979	EVALUATION OF COMPOUND MCTR-12-79 (MRI #248) FOR MUTAGENIC POTENTIAL EMPLOYING THE L5178Y TK+/- MUTAGENESIS ASSAY ADAMA Agan Ltd. 406963, 595-248-7 GLP/GEP: no Published: no	ADM
Anonymous	1986	BIOKINETICS AND METABOLISM IN THE MALE AND FEMALE RAT ADAMA Agan Ltd, 26/08/25 not available GLP: yes Published: no	ADM
Anonymous	2001	EXAMINATION OF BIFENOX IN THE SKIN SENSITISATION TEST IN GUINEA PIGS ACCORDING TO MAGNUSSON AND KLIGMAN (MAXIMISATION TEST) ADAMA Agan Ltd, 14261/01 GLP: yes Published: no	ADM
Anonymous	2005a	MUTAGENICITY STUDY OF BIFENOX IN THE SALMONELLA TYPHIMURIUM REVERSE MUTATION ASSAY (IN VITRO) ADAMA Agan Ltd, 18627/04 GLP: yes Published: no	ADM
Anonymous	2005b	MUTAGENICITY STUDY OF BIFENOX IN THE MOUSE LYMPHOMA FORWARD MUTATION ASSAY - IN VITRO - ADAMA Agan Ltd, 18628/04 GLP: yes Published: no	ADM
Anonymous	2003	MICRONUCLEUS TEST OF BIFENOX TECH. IN BONE MARROW CELLS OF THE NMRI MOUSE BY ORAL ADMINISTRATION" ADAMA Agan Ltd, 17124/1/03 GLP: yes Published: no	ADM
Anonymous	1982	24-MONTH CARCINOGENICITY STUDY IN MICE BIFENOX (MCTR-1-79) ADAMA Agan Ltd, 404836, 21063 GLP: yes Published: no	ADM
Anonymous	1986	RABBIT TERATOLOGY STUDY BIFENOX TECHNICAL REVISED FINAL REPORT ADAMA Agan Ltd, 656-125 GLP: yes Published: no	ADM
Anonymous	1981	EVALUATION OF BIFENOX TECHNICAL (LOT #16230) (MCTR-1-79) IN THE PRIMARY RAT HEPATOCYTE UNSCHEDULED DNA SYNTHESIS ASSAY ADAMA Agan Ltd, 440147, 2314-80 GLP: yes Published: no	ADM
Anonymous	1987	BIFENOX POTENTIAL TUMORIGENIC AND TOXIC EFFECTS IN PROLONGED DIETARY ADMINISTATION TO RATS ADAMA Agan Ltd, 440137, RNP 220/87642 GLP: yes Published: no	ADM

Anonymous	2016	REVERSE MUTATION ASSAY USING BACTERIA (SALMONELLA TYPHIMURIUM AND ESCHERICHIA COLI) WITH BIFENOX TECHNICAL ADAMA Agan Ltd, 160130, 90019663 GLP: yes Published: no	ADM
Anonymous	1981	METAPHASE ANALYSES OF RAT BONE MARROW CELLS TREATED IN VIVO WITH BIFENOX TECHNICAL ADAMA Agan Ltd, 440144, 2312-80 GLP: yes Published: no	ADM
Anonymous	1985	DELAYED CONTACT HYPERSENSITIVITY IN THE GUINEA-PIG WITH BIFENOX, TECHNICAL ADAMA Agan Ltd, 440130, 84676D/RNP 229/SS (G) GLP: yes Published: no	ADM
Anonymous	1985	AN ACUTE INHALATION TOXICITY STUDY OF BIFENOX (TECHNICAL) IN THE RAT ADAMA Agan Ltd, 440127, 85-7809 GLP: yes Published: no	ADM
Anonymous	1985	IN VITRO CHROMOSOMAL ABERRATION ASSAY ON BIFENOX TECHNICAL ADAMA Agan Ltd, 440142, 850027 GLP/GEP: no Published: no	ADM
Anonymous	2016	IN VITRO MAMMALIAN CELL GENE MUTATION TEST (HPRT-LOCUS) IN CHINESE HAMSTER V79 CELLS WITH BIFENOX TECHNICAL ADAMA Agan Ltd, 160131, 90018294 GLP: yes Published: no	ADM

14.3 Environmental Hazard

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	2000a	[14C]-BIFENOX: HYDROLYSIS UNDER LABORATORY CONDITIONS AT PH 4, 5, 7 AND 9 ADAMA Agan Ltd Report-no. RNP 636/002253, 202529 GLP: yes Published: no	ADM
Anonymous	1981	DYNAMIC TOXICITY OF BIFENOX TO BLUEGILL SUNFISH (LEPOMIS MACROCHIRUS) ADAMA Agan Ltd Report-no. 440247, 27115 GLP: yes Published: no	ADM
Anonymous	1986	UPTAKE, DEPURATION AND BIOCONCENTRATION OF 14C-BIFENOX BY BLUEGILL SUNFISH (LEPOMIS MACROCHIRUS) ADAMA Agan Ltd Report-no. 440205 GLP: yes Published: no	ADM
Anonymous	2016	FIELD SOIL DISSIPATION STUDY WITH ONE AUTUMN APPLICATION OF FOX (AG-B2-480 SC) A FORMULATED PRODUCT CONTAINING BIFENOX ON 3 SITES IN NORTH EUROPE AND 2 SITES IN SOUTH EUROPE IN 2014-2015 ADAMA Agan Ltd, S14-04459, R-90017806 GLP: yes Published: no	ADM
Anonymous	1983	BIFENOX SOIL SORPTION STUDY ADAMA Agan Ltd Report-no. 440155, AG/CRLD/An/102.83 GLP/GEP: no Published: no	ADM
Anonymous	1991	THE PROLONGED TOXICITY OF BIFENOX TO RAINBOW TROUT (ONCORHYNCHUS MYKISS) ADAMA Agan Ltd Report-no. 426191, 282/113 GLP: yes Published: no	ADM
Anonymous	1993	THE ACUTE TOXICITY OF BIFENOX TO RAINBOW TROUT (ONCORHYNCHUS MYKISS) ADAMA Agan Ltd Report-no. 432068, 282/388 GLP: yes Published: no	ADM
Anonymous	1999	BIFENOX TECHNICAL - TOXICITY TO THE FRESHWATER DIATOM, NAVICULA PELLICULOSA ADAMA Agan Ltd Report-no. 604634, 10566.6577 GLP: yes Published: no	ADM
Anonymous	1998	BIFENOX - TOXICITY TO THE DUCKWEED, LEMNA GIBBA ADAMA Agan Ltd Report-no. 603461, 98-10-7499 GLP: yes Published: no	ADM

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	2016a	ANAEROBIC TRANSFORMATION OF BIFENOX IN SOIL ADAMA Agricultural Solutions Ltd., Israel, ADM-001/5-31, 90017808 GLP: yes Published: no	ADM
Anonymous	2016b	HYDROLYSIS OF BIFENOX ACID AS A FUNCTION OF PH ADAMA Agricultural Solutions Ltd., Israel, ADM-002/1-35, 90018351 GLP: yes Published: no	ADM
Anonymous	2016c	PHOTOTRANSFORMATION OF BIFENOX IN WATER - DIRECT PHOTOLYSIS ADAMA Agricultural Solutions Ltd., Israel, ADM-001/5-40, 90017809 GLP: yes Published: no	ADM
Anonymous	1994a	SOIL SURFACE VOLATILITY STUDY OF MCPP-P AND BIFENOX FORMULATED AS EXP04404 (OFFICIAL GERMAN REFERENCE N°RPA44040H) ADAMA Agan Ltd Report-no. 94-39, 9416036 GLP: yes Published: no	ADM
Anonymous	1994b	SOIL SURFACE VOLATILITY STUDY OF MCPP-P AND BIFENOX FORMULATED AS EXP30535 (OFFICIAL GERMAN REFERENCE N°RPA30535H) ADAMA Agan Ltd Report-no. 94-38, 9416286 GLP: yes Published: no	ADM
Anonymous	1994a	INVESTIGATION OF THE VOLATILIZATION OF 14C-MCCPP-P AND 14C-BIFENOX FORMULATED ACCORDING TO FOXTRIL SUPER (RPA 30535H) FROM PLANT SURFACES UNDER LABORATORY CONDITIONS ADAMA Agan Ltd Report-no. 94-26, RPA15 GLP: yes Published: no	ADM
Anonymous	1994b	INVESTIGATION OF THE VOLATIZATION OF 14C-MCPP-P AND 14C BIFENOX FORMULATED ACCORDING TO VERIGAL D (RPA44040H) FORM PLANT SURFACES UNDER LABORATORY CONDITIONS ADAMA Agan Ltd Report-no. 94-25, RPA14 GLP: yes Published: no	ADM

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	1989	STUDY ON THE BIODEGRADABILITY OF BIFENOX: ACCORDING TO MODIFIED STURM TEST (OECD GUIDELINE 301 B FOR TESTING CHEMICALS AND THE 6TH AMENDMENT OF THE COUNCIL DIRECTIVE 67/548/EEC, 1984) ADAMA Agan Ltd Report-no. 440153, R 67 006 04 GLP: yes Published: no	ADM
Anonmyous	1992	ADSORPTION OF BIFENOX ACID (5-(2,4-DICHLOROPHENXY)-2-NITROBENZOIC ACID) AND AMINO-BIFENOX (METHYL 5-(2,4-DICHLOROPHENOXY)-2-AMINOBENZOATE) TO SOIL PARTICLES IN THREE SOIL TYPES ADAMA Agan Ltd Report-no. 200131, IMW-R 92/202 GLP: yes Published: no	ADM
Anonymous	1996	BIFENOX TOXICITY TO THE SEDIMENT DWELLING CHIRONOMID LARVAE (CHIRONOMUS RIPARIUS) UNDER STATIC CONDITIONS ADAMA Agan Ltd Report-no. 601283, SA 95480 GLP: yes Published: no	ADM
Anonymous	2005c	DETERMINATION OF THE ADSORPTION/DESORPTION BEHAVIOUR OF AMINOBIFENOX ACID IN THREE DIFFERENT SOILS ADAMA Agan Ltd, 20051049/01-PCAD GLP: yes Published: no	ADM
Anonymous	2015	STATEMENT ON LONG-RANGE TRANSPORT OF BIFENOX IN AIR ADAMA Agan Ltd, 2491115-CA-070302-01 GLP/GEP: no Published: no	ADM

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	2016a	CALCULATION OF SOIL DEGRADATION VALUES FOR BIFENOX AND MAJOR METABOLITE BIFENOX ACID ACCORDING TO THE RECOMMENDATIONS OF THE FOCUS DEGRADATION KINETICS WORKGROUP - STUDY SIMMONDS AND BURR, 1999 ADAMA Agan Ltd, 2491115-CA-070102-01 GLP/GEP: no Published: no	ADM
Anonymous	2016b	CALCULATION OF SOIL DEGRADATION VALUES FOR BIFENOX AND MAJOR METABOLITE BIFENOX ACID ACCORDING TO THE RECOMMENDATIONS OF THE FOCUS DEGRADATION KINETICS WORKGROUP - STUDY SIMMONDS AND BURR, 2000 ADAMA Agan Ltd, 2491115-CA-070102-02 GLP/GEP: no Published: no	ADM
Anonymous	2016c	CALCULATION OF SOIL DEGRADATION VALUES FOR THE METABOLITE BIFENOX ACID ACCORDING TO THE RECOMMENDATIONS OF THE FOCUS DEGRADATION KINETICS WORKGROUP - STUDY HEINTZE, 2003 ADAMA Agan Ltd, 2491115-CA-070102-03 GLP/GEP: no Published: no	ADM
Anonymous	2016d	CALCULATION OF SOIL DEGRADATION VALUES FOR THE METABOLITE AMINOBIFENOX AND AMINOBIFENOX ACID ACCORDING TO THE RECOMMENDATIONS OF THE FOCUS DEGRADATION KINETICS WORKGROUP - STUDIES ANONYMOUS, 2005A AND 2005B ADAMA Agan Ltd, 2491115-CA-070102-04 GLP/GEP: no Published: no	ADM
Anonymous	1999	[14C]-BIFENOX: PHOTODEGRADATION ON SOIL ADAMA Agan Ltd Report-no. 15750, 202111 GLP: yes Published: no	ADM
Anonymous	1999	TECHNICAL BIFENOX DAPHNIA MAGNA REPRODUCTION TEST ADAMA Agan Ltd Report-no. 603539, SA 98275 GLP: yes Published: no	ADM
Anonymous, M.	1998a	TECHNICAL BIFENOX FRESHWATER ALGAL GROWTH INHIBITION STUDY AND RECOVERY PHASE (SCENEDESMUS SUBSPICATUS) ADAMA Agan Ltd Report-no. SA 98087, 603317 GLP: yes Published: no	ADM
Anonymous	1984	SOIL ADSORPTION/DESORPTION OF 14 C-BIFENOX ADAMA Agan Ltd Report-no. 440156, 83-E-354-SD GLP/GEP: no Published: no	ADM
Anonymous	2016	CALCULATION OF WATER/SEDIMENT DEGRADATION VALUES FOR BIFENOX AND MAJOR METABOLITES ACCORDING TO RECOMMENDATIONS OF THE WORK GROUP ON DEGRADATION KINETICS OF FOCUS ADAMA Agan Ltd, 2491115-CA-070202-01 GLP/GEP: no Published: no	ADM

Author(s)	Year	Title Owner Report No. Source (where different from owner) GLP or GEP status Published or not	Owner
Anonymous	1985a	ACUTE TOXICITY OF BIFENOX TO BLUEGILL (LEPOMIS MACROCHIRUS) UNDER FLOW-THROUGH CONDITIONS ADAMA Agan Ltd Report-no. 10566.0985.6102.105, BW-85-10-1867 GLP: yes Published: no	ADM
Anonymous	1985b	ACUTE TOXICITY OF BIFENOX TO DAPHNIA MAGNA UNDER FLOW-THROUGH CONDITIONS ADAMA Agan Ltd Report-no. BW-85-10-1871, 440169 GLP: yes Published: no	ADM
Anonymous	2015	AEROBIC MINERALISATION OF [DICHLOROPHENYL RING-U-14C]BIFENOX IN SURFACE WATER ADAMA Agan Ltd, S14-03889, R-90017805 GLP: yes Published: no	ADM
Anonymous	2016c	MACROPHYTE, GROWTH INHIBITION TEST - BIFENOX (TECHNICAL): SEDIMENT-FREE MYRIOPHYLLUM SPICATUM TOXICITY TEST (OECD 238) SEMI-STATIC CONDITIONS ADAMA Agan Ltd Report-no. ADM-001/4-13/K, 90018357 GLP: yes Published: no	ADM
Anonymous	2016h	MACROPHYTE, WATER-SEDIMENT TOXICITY TEST (OECD 239): BIFENOX (TECHNICAL): SEMI-STATIC WATER-SEDIMENT MYRIOPHYLLUM SPICATUM TOXICITY TEST - TESTING FOR RECOVERY OF GROWTH ADAMA Agan Ltd Report-no. ADM-001/4-12/K, 90019665 GLP: yes Published: no	ADM
Anonymous	1990	21-DAY CHRONIC STATIC RENEWAL TOXICITY OF BIFENOX TO DAPHNIA MAGNA ADAMA Agan Ltd Report-no. 441956, 38461 GLP: yes Published: no	ADM

15 ANNEXES

Annex I to the CLH report