Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Fenoxycarb

EC number: 276-696-7
CAS number: 72490-01-8

ECHA/RAC/CLH-O-0000001884-67-03/A1

Adopted

14 September 2012

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Fenoxycarb**

EC Number: **276-696-7**

CAS number: **72490-01-8**

Registration number (s): -

Purity: Min. > 96%

Impurities: This information is confidential and provided in the confidential part of the dossier (appendix 1).

Proposed classification based on Directive 67/548/EEC:

Carc. Cat. 3; R40

N; R50-53

Proposed classification based on Regulation (EC) No 1272/2008:

	Classification	Wording
Hazard classes, Hazard categories	Carc. 2 Aquatic Acute 1, M-factor 1 Aquatic Chronic 1, M-factor 10 000**	
Hazard statements	H351 *H400 *H410	Suspected of causing cancer Very toxic to aquatic life Very toxic to aquatic life with long lasting effects

*According to the 2nd ATP to CLP Regulation
** Fenoxycarb is not readily biodegradable

Proposed labelling based on Directive 67/548/EEC:

	Labelling	Wording
Hazard Symbols, Indications of danger	Xn N	Harmful Dangerous for the environment
R-phrases	R40 R50/53	Limited evidence of a carcinogenic effect Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-phrases	(S2) S22 S36/37 S60 S61	Keep out of the reach of children Do not breathe dust Wear suitable protective clothing and gloves This material and its container must be disposed of as hazardous waste Avoid release to the environment.

		Refer to special instructions/Safety data sheet.

Proposed labelling based on Regulation (EC) No 1272/2008:

	Labelling	Wording
Pictograms	GHS08 GHS09	
Signal Word	Warning	
Hazard statements	H351 *H410	Suspected of causing cancer Very toxic to aquatic life with long lasting effects.
Precautionary statements	(P102) P260 P273 P281 P308 + P313 P363 P391 P405 P501	(Keep out of reach of children) Do not breathe dust Avoid release to the environment Use personal protective equipment as required IF exposed or concerned: Get medical advice/ attention Wash contaminated clothing before reuse Collect spillage Store locked up Dispose of contents/container to …

*According to the 2nd ATP to CLP Regulation

JUSTIFICATION

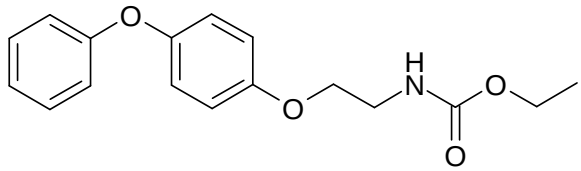
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Fenoxycarb
EC Name:	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate
CAS Number:	72490-01-8
IUPAC Name:	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate

1.2 Composition of the substance

For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.

Chemical Name:	Fenoxycarb
EC Number:	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate
CAS Number:	72490-01-8
IUPAC Name:	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate
Molecular Formula:	$C_{17}H_{19}NO_4$
Structural Formula:	
Molecular Weight:	301.4 g/mol
Typical concentration (% w/w):	
Concentration range (% w/w):	Min. > 96%

1.3 Physico-chemical properties

Table 1 Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	Pure active substance: Odourless white solid (flakes) (purity: 99.2%). Technical active substance: Odourless and colourless to white solidified melt (97.6%).	Das, R. 1999
VII, 7.2	Melting/freezing point	3.2	54.6 °C (purity 99.5 %)	Geoffroy, A. 2007
VII, 7.3	Boiling point	3.3	no boiling until decomposition (> 180 °C) (purity 99.5 %)	Geoffroy, A. 2007
VII, 7.4	Relative density	3.4 density	1.23 (T = 22 °C) (purity: 99.2 %)	Füldner, H. 1992
VII, 7.5	Vapour pressure	3.6	8.67 · 10-7 Pa (25 °C), extrapolated	Rordorf, B. 1992
VII, 7.6	Surface tension	3.10	62.7 mN/m (20 °C) (purity: 97.6 %)	Martin-Keusch, 2007
VII, 7.7	Water solubility	3.8	4.45 mg/L at 10°C, 7.09 mg/L at 20°C, 11.05 mg/L at 30°C (purity: 99.5 %)	Weissenfeld, 2007
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	log Pow: 4.07 at 25 °C (purity: 99.2 %)	Rodler, M. 1992
VII, 7.9	Flash point	3.11	Not required	-
VII, 7.10	Flammability	3.13	Flammable solids: The molten substance does not sustain a flame. Not a highly flammable solid in the sense of Guideline 84/449/EEC, A.10 Flammability in	Schürch, H. 1992a BAM Federal Institute for Materials Research and Testing, Section

			contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids. Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).	II.2 2010

VII, 7.11	Explosive properties	3.14	Guideline 84/449/EEC, A.14: non explosive The substance is not thermally sensitive (effect of a flame). The substance is not mechanical sensitivity of shock. The substance is not mechanical sensitivity of friction.	Schürch, H. 1992c
VII, 7.12	Relative Self-ignition temperature for solids		No self-ignition according Guideline 84/449/EEC, A.16 up to melting point.	Schürch, H. 1992b
VII, 7.13	Oxidising properties	3.15	Max. burning rate test Mixture: 2. 6 mm/s Max. burning rate reference mixture: 3. 4 mm/s The substance has not oxidising properties in the sense of Guideline 84/449/EEC, A.17.	Schürch, H. 1992d
VII, 7.14	Granulometry	3.5	-	-
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	Not applicable	-
XI, 7.16	Dissociation constant	3.21	no dissociation constant	Jäkel, K. 1992
XI, 7.17,	Viscosity	3.22	Not applicable	-
	Auto flammability	3.12	Not Required	-
	Reactivity towards container material	3.18	Fenoxycarb is not corrosive against tin plate, iron steel ST 37 and stainless steel DIN 1.4541	Meyer, 1991
	Thermal stability	3.19	Not applicable	-
	Henry's Law Constant	3.2.1	$3.3 \cdot 10^{-5}$ Pa · m³ / mol (25 °C)	Burkhard, 1998

2 MANUFACTURE AND USES

No registration dossier(s) were available for this substance on 2 August 2011.

3 CLASSIFICATION AND LABELLING

3.1 Current classification based on Directive 67/548/EEC

N; R50-53
(Index number: 006-086-00-6)

3.2 Current labelling based on Directive 67/548/EEC

	Labelling	Wording
Hazard Symbols, Indications of danger	N	Dangerous for the environment
R-phrases	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-phrases	S60 S61	This material and its container must be disposed of as hazardous waste Avoid release to the environment. Refer to special instructions/Safety data sheet.

3.3 Current classification based on Regulation (EC) No 1272/2008

Aquatic Acute 1, H400
Aquatic Chronic 1, H410
(Index number: 006-086-00-6)

3.4 Current labelling based on Regulation (EC) No 1272/2008

	Labelling	Wording
Pictograms	GHS09	
Signal Word	Warning	
Hazard statements	H410	Very toxic to aquatic life with long lasting effects
Precautionary statements		

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier. There is no need for an amendment of the current environmental classification.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

In rats, fenoxycarb was rapidly and almost completely (≥ 90 % of total recovery) absorbed from the gastrointestinal tract (Cheng, 1993, study according to OECD TG 417). The systemically absorbed dose was extensively metabolised and the metabolites were almost completely excreted via faeces (70-80 %) and urine (15-20 %). Neither blood kinetics (C_{max}, AUC, T_{max}, $T_{1/2}$) nor initial tissue distribution of fenoxycarb were explored. Residues after 7 d were low; tissue distribution at this time-point as well as observations in other toxicological studies suggests wide distribution, including main excretory organs (liver, kidney, and lung) and fat. No potential for accumulation was seen.

At least 19 metabolites were observed and the structures of 9 major compounds could be elucidated, while 10-30 % of excreted radioactivity were not identified (Itterly, 1995, study according to OECD TG 417). Although not explored any further *in vivo*, a metabolite of toxicological concern, urethane or O-ethyl carbamate [currently (29^{th} ATP) listed in Annex I to Dir. 67/548/EEC as Carc. Cat. 2; R45], is formed as an intermediate. This minor pathway (about 3-7 % of dose in rats) involves N-dealkylation at the carbamate moiety to yield an acid metabolite and, presumably, urethane. However, up to 20 % of the metabolites remained unidentified and the radiolabel was not designed to follow the fate of the carbamate moiety, so that the actual urethane production from fenoxycarb could be higher. The presence of another, not very well separated but probably minor metabolite implies formation of 1,4-dihydroxybenzene (hydroquinone, Xn, R22-40-41-43-68) and its oxidation product 1,4-benzoquinone (T, R23/25-36/37/38), respectively. For further characterisation, two supplementary *in vitro* metabolism studies were performed in liver and lung microsome cultures derived from different species incl. man. Based on the overall evidence available, the absence of these metabolites in humans could not be proven with sufficiently high certainty (cf sec 5.8 carcinogenicity). It is therefore suggested to treat both urethane and 1,4-benzoquinone as toxicologically relevant metabolites of fenoxycarb.

The dermal absorption of fenoxycarb (formulated as INSEGAR 25 WG) was investigated in a comparative *in vitro* test using rat and human split-thickness skin membranes (Hassler, 2003b, study according to OECD TG 428), and in an *in vivo* test in rats (Hassler, 2003a, Study according to OECD 427). Both, the biocidal product Basilit FP and INSEGAR® 25 WG contain emulsifiers that have the tendency to increase dermal absorption. The presence of such formulants in Basilit FP is therefore accounted for by employing INSEGAR® 25 WG as a test substance. By combining the results from theses studies, the following equation was used to determine the dermal absorption for humans *in vivo*:

$$\%\ \text{absorption [human in vivo]} = \frac{\%\ \text{absorption [human in vitro]}}{\%\ \text{absorption [rat in vitro]}} \times \%\ \text{absorption [rat in vivo]}$$

Absorption rates of approximately 25, 5, and 0.2 % were established for concentrations of 0.05, 0.75, and 61 g/L (corresponding to applied dosages of 0.5, 7.5, and 612 µg/cm2), respectively.

Although not specifically tested, placental transfer of fenoxycarb or metabolites at least in the foetal period can be inferred from the increase in subcutaneous haemorrhages observed in newborn rats in the 2-generation study. Conclusions regarding the excretion with milk cannot be drawn based on the available data.

Absorption of inhaled fenoxycarb has not been studied. Increased liver weights and effects on clinical chemistry parameters in the 21-day inhalation study indicate that absorption occurs in rats; a quantification is not possible, however.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

When administered orally, fenoxycarb was of low acute toxicity with 2/5 mortalities in the high dose females. Histopathology of these animals revealed slight to moderate unicellular and multicellular necrosis in the liver. Common signs of toxicity recorded most pronounced in animals of the high dose groups included sedation, dyspnoea, ventral, latero-abdominal or curved body position, diarrhoea, ruffled fur, spasms and tremor. All surviving animals recovered within 7 to 9 days.

Table 2 Summary of acute oral toxicity

Animal species & strain	**Number of animals per dose level**	**Doses, route of administration, vehicle**	**LD_{50} (mg/kg bw)**	**Reference year**
Rat, KFM-Han Wistar,	5 M + 5 F	3000-5000-8000-10000 mg/kg bw, oral, gavage, polyethylene glycol 400	> 10000 mg/kg bw (limit test); mortality at limit dose: 2/10	Ullmann L (1982), Report No. 007402 Similar to OECD TG 401, non-GLP

5.2.2 Acute toxicity: inhalation

No mortalities were observed. Animals of both sexes exposed to fenoxycarb showed piloerection, hunched posture, dyspnoea and reduced locomotor activity, with recovery within 4 days. A significantly lower body weight gain in the first week of the study was observed, with a compensatory increase in the second week, particularly in females.

Table 3 Summary of acute inhalation toxicity

Animal species & strain	**Number of animals per dose level**	**Doses, route of administration, vehicle**	**LC_{50} (mg/l)**	**Reference year**
Rat, Tif: RAI f albino	5 M + 5 F	4.4 mg/L air x 4h, inhalative, nose-only ethanol (aerosol)	> 4.4 mg/L air (limit test); no mortalities at limit concentration	Hartmann HR (1992), Report No. 911362 OECD TG 403

5.2.3 Acute toxicity: dermal

There were no mortalities or clinical observations related to dermal administration of fenoxycarb.

Table 4 Summary of acute dermal toxicity

Animal species & strain	**Number of animals per dose level**	**Doses, route of administration, vehicle**	**LD_{50} (mg/kg bw)**	**Reference year**

Rat, CD (Sprague-Dawley derived)	5 M + 5 F	2000 mg/kg bw, dermal, corn oil	> 2000 mg/kg bw (limit test), no mortalities at limit dose	Kynoch SR et al. (1981), Report No. 80648D/HLR85/AC Similar to OECD TG 402

5.2.4 Acute toxicity: other routes

No studies with application via other routes are available.

5.2.5 Summary and discussion of acute toxicity

Fenoxycarb exhibited low acute toxicity. As the results do not meet the criteria laid down in Directive 67/548/EEC and Regulation (EC) 1272/2008, no classification and labelling for acute toxicity are needed.

5.3 Irritation

5.3.1 Skin

Fenoxycarb is not irritating to the skin of rabbits.

Table 5 Summary of skin irritation

Animal species & strain	**Number of animals**	**Doses**	**Result**	**Reference**
Rabbit, Hra: (NZW) SPF albino	3 M + 3 F	0.5 g, semi-occlusive, moistened with saline	Negative (according to Draize score, erythema: 0; oedema: 0)	Glaza SM (1992a), Report No. HWI 20800881

5.3.2 Eye

Redness of conjunctiva and chemosis were seen 1 h after instillation of test compound. Effects declined with time and were absent within 72 h. Signs of eye irritation were less severe than the criteria for classification would require.

Table 6 Summary of eye irritation

Animal species & strain	**Number of animals**	**Doses**	**Result** (24/48/72 h)	**Reference**
Rabbit, Hra: (NZW) SPF albino	6 M + 3 F	0.04 g	Negative Cornea opacity: 0.0/0.0/0.0 Iris: 0.0/0.0/0.0 Redness of conjunctivae: 0.9/0.1/0.0 Chemosis: 0.0/0.0/0.0	Glaza SM (1992b), Report No. HWI 20800882

5.3.3 Respiratory tract

Studies on respiratory tract irritation by fenoxycarb are not available.

5.3.4 Summary and discussion of irritation

Fenoxycarb exhibited no irritating potential to skin or eye of rabbits. As the results do not meet the criteria laid down in Directive 67/548/EEC and Regulation (EC) 1272/2008, no classification and labelling for irritation are needed.

5.4 Corrosivity

No corrosion was observed in the studies for dermal or eye irritation. Hence, no classification for corrosivity is needed.

5.5 Sensitisation

5.5.1 Skin

A maximisation test in guinea pigs according to Magnusson and Kligman was performed (Cantoreggi, 1998). At 24 h following administration of a 10 % preparation of fenoxycarb in vaseline, 4/20 animals (20 %) showed an erythematous response.

Table 7 Summary of skin sensitisation

Animal species & strain	Number of animals	Doses	Result	Reference Method
Guinea pig, Himalayan Spotted	10 M + 10 F treated, 5 M + 5 F control	Intradermal: 5 % fenoxycarb in peanut oil Topical: 10 % fenoxycarb in vaseline	Animals sensitised: 24 h after challenge: 4/20 (pos. control: 8/20) 48 h after challenge: 3/20 (pos. control: 9/20) Not sensitising: positive response below classification threshold	Cantoreggi S (1998), Report No. 972170 OECD TG 406 (M&K)

5.5.2 Respiratory system

Studies on respiratory sensitisation by fenoxycarb are not available. Respiratory tract sensitisation is not anticipated

5.5.3 Summary and discussion of sensitisation

According to the classification criteria laid down in directive 67/548/EEC and directive 1272/2008/EC, no classification and labelling for sensitisation are needed.

Classification for respiratory sensitisation is considered not necessary.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

In rats, the main target organ following repeated oral administration of fenoxycarb was the liver as indicated by increased liver weight, hepatocellular hypertrophy, increased cholesterol levels at 50 mg/kg bw/d and above. Other signs of toxicity comprised changes in hematology and thyroid hyperplasia. Hepatomegaly was reversible after a 4-wk recovery period.
In dogs, repeated oral exposure resulted in a reduction in body weight gain, increased liver and kidney weights and a decrease of inorganic phosphorus in plasma.

Table 8 Summary of oral RDT

Animal species & strain	**Number of animals**	**Doses, vehicle, duration**	**Result**	**Reference**
Rat, KFM Han, SPF, Wistar	10 M + 10 F	0-10-50-200-1000 mg/kg bw/d, gavage, carboxymethlycellulose, 28 d	NOAEL: 10 mg/kg bw/d LOAEL: 50 mg/kg bw/d Main effects: *Liver*: Hepatomegaly *Thyroid*: Follicular hyperplasia *Hematology:* ↓ prothrombin time (F)	Suter P (1986), Report No. 056283 / 850908
Rat, Tif:RAIf (Sprague-Dawley derived)	10 M + 10 F	2.2/2.3-9.7/10,1-45/50-199/203 (M/F), (0-30-150-750-3000 ppm), dietary, no vehicle, 3 mo	NOAEL: 10 ,mg/kg bw/d LOAEL: 45 mg/kg bw/d Main effects: *Liver*: Hepatocyte hypertrophy *Clinical chemistry*: Changes in plasma protein, cholesterol and liver enzyme levels *Thyroid*: Hypertrophy of follicular epithelium	Bachmann M (1993), Report No. 922116
Dog, beagle	4 M + 4 F	0-25-80-260 mg/kg bw/d, capsule, no vehicle, 1 yr	NOAEL: 25 mg/kg bw/d LOAEL: 80 mg/kg bw/d Main effects: *Liver*: Increased weight *Adrenal*: Decreased weight *Clinical chemistry*: Decreased inorganic phosphorus	Keller-Rupp P (1988), Report No. B-153778

5.6.2 Repeated dose toxicity: inhalation

The inhalation study in rats revealed a reversible effect on the lung (increase in relative organ weight in M) and increased liver weight (14 % in M (relative) and 27/36 % in F

(absolute/relative) at a concentration of 1 mg/L air. No changes in clinical chemistry parameters were observed.

Table 9 Summary of inhalation RDT

Animal species & strain	**Number of animals**	**Doses, vehicle, duration**	**Result**	**Reference**
Rat, Wistar, KFM-Han., outbred,	5 M + 5 F	0.01-0.1-1.0 mg/L, ethanol, nose-only exposure, 6 h/d, 21 d	NOAEL: 0.1 mg/L; LOAEL: 1 mg/L, Main effects: *Liver, lung*: Increase in weight	Bernstein DM, et al. (1987), Report No. RCC-085500

5.6.3 Repeated dose toxicity: dermal

After repeated dermal exposure an increased liver weight and hepatocellular hypertrophy were observed in rats.

Table 10 Summary of dermal RDT

Animal species & strain	**Number of animals**	**Doses, vehicle, duration**	**Result**	**Reference**
Rat, Wistar, KFM-Han.	5 M + 5 F	0, 20, 200, 2000 mg/kg bw/d, occlusive, corn oil, 6 h/d, 21 d	NOAEL: 200 mg/kg bw/d LOAEL: 2000 mg/kg bw/d Main effects: *Liver*: Increase in weight, hepatocellular hypertrophy	Varney P (1985), Report No. 4552-161/157

5.6.4 Other relevant information

None

5.6.5 Summary and discussion of repeated dose toxicity:

The oral NOAEL in rats was 10 mg/kg bw/d based on liver effects (increased liver weight, hepatocellular hypertrophy (F) and increased cholesterol levels) at 45 mg/kg bw/d in the 90-d study. The dermal NOAEL in rats was 200 mg/kg bw/d, based on the results of the 21-d study. The inhalative NOAEL in rats was 0.1 mg/L air based on liver and lung weight increase at 1.0 mg/L air in the 21-d study (6 h exposure/day). The oral NOAEL in dogs was 25 mg/kg bw/d.
No respective classification and labelling are required.

RAC evaluation of Repeated dose toxicity

Summary of the dossier submitter's proposal

In rats, the main target organ following repeated oral administration of fenoxycarb was the liver as indicated by increased liver weight, hepatocellular hypertrophy, increased cholesterol levels at 50 mg/kg bw/d and above. Other signs of toxicity comprised changes in hematology and thyroid hyperplasia. Hepatomegaly was reversible after a 4-wk recovery period.

In dogs, repeated oral exposure resulted in a reduction in body weight gain, increased liver and kidney weights and a decrease of inorganic phosphorus in plasma.

The inhalation study in rats revealed a reversible effect on the lung (increase in relative organ weight in M) and increased liver weight (14 % in M (relative) and 27/36 % in F (absolute/relative) at a concentration of 1 mg/L air. No changes in clinical chemistry parameters were observed.

After repeated dermal exposure an increased liver weight and hepatocellular hypertrophy were observed in rats.

<u>*Summary and discussion of repeated dose toxicity*</u>
The oral NOAEL in rats was 10 mg/kg bw/d based on liver effects (increased liver weight, hepatocellular hypertrophy (F) and increased cholesterol levels) at 45 mg/kg bw/d in the 90-d study. The dermal NOAEL in rats was 200 mg/kg bw/d, based on the results of the 21-d study. The inhalative NOAEL in rats was 0.1 mg/L air based on liver and lung weight increase at 1.0 mg/L air in the 21-d study (6 h exposure/day). The oral NOAEL in dogs was 25 mg/kg bw/d.
No classification and labelling was proposed by the dossier submitter.

Comments received during public consultation

One MSCA comments that the dossier submitter states that liver effects are observed at 45 mg/kg bw/day in the 90 day rat study. The MSCA further comments that these effects occur within the range for classification in STOT-RE 2 (10<C≤100 mg/kg bw/day), but that without more information on the severity of these effects the reader cannot form an opinion on whether they are relevant for classification. The dossier submitter is asked to provide, in the response to comments table, an indication of the severity of these effects and a justification as to why you did not consider these effects relevant for classification.
The dossier submitter is also asked to consider that fenoxycarb is a peroxisome proliferator type enzyme inducer in discussions on the relevance of observed liver effects to humans.

The dossier submitter provided data from the the 90-d rat study by Bachmann (1993); larger liver was seen in 2/10 females and centrilobular hypertrophy in 8/10 females at a dose level of 750 ppm (49.6 mg/kg bw/d). No effects on liver were observed in males of this dose level. The dossier submitter maintains that these findings are considered not sufficient to propose classification with STOT-RE 2

RAC assessment - comparison with the classification criteria and justification

The CLP Regulation and the guidance give the following criteria for classification :
"Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations" CLP table 3.9.1

"Significant means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant" CLP guidance 3.9.2.2

<u>Guidance ranges are by oral exposure : 10<C<or = 100 mg/kg body weight/day, by inhalation</u>

0.02<C<or = 0.2 mg/litre/6 h/day and for dermal exposure 20<C<or = 200 mg/kg body weight/day

Considering the available data by oral route hepatomegaly was observed at 50 mg/kg. This is within the guidance values for STOT RE 2 but effect was reversible after 4 weeks recovery period. By inhalation and dermal route of exposure an increased liver weight and hepacellular hypertrophy were observed. No information was given on the reversibility but it was above the guidance values for classification in Category 2.

Although an impact on liver was observed in several studies, of different duration of exposure, and among several species, even when effects were above guidance values for oral route, the effects were considered as not severe enough to warrant classification : reversible [hypertrophy reversible, few females with enlarged liver (2/10 F)] and adaptative. Since effects are not considered for classification, no further consideration was given on potential of peroxisome proliferation in this section of the report but further details is considered in carcinogenicity section.

No classification for STOT RE is proposed.

5.7 Mutagenicity

5.7.1 In vitro data

In vitro and *in vivo* tests provided no evidence for a genotoxic potential of fenoxycarb.
An Ames test performed with and without S9 mix in the *S. typhimurium* strains TA1535, TA 1537, TA 1538, TA 97, TA 98, TA 100 and TA 102 revealed no increased incidence of back mutations, indicative of a mutagenic response in any strain. The test material did not induce growth inhibiting effects at the concentrations tested in the original experiment, but slight reduction in background growth was observed occasionally in the confirmatory experiment (preincubation assay).
In an *in-vitro* mammalian chromosome aberration test in CHO cells no statistically significant increase in the number of metaphases with specific chromosomal aberrations was detected at any concentration tested. There was no significant increase in the number of specific and unspecific chromosomal aberrations at any concentration. Marked cytotoxicity was observed at the concentrations of 25 µg/mL and above.
In an HPGRT forward mutation assay in CHO cells performed with and without microsomal activation comparison of the number of 8-azaguanine resistant cells (Ag^r cells) revealed no significant deviations between cultures treated with fenoxycarb and negative solvent controls. Cytotoxicity after treatment was observed at 1 µg/mL without and 50 µg/mL with metabolic activation.

Table 11 Summary of in vitro mutagenicity

Test system	**Test object**	**Concentration**	**Results**	**Reference and year**

Ames test Similar to OECD TG 471	*S. typhimurium*, strains TA 1535, TA 1537, TA 1538, TA 97, TA 98, TA 100 and TA 102	*Original test*: 0-15.8-50.0-158-500-1580 µg/plate *Confirmatory test (preinc.)*: 0-10-31.6-100-316-1000 µg/plate	- S9: negative + S9: negative Slight reduction in background growth in preincubation assay	Gocke E (1988), Report No. B-153'219
Mammalian chromosome aberration test, OECD TG 473	Chinese hamster ovary cells	*–S9*: 6.3-9.4-12.5-18.8-25.0 µg/mL *+S9*: 9.8-19.5-30.0-39.1-40.0-60.0 µg/mL	- S9: negative + S9: negative - *S9*: Marked cytotoxicity ≥ 25 µg/mL + *S9*: Cytotoxicity ≥ 60 µg/mL	Ogorek B (1998), Report No. 972169
HGPRT-forward mutation assay, pre-guideline	Chinese hamster V79 lung fibroblasts	–S9: 0-1-5-25 µg/mL *+S9*: 0-25-50-100 µg/mL	- S9: negative + S9: negative - *S9*: Cytotoxicity at ≥ 1 µg/mL + *S9*: Cytotoxicity at ≥ 50 µg/mL	Strobel R (1982), Report No. B-96728

5.7.2 In vivo data

In vivo, a micronucleus test was performed. At all sampling times (16, 24, and 48 hours), no significantly increased incidence of micronucleated polychromatic erythrocytes were noted after treatment of the animals with the various doses of fenoxycarb. In contrast, a significant increase in the number of micronucleated polychromatic erythrocytes was noted in the positive control group.
The ratio of polychromatic to normochromatic erythrocytes after treatment with fenoxycarb indicated no cytotoxic effects on blood forming cells. The animals treated at all doses of fenoxycarb showed no symptoms of toxicity.

Table 12 Summary of in vivo mutagenicity

Test system	**Method**	**Route of administration, doses vehicle, sampling times**	**Toxic dose**	**Result**	**Reference**
Mouse, Tif:MAGf	Micronucleus test, bone marrow, OECD TG 474	Gavage, 0-1250-2500-5000 mg/kg bw in arachis oil, 16 h, 24 h, 48 h (16, 48 h: control and high dose only)	-	No symptoms of toxicity at all dose levels and sampling times. No increase in micronuclei	Ogorek B (1996), Report No. 962052

5.7.3 Human data

No human data are available.

5.7.4 Other relevant information

No other relevant information is available.

5.7.5 Summary and discussion of mutagenicity

In vitro and *in vivo* tests provided no evidence for a genotoxic potential of fenoxycarb.
No classification and labelling regarding mutagenicity are required.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

No increased rate of neoplastic lesions was observed in rats up to and including 74 mg/kg bw/d. The NOAEL in mice was 6 mg/kg bw/d based on an increased rate of lung and liver tumours in males at 61 mg/kg bw/d in the 78-wk study when compared to concurrent and historic controls.

Table 13 Summary of oral carcinogenicity

Animal species & strain	**Number of animals**	**Doses, vehicle, duration**	**Result**	**Reference**
Rat, Crl:CD(SD)BR	50 M + 50 F, interim sacrifice: 10 M + 10 F	8.1-24.7-74.4 mg/kg bw/d (200-600-1800 ppm) 102 wk	No increased tumour incidence	Goodyer MJ (1992), Report No. 5191-161/123 R
Mouse, Tif:MAGf (SPF)	60 M + 60 F	1-6-61/57-247/224 mg/kg bw/d (M/F) (10-50-500-2000 ppm) 78 wk	≥ 61 mg/kg bw/d (≥ 500 ppm): Increased incidence of lung adenoma/carcinoma (M), hepatoma, hepatocellular carcinoma (M) 224 mg/kg bw/d (2000 ppm): Increased incidence of lung adenoma/carcinoma (M+F)	Bachmann M (1995), Report No. 922117

Table 14 Summary of neoplastic findings in the mouse

Intergroup comparison of incidence of neoplastic microscopic findings in males

		Dietary concentration of fenoxycarb (ppm)					
Findings		**hist. contr.**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		**300**	50	50	50	50	50
Lung	**Adenoma**	57 19 %	8 16 %	8 16 %	4 8 %	14 28 %	16 32 %
	Carcinoma	17 6 %	1 2 %	3 6 %	1 2 %	10 20 %**	10 20 %**
	adenoma or carcinoma	72 24 %	9 18 %	11 22 %	5 10 %	21 42 %**	22 44 %**
Liver	**Benign hepatoma**	83 28 %	11 22 %	12 24 %	9 18 %	13 26 %	16 32 %
	Hepatocellular carcinoma	25 8 %	8 16 %	4 8 %	12 24 %	17 34 %*	21 42 %**
	Benign hepatoma or hepatocellular carcinoma	91 30 %	16 32 %	13 26 %	17 34 %	25 50 %**	29 58 %**

*p<0.05, ** p < 0.01

Intergroup comparison of incidence of neoplastic microscopic findings in females

		Dietary concentration of fenoxycarb (ppm)					
Findings		**hist. contr.**	**0**	**10**	**50**	**500**	**2000**
Number of tissues examined		300	50	50	49	50	50
Lung	**Adenoma**	21 7 %	1 2 %	5 10 %	4 8 %	6 12 %	11 22 %**
	Carcinoma	13 4 %	2 4 %	2 4 %	2 4 %	3 6 %	9 18 %*
	Adenoma or carcinoma	33 11 %	3 6 %	7 14 %	6 12 %	9 18 %	20 40 %**

*p<0.05, ** p < 0.01

5.8.2 Carcinogenicity: inhalation

No data are available.

5.8.3 Carcinogenicity: dermal

No data are available.

5.8.4 Carcinogenicity: human data

No data are available.

5.8.5 Other relevant information

Mechanistic considerations:

Fenoxycarb strongly induces hepatic xenobiotic metabolising enzymes in mice and can be classified as a peroxisome proliferator type inducer, but does not show inductive properties on pulmonary xenobiotic metabolising enzymes *in vitro*.

Following *in vitro* incubation of liver microsomes from rat, mouse, marmoset, and man with fenoxycarb, formation of two potential carcinogens, O-ethyl carbamate (urethane) and benzoquinone/hydroquinone was observed and monitored via HPLC and GC-MS.

When compared with mice and rats, human liver microsomes showed on average an at least ten-fold lower formation rate of ethyl carbamate and benzoquinone/hydroquinone. Carcinogenicity of hydroquinone in the animal model is predominantly associated with renal adenoma in the rat by a presumably non-genotoxic mode of action via exacerbation of chronic progressive nephropathy in rats (McGregor, 2007) which was considered non-relevant for humans. IARC concluded 1999 that there is inadequate evidence in humans for the carcinogenicity of hydroquinone and limited evidence in experimental animals for the carcinogenicity of hydroquinone.

Lung tumour induction by urethane reveals a clear dose-response relationship (Schmaehl et al., 1977; Inai et al., 1991). The NOAEL for this endpoint was 0.5 mg/kg bw/d and the LOAEL 2.5 mg/kg bw/d in rodents. In the present 18-month mouse study the LOAEL was 57 mg/kg bw/d. Taking into account that 5-10 % of fenoxycarb in rats are possibly metabolised to urethane and that urethane formation is, at least *in vitro,* more prominent in mice, approx. 2 mg/kg bw/d urethane (~ the neoplastic LOAEL of urethane) could have been formed in the 18-month mouse study. This mechanism is relevant for human exposure since it could be shown in a mechanistic study that human liver microsomes metabolise fenoxycarb to urethane. In an assay containing fenoxycarb at 100 µmol/L, the microsomal production of urethane in descending order was male mouse (pretreated with fenoxycarb) > marmoset > female mouse (pretreated), male mouse (control) > male rat > female rat, female mouse (control) > human, resulting in normalised rates (nmol/mg protein) of 2.83 > 1.41 > 0.90, 0.89 > 0.50 > 0.44, 0.43 > 0.05 (0.00, 0.06, 0.10 in the three individual human samples), respectively. The formation of urethane is 11-350 times slower in human microsomes than it is in mouse microsomes and urethane concentrations in human microsomes are 3-70fold lower, but due to the high interindividual variation of urethane formation in human microsomes this metabolite is regarded relevant for man. Fenoxycarb was not metabolised by lung microsomes from any of the species tested under the conditions of the assay but the quality of the lung microsome fractions with regard to metabolising capacity is not clear. Their preparation is considered to be more difficult than liver microsome preparations (personal communication, U. Bernauer, BfR) and positive controls for metabolic function were not included in the assay. If the finding is reliable, it would indicate that local production of urethane in the lung is unlikely to play a prominent role in the induction of lung cancer but also that this metabolite is stable enough *in vivo* to be transported to the lung from the tissue of origin (presumably the liver).

Regarding the *in vivo* situation, there are recent findings that different mice strains reveal dissimilar lung cancer susceptibility towards urethane: BALB/c and A/J mice are susceptible for lung cancer formation while C57B6 are resistant (Stathopoulos et al. 2007; Manenti et al., 2008) suggesting that there might be toxicokinetic or toxicodynamic differences that could alter susceptibility. Several lines of evidence suggest that urethane has to be activated by P450 enzymes to yield vinyl carbamate epoxide which forms DNA and protein adducts and acts as the ultimate carcinogen. CYP2E1 has been identified as the main enzyme responsible for this oxidation of urethane, demonstrated by the resistance of Cyp2e1 knock-out mice to urethane-induced tumours. It has been estimated that 96 % of an urethane dose are metabolised to vinyl carbamate by Cyp2e1 in mice and that other P450 enzymes account for most of the remainder (Ghanayem, 2007). Moreover, the tumour susceptibility of different strains of mice shows a positive correlation with the amount and activity of Cyp2e1 protein in their lung tissue (reviewed by Forkert, 2010). With respect to CYP2E1 expression and activity in human tissues, results appear contradictory. While Choudhary et al. (2005) noted expression of this enzyme in human liver but not in lung, Forkert et al. (2001) detected

CYP2E1 activity in human lung microsomes. Therefore, it must be assumed that, even though fenoxycarb is not metabolised to any great extent by human lung microsomes, the tissue is capable of activating urethane that is generated in other tissues and distributed to the lung. The higher sensitivity of mice as compared to rats for carcinogenic effects of fenoxycarb exposure can be considered to result from the combination of at least two parameters: an inducible metabolism of fenoxycarb by liver enzymes which yields greatly increased amounts of urethane, especially in the males, and the presence/activity of Cyp2e1 in lung tissue which results in formation of the ultimate carcinogen.
In contrast to urethane, no positive findings were seen with fenoxycarb in an *in vivo* micronucleus assay in mice (cf. 5.7.2) and in a mechanistic study for DNA adduct formation after treatment with 440 mg/kg bw fenoxycarb. In the positive control group treated with 20 mg/kg bw urethane 38 % of the recovered radioactivity in liver DNA associated with adducts. The result of the micronucleus test could be considered a false negative as the amount of urethane produced after a single dose of fenoxycarb must have been far below the doses which have been associated with positive micronuclei findings in published studies on urethane. The situation could be different in repeat-dose studies, such as the carcinogenicity study. In addition, the sensitivity of the DNA adduct study can be questioned on the grounds that urethane itself which was used as a positive control gave only very slightly positive results (CBI 0.09-0.8). This is not in accordance with published data for urethane (CBI 23-80, Review: see Lutz, 1979) nor in accordance with the applicant's statement, that a genotoxic substance with a TD_{50} of 1-10 mmol/kg bw has an expected CBI of 2-9. However, both tests in combination seem to indicate the existence of a threshold for genotoxicity from fenoxycarb.

Table 15 Mechanistic studies – formation of possible carcinogenic metabolites

Method/ Guideline	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results**	**Carcinogenic metabolites**	**Remarks**	**Reference**
In vitro metabolism in liver and lung No guideline applicable Non-GLP study	Lung and liver microsomes *Rat*: Tif:RAIf(SPF), 6 M + 6 F *Mouse*: Tif:MAGf(SPF), 30 M + 30 F *Marmoset*: 1 M + 2 F *Human*: 3 (liver) + 2 (lung), sex of donors not specified	100 µmol/L 30 mice/sex were pretreated for 14 days with 5000 ppm fenoxycarb (admixed to the diet)	*Lung*: No metabolism *Liver*: Extensive oxidative metabolism, >15 metabolites found	Urethane (O-ethyl carbam-ate), 1,4-dihydroxy-benzene (hydroquinone)/1,4-benzo-quinone	None	Beilstein P (1997), Report No. CB 95/45

Method/ Guideline	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results**	**Carcinogenic metabolites**	**Remarks**	**Reference**
In vitro formation of urethane No guideline applicable Non-GLP study	Mouse (Tif:MAGf) and human microsomal fractions from previous *in vitro* metabolism study [Beilstein P (1997), Report No. CB 95/45]	100 µmol/L 30 mice/sex were pretreated for 14 d with 5000 ppm fenoxycarb (admixed to the diet)	Formation of urethane *Mice*: Specific activities of 162.7 and 331.9 pmol/min/mg protein for control and pretreated animals, respectively *Humans*: High inter-individual variation in humans: specific activities ranging from 0.94 – 14.84 pmol/min/mg protein	Urethane	None	Beilstein P (1998), Report No. CB 97/16
Formation of urethane-derived DNA adducts *in vivo/in vitro* No guideline applicable	*Mouse*: Tif:MAGf(SPF) hybrids of NIH x MAG 56 M (9 groups)	Pretreatment group: 200 ppm for 14 d, All mice (d 17): single dose of [^{14}C]fenoxycarb (2-440 mg/kg bw) or [^{14}C]urethane (20 mg/kg bw) + control	*Liver*: peroxisome proliferator-type enzyme induction *DNA*: No urethane-derived DNA adducts in liver	Urethane	No analysis performed with lung DNA	Sagelsdorff P (1998), Report No. CB 96/48

Table 16 Mechanistic studies – liver enzyme induction

Method/ Guideline	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results**	**Reference**
Induction of liver enzymes No guideline applicable, non-GLP	Mouse, Tif:MAGf(SPF) 20 M + 20 F	Oral, dietary 0-10.1/10.0-92.9/91.7-365.0/361.6 (M/F) (0-50-500-2000 ppm) 14 d	Increase in cytochrome P450 content: up to 166% (high-dose M) Increase in lauric acid 12-hydroxylation: up to 1254 % (high-dose females) Increase in fatty acid beta-oxidation: up to 243 % (high-dose females) Increase in CYP4A isoenzymeprotein levels: 5.2 fold increased intensity in Western Blot analysis NOEL: < 10 mg/kg bw/d LOEL: 10 mg/kg bw/d	Beilstein**,** 1996a Report No. CB 95/36

Enzyme induction in murine lung No guideline applicable	Mouse, Tif:MAGf(SPF) 20 M + 20 F	Oral, dietary 0-10.1/10.0-92.9/91.7-365.0/361.6 (M/F) (0-50-500-2000 ppm) 14 d	No effects detected	Beilstein, 1996b Report No. CB 95/46
DNA replication in murine lung and liver No guideline applicable	Mouse, Tif:MAGf(SPF) 5 M	Oral, dietary 7-d and 42-d treatment groups, 28-d recovery group: 0-302.9/271.1 (M/F) (0-2000 mg/kg feed) 14-d and 42-d treatment groups: 0-8.5/7.2-75.0/68.7-297.5/259.5 (M/F) (0-50-500-2000 mg/kg feed)	Liver: Slightly increased DNA replication index Lung: No effect	Weber, 1996 Report No. CB 95/03

5.8.6 Summary and discussion of carcinogenicity

Increased rates of tumours were observed in a 18-month study in mice. A NOAEL of 6 mg/kg bw/d established for neoplastic lesions in lung (adenoma, carcinoma) and liver (benign hepatoma, carcinoma) with a LOAEL of 57 mg/kg bw/d.
In principle, it could be shown that the formation of two potential carcinogenic metabolites, O-ethyl carbamate (urethane) and benzoquinone/hydroquinone is possible in human liver microsomes, even though the amounts produced are lower than for the other mammalian species tested. In addition, it has been shown that human lung and liver have the enzymatic capacity of metabolising urethane to the more proximal carcinogenic metabolites vinyl carbamate and vinyl carbamate epoxide. Thus, it is not possible to rule out the toxicological relevance of these potentially carcinogenic metabolites for humans *in vivo*.
Since all mutagenicity tests with fenoxycarb including an *in vivo* micronucleus test were negative and a mechanistic study with urethane as positive control indicated that no urethane-like DNA adducts were detected after exposure to 440 mg/kg bw fenoxycarb, a threshold *in vivo* could be anticipated for tumour formation. Based on the findings described above, fenoxycarb is a suspected human carcinogen contingent on dose level and exposure duration.
According to Directive 67/548/EEC, classification of fenoxycarb regarding carcinogenicity as Carc. Cat. 3; R40 and labelling with Xn, R40 is proposed.
According to Regulation (EC) No 1272/2008, classification of fenoxycarb regarding carcinogenicity as Carc. 2 (H351) is proposed.

RAC evaluation of Carcinogenicity

Summary of the dossier submitter's proposal

The dossier submitter's proposal is based on carcinogenicity studies and mechanistic consideration.

Two carcinogenicity bioassays (1 rat, 1 mice) are reported, with information presented in the dossier limited to a brief summary and two summary tables. No effects were observed in the rat carcinogenicity study (Goodyear, 1992). In the mice study (Bachmann, 1995), a statistical increase in incidence of lung carcinoma and hepatocellular carcinoma were found in males from 500 ppm (corresponding to 61 mg/kg bw/day) dietary concentration of fenoxycarb. In females, a statistical increase in incidence of lung adenoma and adenocarcinoma were found at the high dose of 2000 ppm (corresponding to 224 mg/kg bw/day) in the diet. The dossier submitter concluded that increased rates of lung and liver tumours were observed in the study in mice.

Note: At the end of the CLH dossier, in section "Other information", an additional comment (initially presented under the biocidal evaluation) is presented to justify classification for carcinogenicity and a mice study (Everett, 1987) is mentioned with no details are provided ; besides this information is apparently not further considered in the conclusion of the dossier submitter.

Detailed information is also presented on investigative work supportive of the plausible link between **lung** tumors in mice and formation of two potential carcinogenic **metabolites (urethane** and benzoquinone/hydroquinone**)** on one hand and the possible role of **peroxisome proliferation for liver** tumors on the other hand**.**

The dossier submitter concluded that it is not possible to rule out the toxicological relevance of the formation of these carcinogenic metabolites for human *in vivo* since:

- the formation of these two carcinogenic metabolites is possible un human liver microsomes, although amounts lower than other species tested (mice being the most sensitive species) ;
- human lung and liver have enzymatic capacity of metabolizing urethane (ethylcarbamate) to the more carcinogenic metabolites (vinyl carbamate epoxide).

The dossier submitter discussed the possibility that "the higher sensitivity of mice when compared to rats can be considered to result from the combination of at least two parameters: an inducible metabolism of fenoxycarb by liver enzymes which yields greatly increased amounts of urethane, especially in males, and the presence/activity of Cyp2e1 in lung tissue which results in formation of the ultimate carcinogen."

Furthermore, the dossier submitter view was that the negative results in both a micronucleus test and a DNA adduct study conducted with fenoxycarb in combination seem to indicate the existence of a threshold for genotoxicity from fenoxycarb, despite concerns related to the acceptance of the results (single dose of fenoxycarb only in the micronucleus test, weak positive results with urethane used as positive control in the DNA adduct study).

The dossier submitter assumed that liver tumors in mice could be ascribed to peroxisome proliferation as increases in enzyme activity were shown in the liver at dose levels of fenoxycarb relevant for liver tumour formation. However, this point is not further considered in the conclusion so it is not clear what it is considered for classification (dossier submitter concluded that fenoxycarb induced lung and liver tumours in mice).

Based on the above, according to Regulation (EC) No 1272/2008, classification of fenoxycarb regarding carcinogenicity as **Carc. 2 (H351)** is proposed. According to Directive 67/548/EEC, classification of fenoxycarb regarding carcinogenicity as **Carc. Cat. 3; R40** and labeling with **Xn; R40** is proposed.

Comments received during public consultation

There was no disagreement with the proposed classification in the comments received after public consultation. Member States asked for more detailed information regarding the carcinogenicity study results, specifically regarding the second carcinogenicity mice study (Everett, 1987), with details on Harderian gland tumors, and a clarification of the rationale for classification (comparison with criteria).

- **Information received during public consultation**

Everett study (1987) was presented in the RCOM:

A 80 week combined toxicity study with a 52 weeks interim sacrifice at doses was performed at : 0, 30, 110, 420 mg/kg food for males and 0, 20, 80, 320 mg/kg food for females.

Results for Carcinogenicity:

After 80 weeks of treatment, no effects were noted on mortality, clinical signs, body weights, food consumption and haematology parameters.
At high dose, LDH levels were increased in males after 80 weeks (142 % of controls) and liver weights were increased. Histopathology of livers from all animals did not reveal any morphological changes.

Neoplastic lesions were found in lungs. A statistically significant trend was found for higher incidences of alveolar/bronchiolar tumours (benign and malignant combined) in males of all treated groups. Malignant tumour incidences were not statistically different to controls for any doses. Multiplicity was also increased. All other findings were found to be within the range of normal background pathology or were typical age related degenerative changes in mice.

An expert opinion on the findings in the lungs was included in the study file and arguments were presented to question the biological relevance of higher tumours incidences in the lungs in this study. However this examination was not performed blindly and no individual data were presented. Although full sectioning of the lungs may seem advantageous to detect undiagnosed tumours, comparison with historical data is no longer possible, which is an essential part of the evaluation of carcinogenicity study outcome. Also, proper statistical tests were lacking.

Based on the above considerations, it was concluded that fenoxycarb exhibited an oncogenic potential in mice based on higher incidences of alveolar/bronchiolar tumours in the lungs of males of all treated groups.

Conclusions from this study:

There was an increase in lung tumors in male mice (positive trend but not statistically significant when compared to the controls).
The information in this study is considered limited because of shortcomings :

- The chosen levels for the high dose groups were considered too low to represent a Maximum Tolerated Dose
- No historical data
- No data were presented on clinical signs and statistical evaluations were limited

RAC assessment - comparison with the classification criteria and justification

Results from carcinogenicity data:

3 studies are available. No effects were observed in the rat carcinogenicity study (Goodyear, 1992). In the mouse study of Everett (1987), there was an increase in lung tumors in male

mice: a positive trend but not statistically significant when compared to the controls. The study is considered as insufficient for assessment. In the second mouse study (Bachmann, 1995), performed according to guidelines and GLP, positive findings were reported:

- In **males**: a statistical increase in incidence of **lung** carcinoma and **liver** (hepatocellular) carcinoma were found from 500 ppm (corresponding to 61 mg/kg bw/day) dietary concentration of fenoxycarb. The same incidence was observed at 500 and 2000 ppm.
- In **females**: a statistical increase in incidence of lung adenoma and adenocarcinoma were found at the high dose of **2000** ppm (corresponding to 224 mg/kg bw/day) in the diet

Mechanistic considerations - Discussion on metabolites:

It was emphasized during discussions that genotoxicity of the substance and its metabolite ethylcarbamate should be developed in order to conclude.

*Introduction on **ethyl carbamate (urethane**)*

Ethylcarbamate has been classified as a group 2A carcinogen (probably carcinogenic to humans) by the IARC (2010). Ethylcarbamate has been shown to be carcinogenic in several species including mice following administration by different routes including oral route and producing, among others, lung & liver tumours, as well as harderian gland tumors. It also induces other tumors such as lymphomas, hemangiosarcomas, melanomas and vascular tumours; it is an initiator for skin carcinogenesis in mice (http://www.ncbi.nlm.nih.gov/pubmed/15625555).

A number of publications showed that ethyl carbamate is a genotoxic carcinogen that requires metabolic *in vivo* activation by P450 2E1 to vinyl carbamate epoxide which forms DNA and protein adducts and acts as the ultimate carcinogen, metabolism considered as relevant for humans according to IARC.

Ethylcarbamate and fenoxycarb:

Formation: The formation of ethylcarbamate from fenoxycarb was clearly observed ***in vitro*** in different species including in **humans' liver** cells, although the rate of formation was slower and lower for human (the highest rate was observed for mice). The results from the *in vitro* study in lung cells were negative for all species: human, rat, mouse, marmoset. There is no available data *in vivo*.

Genotoxicity: Fenoycarb is not genotoxic *in vitro* nor *in vivo* then a threshold could be anticipated for tumor formation of fenoxycarb. However, one could consider these negative results are "questionable" as they may reflect the formation of genotoxic metabolite (ethylcarbamate) at levels below the limit of detection level. The involvement of ethylcarbamate cannot be ruled out but whether ethylcarbame is involved or not, it is generally considered that unless proven otherwise by data there is no threshold for genotoxicants.

Tumors' profile: there is some positive trend in tumours formation for ethylcarbamate and fenoxycarb:

- Fenoxycarb and ethylcarbamate provides similar main tumors: lung and liver (and Harderian gland) in mice and not rat (case of Harderian gland clarified during RCOM with data provided, not presented here) and
- Amount seems to correspond if it is assumed that ethylcarbamate is a metabolite of fenoxycarb, see some summarized values in table below.

Table : Incidences of lung tumors for ethylcarbamate and fenoxycarb (synthesized)

LUNG	Ethyl carbamate				Fenoxycarb			
Dose (ppm)	*0*	*10*	*30*	*90*	*0*	*10*	*50*	*500*
Carcinoma or Adenoma M	5/48	18/48	29/47	37/48	9/50	11/50	5/50	21/50
Carcinoma or Adenoma F	6/48	8/48	28/48	39/47	3/50	7/50	6/49	9/50

However, ethylcarbamate also many other tumors not observed with fenoxycarb.

From all these data, it can't be concluded whether ethylcarbamate is responsible for tumors observed with fenoxycarb or not.

Mechanistic considerations - Case of peroxisome proliferation.

Relevance of peroxisome proliferation was discussed (EFSA concluded in 2010 in cat.2 for carcinogenicity due to peroxisome proliferation for liver tumors).

Peroxisome proliferation is considered as an increase in liver enzyme activity and cell proliferation. One mechanistic study in mice (Beilstein, 1996; available in DAR report and with a summary also submitted by Syngenta) provided strong results for fenoyxcarb as inducer, consolidated by 28-D repeated study in rat with peroxisome proliferation and hypertrophy observed by electronic microscopy (Suter, 1986; available in DAR report and a summary also submitted by Syngenta). Fenoxycarb is also considered as peroxisome proliferator according to EFSA (2010).

Conclusion:

According to the criteria, classification as a carcinogen is warranted for fenoxycarb based on the positive carcinogenicity results observed (statistically significant) with occurrence of treatment related lung malignant tumors in both sexes in one convincing study in mice.

Classification in category Carc. 1A is not warranted because of the lack of human data on the carcinogenicity of fenoxycarb.

Classification in category Carc. 1B based on animal studies would normally require sufficient evidence of carcinogenicity demonstrated in either a) two or more species, or b) two or more independent studies in one species, or increased incidence of tumours in both sexes of a single species. However, carcinogenicity in a single animal study (both sexes, ideally in a GLP study) could also be "*sufficient evidence*" and could therefore lead to a Category 1B classification *in the absence of any other data,* which is not the case for fenoxycarb.

For fenoxycarb, positive carcinogenicity results (statistically significant) are observed with occurrence of treatment related lung malignant tumors in both sexes in one convincing study in mice. Other data are also available and were carefully evaluated in line with the criteria "sufficient evidence" to CLP criteria 1B. Indeed, a single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when:

- "Malignant neoplasms occur to an **unusual** degree with regard to incidence, site, type of tumour or age at onset": no unusual dose was used and no unusual degree was reported with the study of fenoxycarb.
- "In combination with positive ***in-vivo*** mutagenicity": genotoxicity results for fenoxycarb are negative although it can be speculated that the formation of genotoxic metabolite ethylcarbamate (identified in vitro) is possile, under detection limit. Thus, it can't be given a clear affirmative answer to this CLP criterion 1B. Besides,

- Since main target organs for tumors are identical for fenoxycarb and the carcinogenic metabolite ethylcarbamate (lung, liver, hardarian glands), one could assume that it may play a role in the development of tumors in vivo in mice fied but profiles are different (ethylcarbamate is a multisite carcinogen)..
- There are no reasons to believe that metabolite (if plays a role) will not be formed in humans, however, mice appear to be more sensitive species for: higher rate of metabolistation in ethylcarbamate and inducible quantity and activity of liver enzyme.

▪ "**Strong** findings of tumours at multiple sites": it does not appear to be the case for fenoxycarb since other tumors' occurrences are of doubtful relevance. Indeed,
- The liver tumors may be related to peroxisome proliferation (although involv**ement** of the genotoxic metabolites cannot be ruled out): this mechanism considered to be of no clear relevance to human. EFSA concluded the same way on this issue.
- The Hardarian gland tumors observed are only adenomas and this is not considered as relevant effect for humans.

▪ "Positive responses in **several species** add to the weight of evidence". No incidence of tumors was reported in rats with fenoxycarb.

RAC regards the available evidence for carcinogenicity to be limited. According to the criteria for Carc. 2 the data suggest a carcinogenic effect, but the data are limited for making a definitive evaluation because there is only a single experiment available demonstrating the carcinogenic effect clearly, with other data which, following a weight of evidence approach, weaken the results observed. From the criteria for carcinogenicity testing and weight of evidence, **classification as Carc. 2 is deemed appropriate.** The corresponding classification according to Directive 67/548/EEC would be Carc. Cat. 3; R40.

This classification is consistent with the position of EFSA (2010).

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

In a rat two-generation study, effects on the parental generations (P, F_1) included slightly reduced body weight gain during the pre-mating period and liver toxicity (periportal hepatocyte hypertropy in males and females, focal necrosis in males) at a dose level of 1800 ppm. No impairment of fertility or fecundity was observed. However, the duration of pregnancy was decreased at 600 and 1800 ppm in the first litters of each generation with a tendency to a decrease at all dose levels in the second litters. Since the lower value of 21 days is inside the normal variation for the rat strain the magnitude of the effect is not considered to be adverse. F_1 and F_2 neonates in treated groups experienced slightly reduced body weight gain during the lactation period and showed an increased incidence in haemorrhages in various regions of the body (mainly on snout, head and back). The evaluation of the latter effect in the neonates is restricted since there was no individual offspring identification and no systematic evaluation.

For parental toxicity, the NOAEL was set at 35 mg/kg bw/d, based on a reduction in body weight gain and liver toxicity.
The reproductive NOAEL was set at 100 mg/kg bw/d, the highest dose tested.
For offspring toxicity, the NOAEL was set at 13 mg/kg bw/d, based on a slight reduction in body weight gain.

Table 17 Summary for effects on fertility

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels (mg/kg bw/d), Duration of exposure	Critical effect Parental, Offspring (F1, F2)	NO(A)EL Parental toxicity	NO(A)EL Reproductive toxicity	Reference
Similar to OECD 416	Rat, (Crl:CD (SD)BR), Sprague-Dawley-derived albino, *F_0* : 30 M + 30 F *F_1*: 25 M + 25 F	Oral, dietary Males: 0-10-35-100 F_0: *Pregnancy*: 0-15-45-130 *Lactation*: 0-30-90-260 F_1: *Pregnancy*: 0-13-40-119 *Lactation*: 0-26-80-238 (Corresponding to 0-200-600-1800 mg/kg feed)	Parental *Liver:* Hypertrophy, focal necrosis Reproduction: *Pregnancy*: Shortened duration (not considered adverse) Offspring *Body weight gain:* Decreased	Parental 35 mg/kg bw/d	Reproduction 100 mg/kg bw/d Offspring 13 mg/kg bw/d	Barker L, Goodyer MJ (1986), Report No. 4623-161/124

5.9.2 Developmental toxicity

In the developmental toxicity studies, no effects of fenoxycarb on the conceptus were observed at dose levels which were already slightly toxic to the mothers. The maternal NOAEL was 50 mg/kg bw/d in rats, based on increased nervousness of the females during the second half of the treatment period at 150 mg/kg bw/d. In rabbits, it was 100 mg/kg bw/d, based on a slight decrease in body weight gain at 300 mg/kg bw/d. The embryo-/foetotoxic NOAELs were 500 mg/kg bw/d and 300 mg/kg bw/d in rats and rabbits, respectively. The slight increase in two malformation types, spina bifida and tail reduction defects, seen in the first rabbit study in treated groups at the dose of 100 and 300 mg/kg bw/d, is considered unrelated to test substance for the following reasons. Detailed reviews of historical control data demonstrate that these malformation types occur spontaneously in fetuses of the Swiss Hare rabbit (Hummler and McKinney, 1986; Gillis and Bürgin, 2006; Regulatory Science Associates, 2010). The observed incidence of the two malformations are within the range reported for the historical control data. The mating records, although not totally conclusive, seem to implicate two male breeders which were used repeatedly in the fenoxycarb study as likely carriers of the trait. In addition, the findings were not reproducible in the follow-up study using a larger number of females at a dose of 200 mg/kg bw/d that should have been high enough to elicit these malformations had they been a consequence of the fenoxycarb treatment.

Table 18 Summary for developmental toxicity

Method / Guideline	Route of exposure, Duration	Species, Strain, No/group	Dose levels mg/kg bw/d	Critical effects 1) dams 2) fetuses	NO(A)EL Maternal toxicity Embryotoxicity Teratogenicity mg/kg bw/d	Remarks	Reference

OECD 414	Oral, gavage, days 7-19	Rabbit, Swiss hare, 20 F	*Initial study*: 0-30-100-300 *Supplementary study*: 200	*Dams*: Initial decrease in body weight gain *Fetuses*: No effects	*Maternal*: 100 *Embryotoxic/teratogenic*: 300	*Post-exposure period*: 11 d	Hummler H, McKinney B (1984), Report No. B-104700
OECD 414	Oral, gavage, days 7-16	Rat, Fü-albino outbred strain, 36 F	0-50-150-500	*Dams*: Increased nervousness *Fetuses*: No effects	*Maternal*: 50 *Embryotoxic/teratogenic*: 500	*Post-exposure period*: 5 d	Eckhardt K (1983), Report No. B-104875

5.9.3 Human data

No human data are available.

5.9.4 Other relevant information

No other information is available.

5.9.5 Summary and discussion of reproductive toxicity

Developmental toxicity studies and a two-generation study provided no evidence for a reproduction toxicity potential of fenoxycarb. No classification and labelling regarding developmental and reproductive toxicity are required.

RAC evaluation of Reproductive Toxicity

Summary of the dossier submitter's proposal

Fertility toxicity
In a rat two-generation study, effects on the parental generations (P, F_1) included slightly reduced body weight gain during the pre-mating period and liver toxicity (periportal hepatocyte hypertropy in males and females, focal necrosis in males) at a dose level of 1800 ppm. No impairment of fertility or fecundity was observed. However, the duration of pregnancy was decreased at 600 and 1800 ppm in the first litters of each generation with a tendency to a decrease at all dose levels in the second litters. Since the lower value of 21 days is inside the normal variation for the rat strain the magnitude of the effect is not considered to be adverse. F_1 and F_2 neonates in treated groups experienced slightly reduced body weight gain during the lactation period and showed an increased incidence in haemorrhages in various regions of the body (mainly on snout, head and back). The evaluation of the latter effect in the neonates is restricted since there was no individual offspring identification and no systematic evaluation.
For parental toxicity, the NOAEL was set at 35 mg/kg bw/d, based on a reduction in body weight gain and liver toxicity.
The reproductive NOAEL was set at 100 mg/kg bw/d, the highest dose tested.
For offspring toxicity, the NOAEL was set at 13 mg/kg bw/d, based on a slight reduction in body weight gain.

Developmental toxicity
Two developmental toxicity were conducted on rat and rabbits.(Hummler H, McKinney B

(1984), Report No. B-104700 and Eckhardt K (1983), Report No. B-104875)
No effects of fenoxycarb on the conceptus were observed at dose levels which were already slightly toxic to the mothers. The maternal NOAEL was 50 mg/kg bw/d in rats, based on increased nervousness of the females during the second half of the treatment period at 150 mg/kg bw/d. In rabbits, it was 100 mg/kg bw/d, based on a slight decrease in body weight gain at 300 mg/kg bw/d. The embryo-/foetotoxic NOAELs were 500 mg/kg bw/d and 300 mg/kg bw/d in rats and rabbits, respectively. The slight increase *in two malformation types, spina bifida and tail reduction defects, seen in the first rabbit study in treated groups*
The dossier submitter concluded that the two malformation types were considered unrelated to treatment for the following reasons:

1/ Historical control data demonstrate that these malformation types occur spontaneously in the rabbit strain used in the studies (Swiss Hare). Three references are presented to support the statement: an addendum to the Roche report (1986, unpublished); a report by Gillis and Burgin (2006); a report by Regulatory Science Associates (2010, unpublished).

2/ The incidence in the study were within the historical range (no reference presented to support the statement).

3/ The mating records, although not totally conclusive, seem to implicate two males which were used repeatedly in the initial study as likely carriers of the trait (no reference presented to support the statement).

4/ The findings were not found in the follow up study at a dose of 200 mg/kg considered to be high enough to elicit the changes had they been related to treatment.

Conclusion by the dossier submitter

Developmental toxicity studies and a two-generation study provided no evidence for a reproduction toxicity potential of fenoxycarb. No classification and labelling regarding developmental and reproductive toxicity are required.

Information and comments received during public consultation

Information presented in the dossier is limited to a brief summary. For the developmental toxicity, more detailed information was found in the EFSA Assessment Report (24/09/2010) and in comments received during consultation.

Effects of potential concern regarding reproductive toxicity were found in two rabbit developmental studies only. In the two rabbit studies conducted, spina bifida and hypoplastic tail were observed as follows (Tables taken from comments received from Netherlands)

Table 6.6.2.1a. Experiment A

Dose (mg/kg bw/day)	0	**30**	**100**	**300**
Total no foetuses	122	101	109	126
External observations				
- spina bifida, sacral region	0	0	1	3
- hypoplastic tail	1 (0.8%)	1 (1.0%)	(0.9%) 0	(2.4%) 4

				(3.2%)

The three foetuses with spina bifida at 300 mg/kg bw/day are from 2 different litters.

One litter: 1 pup with spina bifida + hypoplastic tail and 1 pup with spina bifida.

Another litter: 1 pup with spina bifida + hypoplastic tail

Table 6.6.2.1b. Experiment B

Dose (mg/kg bw/day)	**0**	**200**
Total no foetuses	349	234
External observations - spina bifida, sacral region - hypoplastic tail	 0 1 (0.3%)	 0 0

Comments regarding reproductive toxicity received during the consultation period can be summarized as follows:

1/ Netherlands stated that "A different conclusion regarding the increase in spina bifida and hypoplastic tail in the rabbit developmental study is drawn in the DAR compared to the C&L proposal." However it seems that the two documents we have concluded that there were no treatment related effects, this may need clarification).

2/ Netherlands presented historical data indicating that the incidences of the two malformations at the high dose were above the incidence in controls. They further commented that the effects could not be linked to the maternal toxicity, i.e. decreased body weight gain (80% of control) to conclude that, based on this information, fenoxycarb should be classified with R63.

3/ Netherlands asked the dossier submitter to provide additional details on these historical control values. A conclusion whether classification with R63 should be considered is not possible without this additional information.

4/ UK also requested inclusion of incidence tables in the CLH report together with relevant historical data.

5/ Denmark comments are basically similar to those above. Denmark encourages the dossier submitter to clarify the different interpretations of rabbit study with respect to whether the findings are within the range of historical control data, taking into account the recent conclusions of EFSA.

6/ Syngenta stated that hypoplastic or missing tail at a dose level of 200 mg/kg/day in a supplementary study (234 foetuses). Though recorded as discrete entities, it must be recognised that hypoplastic tail and missing tail are part of a continuum of observations.

They submitted information on controls from 31 studies using the same strain of rabbit conducted at the laboratory between 1977 and 1988. Spina Bifida occurred in 6 studies and tail malformations in 10 studies. One of the studies (conducted around 3 years before the study of fenoxycarb) had incidences of tail malformation and spina bifida higher than in the high dose group in the fenoxycarb study. (See table below extracted from Syngenta document).

Table 1 – Historical Control Data for spina bifida and rudimentary tail in Swiss hare rabbits from F. Hoffmann-La Roche, Basel, Switzerland testing facility between 1977 and 1988.

Report number	Number of foetuses	Tail malformation	Spina bifida
		no. foetuses (%)	no. foetuses (%)
B-0090787	88	3 (3.4)	3 (3.4)

Syngenta concluded that fenoxycarb does not warrant classification for developmental effects. This is based on:

- The incidence of spina bifida and tail malformations were within the historical control range.
- The malformations were not reproducible in a supplementary study conducted on a higher number of dams at a dose level of 200 mg/kg/day.

RAC assessment - comparison with the classification criteria and justification

RAC agrees with the comments that additional information was needed given the rabbit study results and the relevant historical data in order to allow a thorough assessment of the results in the rabbit reproductive toxicity studies. Clarification was provided by Syngenta concerning historical control data (HCD) used for EFSA and the one used for CLH.

A new review of the original documents of HCD was elaborated by Regulatory Science associates (RSA, 2010) as inconsistencies occurred. This new review (RSA, 2010) is considered as the correct data set (includes additional data). This RSA report (2010) was not used by EFSA because of timing procedure: EFSA discussion occurred in July 2010. The RSA report was used for CLH with information on controls from 31 studies using the same strain of rabbit conducted at the laboratory between 1977 and 1988. Spina Bifida occurred in 6 studies and tail malformations in 10 studies. One of the studies (conducted around 3 years before the study of fenoxycarb) had incidences of tail malformation and spina bifida higher than in the high dose group in the fenoxycarb study.

CLP criteria for Cat. 2 for reproductive toxicity is "when there is some evidence from […] experimental animals, possibly supplemented with other information, of an adverse effect on [...] development [...] 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."

With elements clarified, the key points to emphasis are:

- Increase incidence of spina bifida and malformations of tails in rabbits (Hummler & Kimmer study, 1984) occurred at 100 & 300 mg/kg but not in an additional study with larger group at 200 mg/kg.

- Increase occurred without statistical significance, within historical control data set & no other effects where observed.

No classification for reprotoxicity (development) is proposed by RAC.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

In a standard study (Schürch, H. 1992c; report no. AG 91/12T.EXP) Fenoxycarb was found not to exhibit any explosive properties.
No classification for explosivity is proposed.

6.2 Flammability

In standard study (Schürch, H. 1992b; report no. AG 91/12T.AFS) no self ignition according to Guideline 84/449/EEC, A.16 was registered until the melting point.
In a standard study (Schürch, H. 1992a; report no. AG 91/12T.FKS) ignition with a hot platinum wire results in melting of Fenoxycarb. The molten substance does not sustain a flame. The substance is not a highly flammable solid in the sense of Guideline 84/449/EEC, A.10, and did not exhibit any pyrophoric properties.
No experimental data on flammability in contact with water:
Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.10: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids
No classification for highly flammable is proposed.

6.3 Oxidising potential

In a standard study (Schürch, H. 1992d; report no. AG 91/12T.OXP) Fenoxycarb has not oxidising properties in the sense of Guideline 84/449/EEC, A.17.

No classification for oxidising properties is proposed.

7 ENVIRONMENTAL HAZARD ASSESSMENT

It is not proposed to change the current environmental classification of fenoxycarb. However, according to the 2nd ATP to Regulation (EC) No 1272/2008, M-factors for the environmental categories Aquatic Acute 1 and Aquatic Chronic 1 have to be set. Therefore, the aquatic effect studies that are relevant for the selection of the respective M-factors are presented in the following:

7.1 Biodegradation

One study on ready biodegradability according to OECD 301 B was delivered (Lebertz, 1990). Validation of the study was not possible, because the inoculum concentration was not specified, the results for the blanks could not be assessed, and no parallel measuring of the test substance was carried out. A study on the inherent biodegradability was not performed. However, these studies are not deemed to be necessary, since higher tiered studies, namely simulation tests for the relevant environmental compartments 'water/sediment' and 'soil', are available, thus skipping the readily and inherent biodegradation test. Hence, fenoxycarb is considered as not readily biodegradable.

7.2 Aquatic compartment (including sediment)

7.2.1 Toxicity test results

Table 19: Acute toxicity to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg a.s./L]			Remarks	Reference
			design	duration	EC_0	EC_{50}	EC_{100}		
EPA (1985; 1988)	*Oncorhynchus mykiss*	mortality	flow-through	96 h	0.37)	0.66	0.84 – 1.3	results based on mean measured conc. of fenoxycarb	Ward, Boeri, 1993a

Acute toxicity to *Oncorhynchus mykiss* was investigated according to OECD Guideline 203 or U.S. EPA standard guideline which can be compared to OECD Guideline 203. Juveniles of rainbow trout were exposed under flow-through conditions for 96 h to nominal concentrations of 0.6, 1.0, 1.6, 2.4 and 4 mg a.s./L. Mean measured concentrations were 0.26, 0.37, 0.58, 0.84 and 1.3 mg a.s./L. Twenty fish selected impartially were distributed equally between two replicates of each treatment (2 replicates of 10 fish/concentration) and 10 fish per water and per solvent control group. The number of surviving fishes and possible sublethal effects were observed after 24, 48, 72 and 96 h. A 96h-LC_{50} of 0.66 mg a.s./L related to mean measured concentration was determined.

Table 20: Acute toxicity to invertebrates

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [mg a.s./L]			Remarks	Referen
			design	duration	EC_0	EC_{50}	EC_{100}		
EPA (1985; 1988)	*Daphnia magna*	immobilization	flow-through	48 h	0.16 (NOEC)	0.6	not determined	results based on mean measured conc. of fenoxycarb	Ward, Boeri, 1993b

The acute toxicity of fenoxycarb to *Daphnia magna* was determined according to EPA (1985; 1988). Juvenile daphnids were exposed under flow-through conditions to a geometric series of five test concentrations, a solvent control and a control. Two replicate test chambers per treatment and controls groups were maintained with 10 daphnids in each test chamber for a total of 20 daphnids per concentration. The test was performed in 20 litre glass aquaria

containing 15 L of test solution in which test organisms were exposed in glass cylinders to the test solution, suspended within each test vessel. Nominal concentrations of fenoxycarb were 0.38, 0.62, 1.0, 1.5 and 2.5 mg/L. Mean measured concentrations were 0.16, 0.26, 0.39, 0.6 and 0.84 mg/L levels. A 48 h-LC_{50} of 0.6 mg a.s./L related to mean measured concentration was determined.

Table 21 Long-term toxicity to invertebrates

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results [µg a.s./L]		Remarks	Reference
			design	duration	NOEC	LOEC		
OECD 202 (1984) ASTM (1979; 1981) EPA (1978)	*Daphnia magna*	survival; immobilization; growth; reproduction (number of young per female)	flow-through	21 d	0.0016 (based on reproduction and growth)	0.0023	results based on mean measured conc. of fenoxycarb	Forbis, 1987

Effects of fenoxycarb on reproduction and growth of *Daphnia magna* were investigated according to OECD 202, ASTM and EPA. Daphnids were exposed in a 21-day life cycle study to a geometric series of five concentrations of ^{14}C-fenoxycarb under flow-through test conditions using a proportional diluter system. Seven sets of four replicate one-litre test chambers, designated as control, solvent control and five test concentrations were employed in the study. The test was initiated with 10 first-instar daphnids placed in each of the test chambers. Nominal test concentrations for fenoxycarb were: 0.0010, 0.0017, 0.0035, 0.006 and 0.014 µg ai/L. The mean measured concentration levels, as determined by liquid scintillation counting were 0.0016, 0.0023, 0.0045, 0.0068, 0.017 µg ai/L, thus ranging from 113 to 160% of nominal values.
Biological observations on adult survival, immobilisation and changes in behaviour or appearance were recorded daily. With the onset of brood production, young survival and immobilisation were recorded three times per week.
Survival of *Daphnia magna* exposed to fenoxycarb for 21 days was not significantly affected up to a concentration of 0.017 µg ai/L. The growth length of daphnids was significantly reduced at treatment levels of 0.0023 µg ai/L and higher. A reduced reproduction rate, as measured by the number of young per female was observed at concentrations of 0.0023 µg ai/L and higher. Therefore, the 21 d-NOEC is 0.0016 µg a.s./L based on mean measured concentration.

7.3 Conclusion on the environmental classification and labelling

In acute studies with fish and Daphnia, acute effect values of 0.66 mg/L (*Oncorhynchus mykiss*) and 0.6 mg/L (*Daphnia magna*) were found. These values trigger the environmental classification as H400 with an M-factor of 1.

In a long-term toxicity study with *Daphnia magna* a NOEC for reproduction and growth of 0.0016 µg/L was determined, which triggers the environmental classification H410 with an M-factor of 10,000.

RAC evaluation of Hazards to the Aquatic Environment

Summary of the dossier submitter's proposal

The dossier submitter does not propose to change the current environmental classification of fenoxycarb. The substance has a harmonised entry in Annex VI to Regulation (EC) No

1272/2008, classifying fenoxycarb as hazardous to the aquatic environment with Aquatic Acute 1 (H400; "Very toxic to aquatic life") and Aquatic Chronic 1 (H410; "Very toxic to aquatic life with long lasting effects") according to the criteria of Regulation (EC) No 1272/2008 (CLP Regulation) and N; R50/53 (Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment) according to the criteria of Directive 67/548/EEC (DSD).

However, according to the revised criteria for classifying substances hazardous to the aquatic environment implemented with the 2nd ATP to the CLP Regulation, the dossier submitter proposed to set M-factors for the environmental categories Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410).

The proposal by the dossier submitter for the acute M-factor is based on acute toxicity studies with fish and Daphnia, where acute effect values of 0.66 mg/l (*Oncorhynchus mykiss*) and 0.6 mg/l (*Daphnia magna*) were found, respectively. These values trigger the classification as Aquatic Acute 1 (H400) with an **M-factor of 1**.

The proposal by the dossier submitter for the separate chronic M-factor is based on a long-term toxicity study with *Daphnia magna*, where a 21 d-NOEC of 0.0016 µg a.s./l based on mean measured concentration was determined, which triggers the classification as Aquatic Chronic 1 (H410) with an **M-factor of 10,000.**

Additional key elements

Biodegradation:

The ready biodegradation test result cannot be validated. Two higher tier studies, namely simulation tests for the relevant environmental compartments of "water/sediment" are available (as included in the Biocides Competent Authority Report (CAR), 2010) and considered relevant for the evaluation of degradation.
Conclusions of the Key study (Nicollier, G. (2000)): Fenoxycarb is considered to be not readily biodegradable. The dissipation behaviour of fenoxycarb in aquatic system was studied in two Swiss water/sediment systems (river and pond) resulting in primary degradation half-lives of 14.0 days (river) and 5.0 days (pond) for the water phase as well as 12.0 days (river) and 8.0 days (pond) for the entire system at an average EU outdoor temperature of 12°C. For modelling purposes the recalculated half-lives of the entire systems are 12.0 and 18.0 days. Mineralisation of fenoxycarb to carbon dioxide reached maximum amounts of 40.4 % and 36.3 % of the applied radioactivity (AR) after 119 days in the river and pond test system. Although primary degradation half-lives are below (or very close to) 16 days, there is no information about the hazards of the degradants, and so the substance cannot be considered to be rapidly (or readily) degradable.

Conclusion of the microcosm study (Kennedy, J.H. (1995)): The data obtained in the study may serve only as **supportive information.** The data cannot be considered for the assessment of the biodegradation behaviour of fenoxycarb, as no dissipation half-life for the total system was derived and it was not conducted under controlled conditions (e.g. light, pH, temperature).

Aquatic toxicity:

Fenoxycarb is of high acute toxicity to fish (96h-LC_{50} = 0.66 mg a.s./l), daphnids (48h-EC_{50} = 0.60 mg a.s./l) and green algae (96h-E_bC_{50} = 0.54 mg/l). In long-term studies, *Daphnia magna* was the most sensitive aquatic species with a 21 d-NOEC of 0.0016 µg a.i./l based on mean measured concentrations (Forbis, 1987). This NOEC is by orders lower than the NOECs from the fish early life stage test (NOEC = 48 µg a.s./l). Also for *Chironomus riparius* a high toxicity of fenoxycarb was found with a nominal 25 d-EC_{10} of 0.18 µg a.s./l.

No acceptable study on algal growth inhibition with fenoxycarb has been submitted (the study provided in the DAR is not considered valid). Furthermore, it is concluded that the classification will not change by submitting a test with algae, and given the high sensitivity of

invertebrates, it seems unlikely that M-factors would be affected. For green algae no valid NOEC is available. However, in a mesocosm study, no effects on phytoplankton community were observed at concentrations that have significant effects on invertebrates. The high sensitivity of daphnids *and Chironomus sp.* in long-term tests can be explained by the mode of action of fenoxycarb (inhibiting metamorphosis to the adult stage and interfering with the moulting of early instar larvae by exhibiting juvenile hormone activity).

Comments received during public consultation

During public consultation, comments on hazardous to the aquatic environment were received from two Member states. The comments did not question the proposal of setting M-factors, according to the revised criteria as laid down in the 2nd ATP to CLP, for the existing harmonised environmental classification as Aquatic Acute 1 and Aquatic Chronic 1.

For the full set of comments and responses, see the response to comments document (RCOM) in Annex 2.

RAC assessment - comparison with the classification criteria and justification

Classification according to the 2nd ATP to the CLP Regulation:

According to the requirements of the CLP Regulation the classification of a substance as Aquatic Acute 1 and/or Aquatic Chronic 1 triggers the setting of (a) multiplying factor(s) (M-factor). The revised criteria for classifying substances as hazardous to the aquatic environment in the 2nd ATP furthermore allow setting M-factors for acute and long-term hazards separately the application of a separate M-factor for long-term aquatic hazard. This means that there can be two different M-factors (one for acute and one for long-term hazard) for one substance.

RAC supports the conclusion of the dossier submitter to set an M-factor of 1 for fenoxycarb which is classified as Aquatic Acute 1 (H400) based on the EC_{50} for *Daphnia magna* and fish (*Oncorhynchus mykiss*) which is between 0.1 and 1 mg/l.

RAC also supports the conclusion of the dossier submitter to set a separate M-factor of 10,000 (non-rapidly degradable) for fenoxycarb classified as Aquatic Chronic 1 (H410) based on the chronic NOEC (for reproduction and growth) for *Daphnia magna* which is between 0.000001 and 0.00001 mg/l (according to Table 4.1.3 in Annex I to the 2nd ATP).

Acute (short-term) aquatic toxicity:

The acute aquatic toxicity is based on the lowest of the available toxicity values (*Daphnia magna*: 48h-EC_{50} = 0.60 mg a.s./l and *Oncorhynchus mykiss*: 96h-LC_{50} = 0.66 mg a.s./l) between 0.1 and 1 mg/l.
Conclusion: category Acute 1 applies with an **M-factor of 1**.

Chronic aquatic toxicity:

Adequate chronic toxicity data is available only for fish and crustaceans, not for algae/aquatic plants. The chronic aquatic toxicity based on the lowest of the available toxicity values for fish and crustaceans is between 0.000001 and 0.00001 mg/l (*Daphnia magna* NOEC = 0.0016 µg a.s./l and *Oncorhynchus mykiss* NOEC = 48 µg a.s./l). According to the 2nd ATP the criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if adequate information on chronic toxicity is available allowing long-term hazard classification. In absence of adequate chronic toxicity data for some or all trophic levels, a potential classification is made for the trophic level(s) with chronic data and compared with that made using the acute toxicity data for the other trophic level(s). The final classification shall be made according to the most stringent outcome (Guidance on the application of the CLP criteria, Figure 4.1.1 and Annex I.3.2).

NOEC-based system (Table 4.1.0 (b)(i)): lowest chronic aquatic toxicity NOEC ≤ 1 mg/l, not rapidly degradable, hence category Chronic 1;

Surrogate system (Table 4.1.0 (b)(iii)): lowest acute aquatic toxicity $L(E)C_{50}$ < 1 mg/l, not rapidly degradable (and Log Kow > 4), hence category Chronic 1;

Conclusion: category Chronic 1 applies following the most stringent outcome; since the conclusion is based on the chronic NOEC (Table 4.1.0 (b) (i)) the **M-factor of 10,000** is based on the chronic aquatic toxicity between 0.000001 and 0.00001 mg/l.

Degradation:

The ready biodegradation test cannot be validated. Although primary degradation half-lives are below (or very close to) 16 days in water-sediment simulation studies, there is no information about the hazards of the degradants. Mineralisation to carbon dioxide reached maximum levels of 40.4 % and 36.3 % of the applied radioactivity (AR) after 119 days in the river and pond test system, respectively. Consequently, fenoxycarb does not fulfil the criteria for rapid degradation.

Bioaccumulation:

In a study according to OECD 305 a bioconcentration factor for the aquatic compartment of BCF_{fish} = 569 was measured for fenoxycarb. The BCF-value indicates that fenoxycarb has a potential for bioaccumulation via the aquatic food chain.

Aquatic classification according to the CLP criteria:

Aquatic Acute 1, M = 1 (H400)

Aquatic Chronic 1, M = 10,000 (H410)

Aquatic classification according to the DSD criteria:

Fenoxycarb is very toxic to aquatic organisms and may cause long-term adverse effects to the aquatic environment. It is therefore classified with N; R50/53:
- Acute toxicity ≤ 1 mg/l (most sensitive organism *Daphnia magna:* 48h-EC_{50} = 0.60 mg a.s./l)

- not readily degradable

- log P_{ow} is ≥ 3 and the measured BCF for fish is > 100.

In addition, the following **specific concentration limits (SCL)** shall apply:

Classification	Concentration
N; R50-53	**C ≥ 25%**
N; R51-53	**2,5% ≤ C < 25%**
R52-53	**0,25% ≤ C < 2,5%**

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Fenoxycarb is an active substance in the meaning of Directive 91/414/EEC and 98/8/EC meaning all hazard classes are subject to harmonised classification at Community level and no other justification is needed.

OTHER INFORMATION

During the preparation of the CAR according to Dir. 98/8/EC for Annex I inclusion of fenoxycarb, the applicant submitted a report and statement (Hess & Dayan, 1999) regarding the proposal to classify and label fenoxycarb with R40.

The BfR (dossier submitter) commented on this report:

In carcinogenicity studies in two different mouse strains (CD-1 and Tif:MAGf) an increased incidence of lung adenoma and carcinoma as well as an increased incidence of liver tumours and, in one study, a trend to an increased incidence of Harderian gland tumours, albeit not statistically significant, were evident (Everett et al., 1987; Bachmann, 1995). Three different oncogenic mechanisms are discussed for fenoxycarb:

1) peroxisome proliferation, which is unlikely to be of relevance for carcinogenesis in humans (Klaunig, 2003),
2) metabolic formation of hydroquinone/benzoquinone (Carc. Cat. 3; R40, Muta. Cat. 3; R68, 25. ATP), likely to be relevant for humans, or
3) metabolic formation of ethyl carbamate (urethane, Carc. Cat. 2; R45, 19. ATP), likely to be relevant for humans.

From the spectrum of tumours observed in mice (lung, liver, Harderian gland), it is likely that the mode of action is the metabolic degradation of fenoxycarb to ethyl carbamate (urethane, Carc. Cat. 2; R45, 19. ATP) and further formation of DNA-adducts. The US EPA therefore classifies fenoxycarb as a 'probable human carcinogen (B2)' (OPP, 1997). See Figure 1 for the proposed pathway of fenoxycarb toxification.

Fig. 1: Proposed pathway of fenoxycarb toxification:

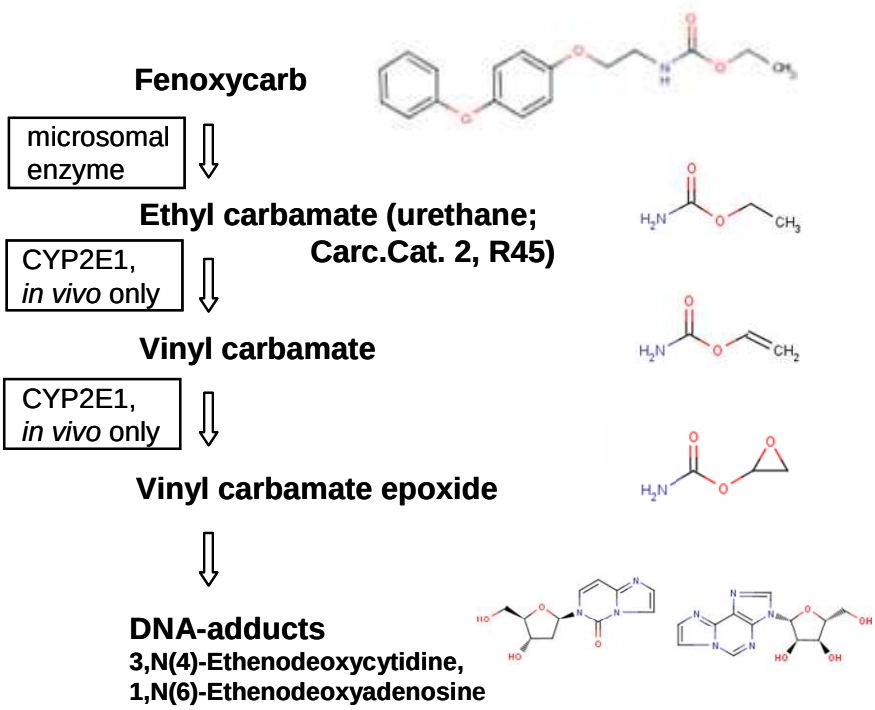


Figure 1 Proposed pathway of Fenoxycarb toxification

The formation of carbamate from fenoxycarb by liver microsomes of different species was qualitatively (mice, rats, marmosets, and humans) and quantitatively (mice, humans) analysed in mechanistic studies *in vitro* and was observed in all investigated species (Beilstein, 1997), albeit highest in mice. In a comparative test of a mouse liver microsome preparation and three human preparations, the formation rate of urethane was 11-173fold slower in human than in mice liver microsomes (Beilstein, 1989). In consideration of these high interindividual differences in humans and the small number of analysed samples, it cannot be ruled out, that part of the human population metabolises fenoxycarb to urethane in the same magnitude as mice.

Although urethane formation from fenoxycarb was observed *in vitro* in human microsomes, the applicant argues against a classification of fenoxycarb for carcinogenic potential (Hess R, Dayan AD, 1999. Carcinogen risk assessment: Relevance of tumor formation in mice. Unpublished Report). The four key arguments of the authors are:

1) No increased tumour rates were observed in a chronic study in the rat (Goodyer, 1992), so the increased rates of liver tumours in mice suggest a species-specific mode of action (e.g. peroxisome proliferation).
2) The lung tumours, which could possibly be the result of urethane formation, are of no relevance for men (and rat). Formation of urethane by liver microsomes *in vitro* was 11-173fold slower in men than in mice, and even in mice urethane levels *in vitro* were low.
3) Two *in vivo* micronucleus tests with fenoxycarb were negative (Proj. No. B-96'679 Hoffmann-La Roche Ltd., 1982; Ogorek, 1996), whereas urethane gives positive results and no DNA-adducts could be detected in fenoxycarb-treated mice whereas exposure to urethane resulted in DNA-adducts. Thus, a genotoxic potential of fenoxycarb could be ruled out.
4) No fenoxycarb metabolism was observed in lung microsomes of mice, rats, and marmosets (Beilstein, 1997).

Response to 1) If the mode of action would be solely peroxisome proliferation, it would be likely that the rat would be equally susceptible for liver tumours. The lung tumours are unlikely to be related to peroxisome proliferation.

Response to 2)
In vitro studies: In principle, formation of urethane from fenoxycarb was shown in human microsomes (Beilstein, 1997, 1998). Quantitation from these studies might be difficult, because the quality of the individual microsome preparations as well as the induction status of microsomal enzymes in each tissue donor are crucial and difficult to compare. Particularly the quality of human microsome preparations is difficult to assess since nothing is known about life style (enzyme induction in the liver), state of health and cause/time of death of the donors.
No *in vivo* metabolism studies are available with fenoxycarb labelled at the carbamate moiety. In a rat metabolism study with fenoxycarb labelled at the aromatic rings, a fenoxycarb metabolite was identified (to 8.4) which lacks urethane at the carbamate moiety. Therefore, it cannot be ruled out that urethane is an *in vivo* metabolite of fenoxycarb in the rat.

Taking into consideration the high interindividual variation of urethane formation from the three human microsomal preparations (16fold) and the high variation in CYP2E1 expression and activity in humans as well as in mice and rats (inter alia strain-dependent) there is a very high uncertainty of the possible formation rate of vinyl carbamate and, subsequently, DNA-adducts. It was not investigated, in how far the rat strain used for the chronic study is capable of this metabolism.

Response to 3) Firstly, in the micronucleus test submitted by the applicant exposure to urethane was not investigated as this would have been the adequate positive control. Secondly, the urethane doses usually used for positive results in published micronucleus test are 900 mg/kg bw/d, the maximum investigated fenoxycarb dose was 5000 mg/kg bw/d. If the fenoxycarb metabolism to urethane is a minor pathway, as stated by the applicant, the fenoxycarb dose might be to low to observe a positive result. In the DNA-adduct study (Sagelsdorff, 1998), on the other hand, urethane was used as a positive control but gave only very slight positive results (CBI 0.09-0.8) neither in accordance with published data for urethane (CBI 23-80, Review: see Lutz, 1979) nor in accordance with the applicant's own statement, that a genotoxic substance, which urethane undoubtedly is, with a TD_{50} of 1-10 mmol/kg bw has an expected CBI of 2-9.

Response to 4) The applicant argues, that no urethane formation was observed in human lung microsomes (Beilstein, 1997) and thus, lung damage by urethane metabolised from fenoxycarb in the liver would be unlikely. In contradiction to this statement, urethane from intake of food or alcoholic beverages is a known lung carcinogen (Schlatter and Lutz, 1990; Inai et al., 1991), showing that the substance is stable enough to passage the intestine and the liver after dietary intake. Additionally, no positive control was included in the study to show that the lung microsome preparations were intact and efficiently working.

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