Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

fenoxaprop-P-ethyl

EC number: -

CAS number: 71283-80-2

CLH-O-0000002445-76-03/F

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Adopted

7 March 2013

7 March 2013
CLH-O-0000002445-76-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: fenoxaprop-P-ethyl

EC number: -

CAS number: 71283-80-2

The proposal was submitted by **Austria** and received by the RAC on **17/04/2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/pl/harmonised-classification-and-labelling-consultation*** on **17/04/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **01/06/2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Hans-Christian Stolzenberg**
Co-rapporteur, appointed by the RAC: **Agnes Schulte**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **7 March 2013** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **fenoxaprop-P-ethyl** should be classified and labelled as follows:

OPINION OF THE RAC

RAC adopted the opinion that **fenoxaprop-P-ethyl** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No entry										
Dossier submitter's proposal		fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propionate		71283-80-2	STOT RE 2 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H373 H317 H400 H410	GHS07 GHS08 GHS09 Wng	H373 H317 H410		 M=1 M=1	
RAC opinion	607-707-00-9	fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propanoate		71283-80-2	STOT RE 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H373 (kidneys) H317 H400 H410	GHS07 GHS08 GHS09 Wng	H373 (kidneys) H317 H410		 M=1 M=1	
Resulting Annex VI entry if agreed by COM	607-707-00-9	fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propionate		71283-80-2	STOT RE 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H373 (kidneys) H317 H400 H410	GHS07 GHS08 GHS09 Wng	H373 (kidneys) H317 H410		 M=1 M=1	

Classification and labelling in accordance with the criteria of DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry	No entry							
Dossier submitters proposal		fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propionate		71283-80-2	R43 N; R50-53	Xi; N R: 43-50/53 S: (2-)13-24-29-37-46-56 - 57-60-61		
RAC opinion	607-707-00-9	fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propionate		71283-80-2	Xn; R48/22 R43 N; R50-53	Xn; N R: 43-48/22-50/53 S: (2-)24-37-46-60-61	N; R50-53: C ≥ 25% N; R51-53: 2,5% ≤ C < 25% R52-53: 0,25% ≤ C < 2,5%	
Resulting Annex VI entry if agreed by COM	607-707-00-9	fenoxaprop-P-ethyl; ethyl (2R)-2-{4-[(6-chloro-1,3-benzoxazol-2-yl)oxy]phenoxy}propionate		71283-80-2	Xn; R48/22 R43 N; R50-53	Xn; N R: 43-48/22-50/53 S: (2-)24-37-46-60-61	N; R50-53: C ≥ 25% N; R51-53: 2,5% ≤ C < 25% R52-53: 0,25% ≤ C < 2,5%	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

Fenoxaprop-P-ethyl is a herbicide for post-emergence use in wheat, rye, triticale, and barley.

Fenoxaprop-P-ethyl is the biologically active enantiomer of fenoxaprop-ethyl; essentially, fenoxaprop-P-ethyl is the (D+)-enantiomer of the racemate fenoxaprop-ethyl, where the herbicidally inactive (L-) enantiomer has been eliminated.

The dossier submitter applies the category approach to read across data for some of the endpoints, based on relevant studies on fenoxaprop-ethyl. Based on a comparison of the toxicological data of fenoxaprop-P-ethyl and fenoxaprop-ethyl, the dossier submitter concluded that the toxicological profile of fenoxaprop-P-ethyl is fully comparable to that of fenoxaprop-ethyl both in qualitative and quantitative terms. It thus appears justified to base the evaluation of two generation reproductive toxicity, chronic toxicity and carcinogenicity for fenoxaprop-P-ethyl on the corresponding long-term studies conducted with fenoxaprop-ethyl.

For repeated dose toxicity/STOT RE the database on fenoxaprop-P-ethyl alone was sufficient and the data on fenoxaprop-ethyl were not included in the opinion. For other endpoints, where no data on fenoxaprop-P-ethyl were available, data on fenoxaprop-ethyl were used for bridging purposes.

Fenoxaprop-ethyl (CAS: 664441-23-4) currently has an entry in Annex VI of CLP as Skin Sens. 1 (based on test data generated with fenoxaprop-P-ethyl, see Background document (BD), section 2.1.), Aquatic Acute 1 and Aquatic Chronic 1.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Fenoxaprop-P-ethyl is of low acute toxicity when tested by the oral route (Wistar rats, NMRI mice) and the dermal route (Wistar rats). In an acute inhalation study in Wistar rats, no mortality occurred at the technically highest administrable concentration of 1.224 mg/l, therefore the acute inhalation toxicity is assumed to be low.

Studies on fenoxaprop-ethyl, supplied as supportive information, demonstrated low acute toxicity when tested by the oral route (Wistar rats, NMRI mice) and the dermal route (Wistar rats). In an acute inhalation study in Wistar rats, 1 of 6 male animals died at the highest concentration of 0.475 mg/l (analytical grade). No definitive conclusions on the acute inhalation toxicity of fenoxaprop-ethyl can be made based on this study.

As all estimated LD_{50} and LC_{50} values are above the criteria for triggering classification and labelling (according to both CLP and DSD), the dossier submitter concluded that classification for this hazard class is not warranted.

Comments received during public consultation

No specific comment on this hazard class was received during public consultation.

Assessment and comparison with the classification criteria

In the oral acute toxicity studies on fenoxaprop-P-ethyl, no lethality occurred at 2000 mg/kg in rats, which is the upper limit dose according to CLP and DSD below which classification may be considered. The absence of mortalities in mice that received 5000 mg/kg is consistent with the low acute toxicity observed in rats and supports the conclusion that no classification is required for this endpoint.

The impairment of respiration and motility or ruffled coat observed during the first 5 days after exposure to the highest technically feasible concentration of 1.224 mg/l fenoxaprop-P-ethyl in air do not justify classification. Due to the absence of mortalities at the maximum achievable test concentration (which was below the upper limit concentration that may trigger classification, i.e. 5 mg/l according to CLP, 2 mg/l according to DSD), classification is not warranted.

The acute dermal study in rats revealed an LD_{50} >2000 mg/kg (which is the limit concentration according to CLP and DSD above which a proposal for classification is not warranted). Neither mortalities nor clinical signs of toxicity were observed at any time of the study.

Fenoxaprop-ethyl data, submitted as supportive information, demonstrated slightly higher oral acute toxicity than fenoxaprop-P-ethyl, but for this substance also, overall low toxicity with mortalities at doses above the guidance values were observed. No mortalities were observed in rats after dermal application of 2000 mg/kg. The LC_{50} value for fenoxaprop-ethyl powder in a 5% dilution in ethanol/polyglycol (1:1) was > 0.475 mg/l; higher concentrations were not tested.

Based on the available data RAC agreed with the dossier submitter's proposal that no classification with regard to acute toxicity is warranted.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal

There was no evidence of any specific, non-lethal target organ toxicity arising from a single exposure to fenoxaprop-P-ethyl. Clinical signs of toxicity, observed after single exposures were considered to be non-specific signs of general acute toxicity. In addition, no human data are available that would support classification for this endpoint. No classification as STOT-SE under the CLP Regulation is therefore proposed.

Comments received during public consultation

No specific comment on this hazard class was received during public consultation.

Assessment and comparison with the classification criteria

Indications of specific target organ toxicity or transient target organ effects were not reported in the available studies. RAC agreed with the dossier submitter's proposal that classification as STOT SE (CLP) is not warranted. No indication of respiratory tract irritation was observed, thus R37 according to DSD (Irritating to respiratory system) is not justified.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

For fenoxaprop-P-ethyl the mean value score for erythema within 72 hours was 0.11. No oedema was observed. Estimated skin irritation scores are below the criteria for triggering classification and labelling (according to both CLP and DSD).

By comparison, the average score obtained for fenoxaprop-ethyl in a similar study (24, 48 and 72 hours) was 1.14 for erythema, and 0.53 for oedema.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

RAC proposed no classification for fenoxaprop-P-ethyl for skin irritation, due to the low mean value of 0.11 for erythema within 72 hours. This is below the mean values triggering skin irritation classification of ≥2.3 - ≤4.0 for erythema according to CLP criteria and of ≥2 for erythema according to DSD, and the proposal for non-classification takes into account the absence of oedema or other signs of toxicity.

RAC evaluation of eye corrosion/irritation
Summary of the Dossier submitter's proposal

For fenoxaprop-P-ethyl, the average scores after 24, 48 and 72 hours were 0.61 for conjunctival redness, 0.22 for conjunctival chemosis, 0.06 for iritis and 0 for corneal opacity. The findings were accompanied by slight to considerable quantities of clear discharge up to 48 hours. No eye effects were noted at the end of the study duration (72 hours).

From supportive information on fenoxaprop-ethyl, the average scores after 24, 48 and 72 hours were 0.83 for conjunctival redness, 0.16 for conjunctival chemosis, 0 for iritis and 0.28 for corneal opacity. The findings were accompanied by slight to considerable quantities of discharge up to 72 hours. At study termination after 72 hours, 1/6 animals showed corneal opacity grade 1, 1/6 animals had discharge and 2/6 animals showed conjunctivae redness grade 1. Normally the observation period is 21 days. However, as the adverse effect clearly decreased within the first 72 hours and no classification is triggered based on the average scores within the first 72 hours, it is likely that no classification would be necessary, as it can be expected that these effects would be reversible within 21 days.

According to the dossier submitter, estimated eye irritation scores are below the criteria values for triggering classification and labelling (according to both CLP and DSD).

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

Estimated eye irritation scores (mean scores after 24, 48, and 72 hours; 0.22 (conjunctival chemosis), 0.61 (conjunctival redness) and 0.06 (iritis) are below the criteria for triggering classification and labelling. According to CLP, classification may be adequate at mean scores of ≥2 for conjunctival chemosis, ≥2 for conjunctival redness and ≥1 for iritis.

RAC agreed with dossier submitter's proposal and concluded that no classification for Eye irritation is warranted.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

A Guinea pig maximisation test according to Magnusson & Kligman was performed only with fenoxaprop-P-ethyl, which resulted in sensitising effects on the skin in 100% of the tested animals. However, in sensitisation tests according to Buehler, neither fenoxaprop-P-ethyl nor fenoxaprop-ethyl (this latter test with limited validity) showed sensitising effects on the skin of Guinea pigs.
The dossier submitter concluded that fenoxaprop-P-ethyl should be classified as a skin sensitiser Category 1B, H317 (May cause an allergic skin reaction) according to CLP and as Xi; R43 (Irritant; May cause sensitisation by skin contact) according to DSD.

Comments received during public consultation

A Danish company suggested that a negative LLNA study with fenoxaprop-P-ethyl in the mouse (Sanders, 2005) be considered, which they submitted to ECHA. They also stated that the substance, as it is an active ingredient in herbicides, has been used by hundreds of thousands of farmers worldwide and no cases of allergy caused by the substance have been reported. The company suggested that the positive results seen in the Maximisation test could be due to the exact composition used in that study. The dossier submitter replied that the impurity profile of fenoxaprop-P-ethyl in the batch used in the new LLNA study was not available, and responded that they had data on the composition in the Maximisation test (confidential information). The dossier submitter further considered that the positive result of the Maximisation test should not be disregarded unless the sensitisation potential can clearly be linked to an impurity present in the respective batch used in the maximisation test (Note: The evaluation of the LLNA study can be found in the RCOM).

The Spanish CA and the Swedish CA supported the proposed classification of fenoxaprop-P-ethyl as Skin Sens. 1B, H317 according to the 2nd ATP of CLP and as Xi; R43 (May cause sensitisation by skin contact) according to DSD.

Assessment and comparison with the classification criteria

Guideline-compliant testing for sensitising properties revealed two negative dermal sensitisation (Buehler) tests and one positive dermal sensitisation Maximisation test. Fenoxaprop-P-ethyl is concluded to have sensitising properties based on the positive Maximisation test, which was given more weight than the inconclusive or negative Buehler tests.

At an intradermal induction concentration of 5% fenoxaprop-P-ethyl in vaseline, 19/20 animals responded 48 hours after treatment with slight to severe erythema, 14/20 animals with slight oedema, and 2/20 animals with scab formation. The incidence of erythema was increased 72 hours after treatment and slight to severe erythema was noted in 20/20 animals, slight oedema (grade 1) in 11/20 animals and scab formation in 3/20 animals.

The classification criteria states that in a Guinea pig maximisation test, when ≥30% to < 60% of the animals respond at > 0,1% to ≤ 1% intradermal induction dose, or ≥ 30% of animals respond at > 1 % intradermal induction dose, classification as Skin Sens. 1B is justified. When fenoxaprop-P-ethyl was tested, 100% of animals responded at 5% fenoxaprop-P-ethyl in vaseline, and hence, in principle, the classification criteria as Skin Sens. subcategory 1B are fulfilled. However, there are no data showing that the reaction will be less than 60% after induction with 1%. Taking note of the high rate of responders (100%) at 5% induction concentration, it cannot be excluded that at 1% more than 60% will respond. Then subcategory 1A would be appropriate. As no definitive decision on the subcategory is possible, Category 1 was proposed by RAC.

RAC agreed on the classification as proposed by the dossier submitter, except for the subcategory 1B. Fenoxaprop-P-ethyl should be classified as Skin Sens. 1, H317 (May cause an allergic skin reaction) according to CLP. The corresponding DSD classification is R43 (Irritant; May cause sensitisation by skin contact).

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The dossier submitter proposed that fenoxaprop-P-ethyl be considered for classification as STOT RE 2, H373, for nephrotoxicity.

In the 28-day mouse study, moderate to marked tubular injury in females was found slightly below the cut-off value in the CLP guidance of 300 mg/kg bw/d. Furthermore, moderate to

marked tubular injury in females in the 90 day mouse study occurred at just above the guidance value for oral STOT RE of 100 mg/kg bw/d. At the next lower dose (11.9 mg/kg bw/d, males (M) and 16.5 mg/kg bw/d, females (F)) minimal tubular injury in one female was observed. In the ADME studies, females showed higher urinary excretion than males, which might be the reason for the higher sensitivity for renal tubular injury of females compared to males.

All other effects seen at doses below the guidance cut off values included changes in bodyweight, bodyweight gain and food consumption, small changes in clinical biochemistry, haematology and urinalysis, as well as changes in organ weights with no evidence of organ dysfunction. These effects did not result in clear functional disturbance or morphological changes of toxicological significance.

Comments received during public consultation

The Spanish and German CAs supported the proposed classification of STOT RE2, H373 for fenoxaprop-P-ethyl, based on the nephrotoxicity findings in mice.

RAC assessment and comparison with the classification criteria

Results from repeated dose studies were summarised and evaluated by the dossier submitter (see Table 97 of the background document), and a comparison with guidance values that are critical for classification as STOT RE 1 and 2 with regard to the study type conducted was recorded.

RAC evaluation of a 28d rat oral study (Suter P. *et al*, 1987a)

RAC's evaluation of each single study on fenoxaprop-P-ethyl and some missing details from the original table in the submitted CLH dossier were added to the table below for information.

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Fenoxaprop-P-ethyl					
Rat - oral (Suter P. *et al*, 1987a)	28 days	30	300	≥ 6 mg/kg bw/d: ↓ phospholipid levels, shorter thromboplastin time (F), ketonuria ≥ 26 mg/kg bw/d: ↓ in body weight gain and food consumption, ↓ cholesterol, ↑ triglycerides, Ketonuria, urobilinogenuria, ↑ rel. kidney and liver weights 95 mg/kg bw/d: Food consumption 80% of controls. BW significantly reduced in M&F. ↑ leucine aminopeptidase and alkaline phosphatase – indicative of	126-144 mg/kg bw/d: severe impairment of food consumption and growth, no further examination was done for the 126-144 mg/kg bw/d group which was terminated earlier. All other dose groups: only changes in bw gain, food consumption and small changes in clinical biochemistry, haematology and urinalysis. Changes in liver weight with no evidence of organ dysfunction

				hepatotoxicity, prolonged thromboplastin and partial thromboplastin times (M), urinalysis: ↓ creatinine and creatinine clearance, ↑ GGT and LDH <u>126 (M) – 144 (F) mg/kg bw/d:</u> group terminated on treatment day 9 due to severe impairment of food consumption, resulting in stagnation of growth, animals sacrificed in extremis (emaciation, ruffled fur and curved position (no further examination))	

↓ = decrease
↑ = increase

Significant impairment of general health status observed at 122-144 mg/kg bw/d and reduced body weight at 95 mg/kg bw/d were considered to be serious health effects that are relevant for classification. Palatability problems were not reported.

Prolonged thromboplastin time (statistically significant) in males at 1280 ppm (corresponding to 95 mg/kg bw/d) may indicate hepatotoxicity. However, by contrast with this finding, a shorter (statistically significant) thromboplastin time was found in females at 80, 320 and 1280 ppm.

Clinical biochemistry and urinalysis indicated liver toxicity (disorders of lipid metabolism and coagulation system) and kidney toxicity (decreased clearance function and increase in marker for cytotoxicity). The conclusion of the dossier submitter that there was no evidence of organ dysfunction appears therefore not to be justified.

The histopathology examination was reported to have been very limited (only the liver and kidneys were examined in controls and rats given 95 mg/kg bw/d). No treatment-related findings were observed. The study was considered to be a range-finding study.

RAC evaluation: 90d rat oral study (Tennekes H. *et al*., 1987)

Species-Route (Reference)	**Study duration**	**Cut-off value STOT RE 1[mg/kg bw/d]**	**Cut-off value STOT RE 2 [mg/kg bw/d]**	**Effects below cut-off value**	**Significance of toxicological effect below cut-off value**
Rat - oral (Tennekes H. *et al*., 1987)	90 days	10	100	<u>≥ 5.8 (M)-6.3 (F) mg/kg bw/d:</u> changes in lipid metabolism, ↑ in liver and kidney weights, ketonuria, urobilinogenuria and bilirubinuria <u>49 (M) – 51.8 (F) mg/kg bw/d only:</u> ↓ in body weight (non-reversible in M). and food consumption (n.s.), ↓ haemoglobin,	Small changes in bw, food consumption and small changes in clinical biochemistry, haematology and urinanalysis Changes in liver weight with no evidence of organ dysfunction

				haematocrit, MCV, ↑ MCHC, alkaline phosphatase, prolonged thromboplastin and partial thromboplastin times (M), shorter thromboplastin time (F), centrilobular hepatocellular hypertrophy	

n.s. = non-significant

Terminal body weight at 49 mg/kg bw/d was significantly lower in males at the end of treatment (15% below controls) and at the end of the 4-week recovery period (14% below controls). Reduced growth may indicate non-specific toxicity, as food consumption was only slightly reduced (-9% and -6% for the respective time periods).

Disorders in lipid metabolism (increased triglycerides, decreased HDL-cholesterol and phospholipid levels) and increased ALP levels were consistent with effects observed in the oral 28-day study and indicated liver dysfunction that was reversible at the end of the observation period. Mild to moderate (reversible) ketonuria may indicate increased catabolism of fatty acids, while the urobilinogenuria and bilirubinuria could be related to haemolysis.

Increased absolute and relative liver and kidney weights corresponded to macroscopic observations of enlarged organs. Microscopically, the only finding was centrilobular hypertrophy of hepatocytes in 5/10 males and 1/10 females at the high dose, which was reversible at the end of the recovery period.

Haematology parameters indicated slight microcytic anaemia. Reductions in haemoglobin and haematocrit were minor (below 10%) and not sufficiently severe for classification (see CLP criteria).

Regarding the results of this study only and the nature of the observed effects, there were indications of non-specific toxicity, liver and kidney dysfunction and haematotoxicity. Overall the adverse effects are not sufficiently severe to justify classification.

RAC evaluation: 28d mouse oral study (Suter P. *et al*., 1987b)

Species-Route (Reference)	**Study duration**	**Cut-off value STOT RE 1[mg/kg bw/d]**	**Cut-off value STOT RE 2 [mg/kg bw/d]**	**Effects below cut-off value**	**Significance of toxicological effect below cut-off value**
Mouse - oral (Suter P. *et al*., 1987b)	28 days	30	300	<u>≥ 56 (M) - 61 (F) mg/kg bw/d:</u> changes in lipid metabolism, ↑ liver weight associated with hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes, tubular injury in the kidney <u>260 (M) - 280 (F) mg/kg bw/d only:</u> ↑ terminal BW (F), food consumption + 25% (M), ↑ aspartate and alkaline aminotransferase, alkaline phosphatase,	Small changes in clinical biochemistry tubular injury: → 56-61 mg/kg bw/d: Minimal tubular injury was noted in the kidneys of 1/5 males and 4/5 females receiving 320 ppm → 260-280 mg/kg bw/d group: Slight unilateral tubular injury in 1/5 males and moderate to marked bilateral tubular injury in 5/5 females Liver: → slight single cell necrosis → changes in liver weight with no evidence of organ dysfunction → adaptive

				albumin and protein levels,↑ kidney weights	response to enzyme induction

The study was considered to be a range-finding study. Histopathology was reported to be very limited (only liver and kidneys were examined in all animals).

Increased activity of liver enzymes (ASAT, ALAT, ALP) at 260/280 mg/kg bw/d gave indications of liver cell dysfunction and may have been related to the observed hepatocellular toxicity.

While hepatocellular hypertrophy may be assumed to be related to increased metabolic enzyme activity, increased incidences of single cell necrosis and increased mitotic activity observed in males at ≥ 56 mg/kg bw/d and in females at 280 mg/kg bw/d (no information on severity grades and distribution) indicate liver damage. Increased incidences of renal tubular necrosis were observed at ≥ 56/61 mg/kg bw/d. Females were more sensitive than males, showing more marked increase in kidney weight, higher incidences of tubular cell toxicity and moderate to marked injury.

Liver toxicity and in particular kidney toxicity observed at doses below the critical guidance values for STOT RE 2 (CLP) and Xn; R48 (DSD) (300 mg/kg bw/d and 150 mg/kg bw/d, respectively) are serious health effects of relevance for classification.

RAC evaluation: 90d mouse oral study (Suter P. and Luetkemeier H., 1987a)

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Mouse - oral (Suter P. and Luetke-meier H., 1987a)	90 days	10	100	≥ 11.9 (M) - 16.5 (F) mg/kg bw/d: ↑ liver weight, tubular injury in the kidney 100.8 (M)- 122.4 (F) mg/kg bw/d only: changes in lipid metabolism, ↑ liver enzymes associated with hepatocellular hypertrophy, ↑ ALAT, ALP, total protein, albumin and urea, ↑ kidney weight	Changes in liver weight with no evidence of organ dysfunction → adaptive response to enzyme induction tubular injury: → 11.9-16.5 mg/kg bw/d group: Only minimal renal unilateral tubular injury in 1 female → 100.8-122.4 mg/kg bw/d group: minimal (4 males: grade 1) to slight (1male: grade 2) tubular injury in 5/10 males; moderate (7 females: grade 3) to marked (3 females: grade 4) tubular injury in all females

Decreased cholesterol and phopholipids in males were indicative of lipid metabolism disorders, and increased ALAT and ALP were indicative of liver toxicity. Increased levels of these enzymes are not likely to be related to liver cell hypertrophy.

Kidney toxicity was more marked in females, where increased urea, increased kidney weight, and in the renal cortex, mild tubular necrosis at 16.5 mg/kg bw/d and at 122.4 mg/kg bw/d moderate to marked tublular cell necrosis were observed. In males, minimal to slight tubular necrosis was observed at 100.8 mg/kg bw/d. Tubular cell injury was accompanied by regenerative hypercellularity, nuclear megaly, interstitial inflammation and basal membrane thickening.

Moderate to marked diffuse hepatocellular hypertrophy in males and slight to moderate hepatocellular hypertrophy in females at 100.8/122.4 mg/kg bw/d alone are not considered to be adverse health effects that warrant classification.

Looking at this study only, there is no doubt that the kidney lesions are serious health effects. The dosage at which these findings were observed in females was 122 mg/kg bw/d, which is just above the guidance value of 100 mg/kg bw/d for STOT RE 2 (CLP) and kidney lesions were also observed, with less marked incidence and severity, in males at 100.8 mg/kg bw/d.

Classification based on DSD criteria as Xn; R48 at a guidance value of 50 mg/kg bw/d would not be justified.

RAC evaluation: 28d dog oral study (Sachsse K. *et al*., 1987a)

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Dog - oral (Sachsse K. *et al*., 1987a)	28 days	? *	? *	≥3.7 mg/kg bw/d (F): ↓ food consumption	-

* was not reported by DS, Rapporteur's proposal is to use the same guidance values as in rodent studies for this duration

It is to be noted that 1 male and 1 female Beagle dog was treated per dose. The study was not relevant for classification purposes.

RAC evaluation: 90d dog oral study (Sachsse K. *et al*., 1987b)

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Dog - oral (Sachsse K. *et al*., 1987b)	90 days	? *	? *	77.7 (M) - 83.4 mg/kg bw/d: ↓ food consumption (F), ↓ body weight gain (M), ↑ aspartate aminotransferase, lactate dehydrogenase, and total protein (M), ↓ alkaline aminotransferase (M + F)	Changes in bw gain and small changes in clinical biochemistry
Rat - inhalation (Hofmann T. *et al*. 1989)	28 applications (6 h/d) within 40 days	0.04 mg/l	0.4 mg/L	≥ 0.015 mg/l: ↑ liver weight (M) ≥ 0.07 mg/l: ↓ thromboplastin time (M) 0.3 mg/l: ↓ body weight gain, ↓ haemoglobin and hematocrit, prolonged activated partial thromboplastin time (F), ↓ cholesterol, total lipids, alpha-1 globulin,↑ triglycerides, urea nitrogen, liver weight (F), kidney weight	Changes in bw gain and small changes in clinical biochemistry, haematology and urinanalysis Changes in liver weight with no evidence of organ dysfunction

* was not reported by DS, Rapporteur's proposal is to use the same guidance values as in rodent studies for this duration

It is to be noted that 4 males and 4 female Beagle dogs were treated per dose. As in rodents,

increased ASAT and LDH can be interpreted in dogs as being indicative of liver cell toxicity. No treatment-related macroscopic or microscopic findings were observed.

Increased enzyme activities were not accompanied by microscopic evidence of organ/cell damage. The observed treatment-related findings are not considered to be serious health effects that warrant classification.

RAC evaluation: rat inhalation stucy (Hofmann T. *et al*. 1989)

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Rat - inhalation (Hofmann T. *et al*. 1989)	28 applications (6 h/d) within 40 days	0.04 mg/l	0.4 mg/L	≥ 0.015 mg/l: ↑ liver weight (M) ≥ 0.07 mg/l: ↓ thromboplastin time (M) 0.3 mg/l: ↓ body weight gain, ↓ haemoglobin and hematocrit, prolonged activated partial thromboplastin time (F), ↓ cholesterol, total lipids, alpha-1 globulin,↑ triglycerides, urea nitrogen, liver weight (F), kidney weight	Changes in bw gain and small changes in clinical biochemistry, haematology and urinanalysis Changes in liver weight with no evidence of organ dysfunction

RAC agreed with the dossier submitter's conclusion that the liver was the main target organ due to increased absolute/relative weight and disordered lipid metabolism. Increased urea nitrogen and kidney weight indicated that the kidney was also affected. Due to the absence of treatment-related microscopic lesions in the liver and the kidney, the functional disorders and organ weight effects alone were considered not to be sufficient for classification.

Reductions in haemoglobin and haematocrit were observed in males only. The extent of the reduction was borderline for haemoglobin (-10% at the end of study, - 8% at the end of the recovery period) and reached 18%-19% for haematocrit. Based on the absence of other corroborating findings indicative for haemolytic anaemia at this level of reduction of haemoglobin (around 10%), it is concluded that the observed adverse effects are not sufficient for classification (see Muller *et al*., 2006).

It is concluded that based on the treatment-related effects observed in this 28-day inhalation study, no classification is warranted.

RAC evaluation: Rat repeat dose dermal study (Ebert E. *et al*. 1988)

Species-Route (Reference)	Study duration	Cut-off value STOT RE 1[mg/kg bw/d]	Cut-off value STOT RE 2 [mg/kg bw/d]	Effects below cut-off value	Significance of toxicological effect below cut-off value
Rat - dermal (Ebert E.	21 applications (6	60	600	≥ 10 mg/kg bw/d: hyperkeratosis and epidermal thickening	Small changes in clinical biochemistry and haematology

et al. 1988)	h/d) within 30 days, Recovery OECD 410 (1981)			<u>≥ 20 mg/kg bw/d:</u> ↑ kidney weight (F) <u>≥ 100 mg/kg bw/d:</u> ↓ haemoglobin, hematocrit and erythrocytes (M), ↓ thromboplastin time (F), ↓ cholesterol, total lipids (M), ↑ liver and kidney weight (M) <u>500 mg/kg bw/d:</u> ↓ terminal BW (n.s.), ↓ thromboplastin time (M), ↓ cholesterol (F), ↑ liver weight (F), heart and spleen weight (M)	Changes in organ weights with no evidence of organ dysfunction

RAC took note of the anaemic effects. Reductions in erythrocytes, haemoglobin and haematocrit were below 10% and not sufficiently severe to justify classification (see Muller *et al*., 2006). Disordered lipid metabolism and increases in liver weight in males at ≥ 100 mg/kg bw/d and in females at 500 mg/kg bw/d were not associated with microscopic liver lesions. Increased kidney weight was the only effect related to the kidney.

The effects of concern that could be considered for classification were the reduced absolute and relative heart weights, which remained lower after recovery. Terminal body weight was slightly (non-significantly) lower and may not explain the lower heart weight. No microscopic lesions were recorded. Data on creatine kinase or other heart muscle specific enzymes were not available. Thus the toxicological significance of this finding is equivocal.

Supportive information:
Repeated dose studies in rats, mice and dogs with fenoxaprop-ethyl alone or on the combined toxicity of fenoxaprop-P-ethyl with mefenpyr-diethyl in rats can be found in the background document. As a sufficient database on the substance of interest for classification purposes (fenoxaprop-P-ethyl) is available, the supportive information from fenoxaprop-ethyl will not be further considered here.

RAC conclusion on repeated exposure

RAC concluded from the eight available repeated-dose toxicity studies on fenoxaprop-P-ethyl that the kidney, liver and haematopoietic system are the main target organs. The most serious effect that triggers classification as STOT RE and as Xn; R48 is the kidney toxicity.

In mice treated orally for 28 days (Suter *et al*., 1987b), liver toxicity and in particular kidney toxicity observed at doses below the critical guidance values for STOT RE 2 (CLP) and R48 (DSD) (300 mg/kg bw/d and 150 mg/kg bw/d, respectively) are serious health effects of relevance for classification.

Consistent findings observed in the 90-day study on mice (Suter and Luethkemeier, 1987a) confirmed the potential for kidney toxicity. The dose at which kidney toxicity was seen in females was slightly above the guidance value of 100 mg/kg bw/d. Lesions were more marked in females than in males, where increased urea, increased kidney weight, and in the renal cortex, mild tubular necrosis were seen at 16.5 mg/kg bw/d. Moderate to marked tubular cell necrosis was observed at 122.4 mg/kg bw/d. In males, minimal to slight tubular necrosis was observed at 100.8 mg/kg bw/d. Tubular cell injury was accompanied by regenerative hypercellularity, nuclear megaly, interstitial inflammation and basal membrane thickening.

Effects indicating disorders of lipid metabolism (e.g., ketonuria) and coagulation system alone are not considered sufficient for classification; no corresponding microscopic liver lesions were observed. It appears questionable whether the level of (lipid or enzyme activity) changes were sufficiently marked to conclude that they represented significant dysfunction which alone would justify classification. The same is true for altered liver enzymes that are recognised as markers of liver cell toxicity.

Although indications of anaemia are not reported for all studies, it seems that this effect, like the adverse effects on the kidney and liver, does occur after administration via several routes. The severity of reductions in haematology parameters indicative of anaemia did not reach the level of significance (20%) recommended in the CLP guidance (or Muller *et al*., 2006) as a stand-alone adverse effect. Reductions by 10 % were observed, but were not accompanied by other adverse effects that may occur secondarily (according to the criteria given in Muller *et al*., 2006) and which would lead to classification.

The effects related to the liver and haematopoietic system are regarded as adverse effects supporting the classification proposal, which is mainly based on the kidney toxicity.

A non-reversible reduction in heart weights in the dermal rat study (Ebert *et al*., 1988) at 500 mg/kg bw/d, which is below the guidance value for STOT RE 2, may or may not have toxicological relevance. No indications of effects on heart weight or morphology were observed at the 6-month and 12-month interim sacrifices (see 4.10 in the background document) in rats of the same strain (Wistar). However, slightly reduced heart weights were also seen in one of two rat developmental studies at 100 mg/kg bw/d (Baeder *et al*., 1985a).

The classification as STOT RE covers all routes and no specific consideration of the dermal route is required. With regard to the DSD, a classification on the dermal route appears not to be justified based on the organ weight effect alone and its equivocal toxicological relevance.

The evidence reviewed in the aforementioned studies demonstrates that classification as STOT RE 1 is not appropriate, as none of the critical effects occurred below the lower guidance values for this category. RAC agreed with the dossier submitter's proposal to classify fenoxaprop-P-ethyl as STOT RE 2, H373 (May cause damage to organs (kidney) through prolonged or repeated exposure). In addition, RAC agreed to classify fenoxaprop-P-ethyl as Xn; R48/22 (Harmful, Danger of serious damage to health by prolonged exposure if swallowed) according to the DSD.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Fenoxaprop-P-ethyl was tested in a battery of *in vitro* and *in vivo* genotoxicity tests. All experiments were performed according to GLP and, if available, to OECD, EPA or EEC test guidelines. None of the *in vitro* tests, including gene mutation, chromosome aberration and DNA repair tests, indicated genotoxicity of fenoxaprop-P-ethyl. These results were confirmed in an *in vivo* micronucleus assay in NMRI mice. In conclusion, there was no indication that fenoxaprop-P-ethyl induced genotoxicity *in vitro* or *in vivo*.

Furthermore, fenoxaprop-ethyl was tested in a battery of *in vitro* and *in vivo* genotoxicity tests including gene mutation, chromosome aberration, DNA repair and micronucleus tests. All experiments were performed according to GLP and, if available, were designed to meet OECD, EPA or EEC test guidelines. However, none of the *in vitro* studies included a second, independent repeat experiment to confirm the results obtained in the genotoxicity testing. For this reason, all the *in vitro* studies were of limited validity on their own. However, given the number of studies performed, all of which were negative, the weight of evidence is still convincing. Further, the *in vivo* micronucleus assay with NMRI mice was conducted according to OECD, EPA or EEC test guidelines and can be considered scientifically valid and acceptable. None of the *in vitro* and *in vivo* genotoxicity tests performed with fenoxaprop-ethyl showed any evidence of genotoxic

potential for fenoxaprop-ethyl. Taken together, it can be assumed that fenoxaprop-ethyl is not genotoxic *in vitro* or *in vivo*.

Comments received during public consultation

No specific comment received.

Assessment and comparison with the classification criteria

Comparison with the criteria

None of the genotoxicity tests with fenoxaprop-P-ethyl showed any indication of genotoxcity. In conclusion, RAC agreed with dossier submitter's proposal that no classification is warranted for this hazard class.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No long term study has been provided for fenoxaprop-P-ethyl. However, the chronic/carcinogenicity studies performed with the closely related fenoxaprop-ethyl have been used, since the two compounds showed a similar profile in acute and short term studies. The long term toxicity of fenoxaprop-ethyl has been tested in rats, mice and dogs (2-year studies). Hepatocellular tumours were observed with incidences increasing with dose in mice, but these findings were shown to be due to a highly species-specific mechanism of peroxisome proliferation. No carcinogenic potential was observed in the other species.

Rats:
A long term toxicity/carcinogenicity study was performed in Wistar rats. Animals were sacrificed after 6, 12, 24 or 28 months, and in additional investigations hepatic enzyme levels, liver and kidney function and residues in the animal carcass were determined. During the whole study, changes in the lipid status were observed in the form of decreased total cholesterol and total lipid levels, which appeared consistently at the highest dose level of 180 ppm. Slight reductions in liver weights were observed after 24 and 28 months in male rats. Effects on kidneys (increased relative weights and calcification) were seen only at the interim sacrifice after 6 months in rats receiving 180 ppm. Adrenals were affected only at the 12 month sacrifice: an increase in organ weight, together with distension of the sinuses of the zona reticularis and medulla were observed in the 180 ppm group. No substance related carcinogenicity was observed in this study. Investigation of hepatic enzymes showed no clear evidence for peroxisomal proliferation. The overall NOAEL for long term toxicity in Wistar rats is considered to be 30 ppm (equivalent to 1.6 mg/kg bw/d in males and 2.0 mg/kg bw/d in females).

Mice:
Two carcinogenicity studies were conducted in NMRI mice. As no treatment-related effects could be observed at doses of 2.5, 10 and 40 ppm in the first study, higher doses (40, 115, 320 ppm) were tested in a second study. Pre-neoplastic changes consisting of hepatocellular hypertrophy and degenerative liver lesions were noted with dose-related incidences and severities predominantly in males at 115 and 320 ppm. In the high dose study, fenoxaprop-ethyl caused carcinogenicity in the liver of mice. Hepatocellular tumours (predominantly adenomas) were observed in 30% of the male animals receiving 320 ppm. The incidences of tumours in females at 320 ppm and males at 115 ppm were low when compared to controls, therefore a relationship to treatment remained unclear.

Peroxisome proliferation was shown to be a non-genotoxic mechanism for the hepatocellular carcinogenesis, using electron microscopy and special biochemical investigations, in the 3-month study in mice for fenoxaprop-ethyl (Ehling, 1993a). The electron microscopy examination showed an increase in the number of peroxisomes in hepatocytes in treated animals of up to 7 to 11 times the number found in the controls, whilst biochemical investigations demonstrated that catalase and malic enzymes, both marker enzymes for peroxisome proliferation, were increased at all dose

levels in both sexes. In addition, specific hepatic enzymes were assessed in 28-day and 13-week rodent and dog studies with fenoxaprop-P-ethyl (Section 4.12.1.3 of the background document – Special Investigations, background document); these studies showed that catalase activity was increased in mice from 80 ppm onwards and in rats from 640 ppm onwards. This mode of action for the induction of hepatic tumours is highly species-specific for rodents.
In the adrenal glands, an increase in adenomas of the subcapsular cells of type B was found in males at the high dose (320 ppm), which was well within the equivalent historical control data range (19.6 - 52.3%). Therefore, this finding was considered not to be treatment-related.
Kidney weights were slightly increased in both sexes in the 320 ppm group, but without any histological correlate. In conclusion, the NOAEL for NMRI mice in both carcinogenicity studies is considered to be 40 ppm (equivalent to 5.67 mg/kg bw/d for males and 6.83 mg/kg bw/d for females).

Dogs:
The long term toxicity of fenoxaprop-ethyl was tested in a 2-year study in Beagle dogs. In this study, a reduction in body weight was observed at the highest dose level of 75 ppm. Some reductions in organ weights (liver, lungs, thyroid, brain) were observed at the same dose level; however, these effects could be a result of inadequate exsanguinations, as stated by the study authors. The NOAEL for long term toxicity in Beagle dogs is considered to be 15 ppm (equivalent to 1.1 mg/kg bw/d in males and 0.9 mg/kg bw/d in females).

No evidence of carcinogenic properties was observed in rats or dogs. Liver adenomas and carcinomas found in NMRI mice were considered to be due to a non-genotoxic mechanism in rodents (peroxisome proliferation).

Comments received during public consultation

The Spanish CA agreed with the dossier submitter that classification for carcinogenicity is not warranted for Fenoxaprop-P-ethyl.

Assessment and comparison with the classification criteria

Comparison with the criteria

Rat:
The dossier submitter prepared a summary table (Table 123 in the background document) on the neoplastic findings in rats at study termination (28 months). Statistical evaluation of the tumour incidences yielded no statistically significant differences between the treated and the control animals.

Increased tumour incidences in high dose animals compared to those of the control groups, were noted for Leydig cell tumours in male testes and for theca granulosa cell tumours in female ovaries. A relationship to treatment could not be excluded, but increases in incidences of both tumour types were small and did not reach statistical significance. No historical control data from the testing laboratory on tumour incidences for the same breeding strain is available. Based on the limited information from a second 28-month carcinogenicity study from the same testing laboratory, the Leydig cell tumours in the control animals of the fenoxaprop-ethyl study was much lower (0% versus 8%) than may be expected. Theca granulosa cell tumours were reported in 2/99 control females in the second 28-month carcinogenicity study. The non-significant, small increase in its incidence in the high dose females in the fenoxaprop-ethyl study is likely to be a chance occurrence. No effects on weight or morphology of the ovaries have been reported from the 6-month or the 12-month interim groups. Thus no hints of precursor lesions were seen.

Carcinogenicity study of fenoxaprop-ethyl in Wistar rats. Benign neoplastic findings in rats at the study termination (Extracted from Table 123 in the background document)

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Benign neoplasms								
Testes - Leydig cell tumor	-	2 (60)	2 (60)	5 (60)				
Ovaries - Papillary Cystadenoma - Theca granulosa cell tumour - Tubular adenoma					1 (59) - -	- 3 (60) -	- 1 (60) -	- 4 (59) 1 (59)

RAC agreed with the dossier submitter's conclusion that fenoxaprop-ethyl had no carcinogenic effect in rats after a treatment period of 28 months.

Mouse:

The dossier submitter documented all neoplastic findings in mice at study termination (24 months) **in a summary table (Table 142 in the background document). Significant increases in neoplastic** findings were observed in the liver and the adrenals of male mice.

Fenoxaprop-ethyl caused hepatocellular tumours (predominantly adenomas) in 30 % of the male animals receiving 320 ppm. The tables below are identical to Tables 143 and 140 in the background document.

Carcinogenicity study of fenoxaprop-ethyl in NMRI mice

24 month sacrifice, neoplastic findings, liver

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Neoplastic liver findings								
Animals examined	50	49	50	50	49	50	49	50
Hepatocellular adenoma % hepatocellular adenoma	1 2.0	1 2.0	2 4.0	12** 24	- -	- -	- -	- -
% historical control range	1.2 (0 – 3.0)				0.2 (0 – 4.0)			
Hepatocellular carcinoma % hepatocellular carcinoma	- -	- -	1 2.0	4 8.0	- -	- -	- -	1 2.0
% historical control range	0.8 (0 – 2.0)				0.2 (0 – 1.0)			
Animals with tumours % animals with tumours	1 2.0	1 2.0	3 6.0	15** 30	- -	- -	- -	1 2.0

* ($p < 0.05$); significantly different from controls; ** ($p < 0.01$); significantly different from controls

With regard to non-neoplastic lesions in the liver the dossier submitter reported that a higher degree of liver cell hypertrophy was observed in male mice:

"Hepatocellular hypertrophy was present to a slight degree in the 320 ppm group in nearly all females and to a moderate degree in nearly all males. In the 115 ppm group, this finding was present only in some females and to a slight degree in the majority of the males. Hepatocellular hypertrophy was also observed to a slight degree in the 40 ppm group (5 males, 5 females). The hypertrophy was discussed to be the morphological correlate of the compound-caused proliferation of the peroxisomes.

At 320 ppm, increased numbers of degenerative liver lesions were observed, such as pigment in macrophages and hepatocellular lipofuscin in both sexes and single cell necrosis only in the males. In the 115 ppm group increased numbers of these degenerative liver lesions occurred only in the males. These findings were considered to be the consequence of chronic metabolic disorder of the liver due to the life-span treatment with the test compound."

Carcinogenicity study of fenoxaprop-ethyl in NMRI mice

24 month sacrifice, non-neoplastic findings, liver

	Dose group level (ppm)							
	Males				**Females**			
	0	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Non-neoplastic liver findings								
Hypertrophy – diffuse – cellular	- -	4 1	31** 4	46** -	- -	5* -	4 2	39** 1
Single cell necrosis	12	13	24*	22*	7	15	11*	12
Pigment in macrophages	2	9	21**	45**	14	25*	15	36**
Lipofuscin deposits	-	-	11**	22**	-	-	-	12**
Foci – basophilic	-	-	2 (1)	3 (2)	-	-	-	1
Foci - eosinophilic	-	-	-	3 (1)	-	-	-	-

* ($p < 0.05$); significantly different from controls; ** ($p < 0.01$); significantly different from controls

With regard to high incidences of hypertrophy or the degenerative lesions in males and females, it seems not to be plausible that increased incidences of hypertrophy or single cell necrosis might be precursor lesions, as no such tumour response was seen in high dose females. The tendency for liver cell foci to be seen in male mice was consistent with the higher incidence of hepatocellular adenomas in male mice. The dossier submitter stated that hepatocellular hypertrophy and degenerative liver lesions were noted, with dose-related incidences and severities, predominantly in males at 115 and 320 ppm. Peroxisome proliferation was discussed as being a non-genotoxic mechanism for the hepatocellular carcinogenesis, which is considered to be highly species-specific for rodents.

A supplementary 12-month study on hepatic enzyme levels revealed no increase in mixed-function oxidases at concentrations up to 40 ppm (which was chosen as low dose in the carcinogenicity study). However, cytochrome c reductase was significantly increased at 10 ppm (males only) and 40 ppm (both sexes), for which the reasons are unclear.

As there was no increase in catalase activity, peroxisomal proliferation could be excluded for the low dose (40 ppm). Additional studies on mice of the same strain (Suter and Luetkemeier, 1987b, c, d) that received higher concentrations of fenoxaprop-ethyl with the diet, showed increased

catalase activity and induction of cytochrome P450 enzymes at 640 ppm. Fenoxaprop-P-ethyl was not tested at 320 ppm, the dose at which fenoxaprop-ethyl produced liver tumours in mice. Treatment with 80 ppm fenoxaprop-ethyl did not result in tumour formation. Some remaining uncertainties, related to its potential to induce peroxisome proliferation in mice below 640 ppm, were resolved by data from an oral 13-week study with NMRI mice that received fenoxaprop-ethyl (Ehling, 1993a). Electron microscopy of liver cells of males demonstrated 7-11 -fold higher numbers of peroxisomes (but there was no information on whether this occurred at all doses (320, 640, and 1280 ppm)). Catalase and malic enzyme activities, both markers for peroxisome proliferation, were increased in males and females at 320 ppm and higher.

Based on the available data, there is evidence of liver enzyme induction and accelerated peroxisome proliferation in mice. No evidence of these effects in the rat was found at dietary concentrations up to 180 ppm in a supplementary study. At present, there are sufficient data that give clear evidence of peroxisome proliferation at the tumour-inducing dose of 320 ppm and higher. Catalase activity was not examined in the liver of the dog.

RAC agreed with the dossier submitter that the increased incidences of liver cell tumours in male mice can be interpreted as being secondary to a rodent-specific peroxisome proliferation. According to the CLP guidance, substance-related increases in liver tumours that were conclusively linked to peroxisome activation are considered not to be relevant for humans. Other non-genotoxic modes not yet identified cannot be excluded.

With regard to the adrenal tumours, a significant increase in adenomas was observed in high dose males (the table is identical to Table 144 in the background document).

Carcinogenicity study of fenoxaprop-ethyl in NMRI mice

24 month sacrifice, neoplastic findings, adrenal glands

	Dose group level (ppm)							
	Males				**Females**			
	0	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Neoplastic adrenals findings								
Animals examined	50	49	50	49	49	50	49	50
Subcapsular adenoma, type B % subcapsular adenoma, type B	11 22	11 22.5	15 30	21* 42.9	- -	- -	- -	- -
% historical control range	32.3 (19.6-52.3)				-			

* ($p < 0.05$); significantly different from controls

The dossier submitter concluded that the incidence of males at the high dose with this lesion (42.9%) was well within the equivalent historical control data range (19.6 - 52.3%); this finding was considered not to be treatment-related.

Whether the source of historical data was internal (same breeding stock, same laboratory, narrow time window in comparison to the study of concern) or whether the data were from published data for this strain, was not reported.

RAC agreed with the dossier submitter that a relationship to treatment- for the increased tumour incidences in the adrenal observed only in male mice can be considered as uncertain, taking into account that increased incidences of such tumours was not seen in female mice, the moderate incidence in the control group and the high range of spontaneous incidences as given by the dossier submitter.

Statistical evaluation of other tumour incidences yielded no significant differences between the treated and the control animals. A mode of action has not been identified for this tumour.

Dog:
No indication on a carcinogenic potential was seen in a 2-year (chronic) toxicity study in a small number of Beagle dogs.

RAC Conclusion on carcinogenicity

In conclusion, fenoxaprop-ethyl had no carcinogenic effect in rats after a treatment period of 24 months. In carcinogenicity studies on mice, liver tumours observed in male mice are considered not to be relevant for humans, due to mouse-specific activation of peroxisomal enzymes. No liver tumours were induced in female mice, and no other significant tumour response related to the treatment with fenoxaprop-ethyl was observed in mice.

Based on information from the carcinogenicity studies in two rodent species that received fenoxaprop-ethyl, RAC agreed with the dossier submitter's proposal and concluded that classification of fenoxaprop-P-ethyl is not warranted for carcinogenicity. RAC noted that uncertainties remained due to the testing with fenoxaprop-ethyl instead of testing with the biologically active isomer fenoxaprop-P-ethyl.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

No multi-generation study has been performed with fenoxaprop-P-ethyl. As the short term and developmental toxicological profiles of fenoxaprop-P-ethyl and fenoxaprop-ethyl were similar and at comparable effect levels, it was considered justified to use the multi-generation study with fenoxaprop-ethyl for the evaluation of the reproductive toxicity of fenoxaprop-P-ethyl. In the available study with fenoxaprop-ethyl, no effect on reproduction parameters, fertility or offspring development were observed. Based on organ weight changes (liver and kidney) and clinical chemistry parameters, in addition to reduced body weight gain in the offspring during lactation, the parental and the offspring NOAELs were 1.42 mg/kg bw/d, whereas the reproductive NOAEL was 8.77 mg/kg bw/d.

Developmental toxicity studies with fenoxaprop-P-ethyl have been conducted in rats and rabbits. All of the studies were performed according to GLP, and, when applicable, close to international test guidelines, although that was not specifically stated in the study reports.

In the embryotoxicity study in Wistar rats, maternal toxicity was observed at the highest dose of 100 mg/kg bw/d, as evidenced by decreased food consumption and decreased body weight gain. Also, placental and heart weights were reduced. These findings were confirmed in the embryo- and post-natal toxicity study in Wistar rats, where a decrease in food consumption, a decrease in body weight and a slightly increased duration of pregnancy was noted at 100 mg/kg bw/d. Foetal toxicity was demonstrated as embryonic death, reduced pup weight and pup length at 100 mg/kg bw/d. An increased rate of weak or no ossification of at least 1 cranial bone was observed at 32 mg/kg bw/d which was considered to be a treatment-related foetal development effect. However, since the incidence (56.8%) was only marginally outside the historical control range (min. 13.1 – max. 56%), in the absence of any other foetal findings at this dose level, according to the notifier, this common spontaneous variant finding, with no long term adverse consequences, could be considered a NOAEL for foetal toxicity. For the notifier this argumentation was supported by the fact that additionally, no effect on offspring was observed in the embryo- and postnatal toxicity study (Pensler 1987a) at a higher dose level of 100 mg/kg bw/d.

However, at the EFSA's PRAPeR expert meeting No. 19 (26-30.3.2007), it was agreed that the relevant developmental NOAEL was 10 mg/kg bw/d and the maternal NOAEL 32 mg/kg bw/d. An embryotoxicity study in Himalayan rabbits (Baeder *et al*., 1986a) also showed maternal toxicity at 100 mg/kg bw/d, resulting in decreased food consumption, decreased body weight gain during the treatment period, and slightly increased kidney weights. With respect to foetotoxicity, the only effect observed was an increase in the incidence of a 13th rib in the 100 mg/kg group, which was also slightly above the historical control value. A NOAEL for both maternal and fetal toxicity of 32 mg/kg bw/d was established.

Developmental toxicity of fenoxaprop-ethyl was studied in a range of studies in rats, rabbits, mice and monkeys. Furthermore, a study on embryotoxicity and postnatal development was conducted in rats. All of the studies were performed according to GLP, and, where applicable, closely followed the requirements in international test guidelines, although that was not specifically stated in most

of the study reports. With the exception of the study in monkeys, all studies were considered to be scientifically valid and acceptable.

The developmental study in Wistar rats showed maternal toxicity at the highest dose level of 100 mg/kg bw/d. Clinical signs (piloerection) and a decrease in food consumption and body weight were noted in the dams. The results of the embryo- and postnatal toxicity study in Wistar rats confirmed these findings, as similar maternal toxic effects such as decreased food consumption and body weight, and a slightly increased duration of pregnancy were observed at the same dose level. Foetotoxicity was demonstrated by empty implantation sites, reduced pup weight and length, and a slightly delayed ossification observed at 100 mg/kg. Diaphragmatic hernia occurred in control and treated animals; these were not considered related to treatment, as the incidences were within the historical control range. Deformities of the head which were found in one foetus at 32 mg/kg bw/d and three foetuses at 100 mg/kg bw/d could not be repeated in an additional 100 mg/kg dose group. In the embryo- and postnatal toxicity study, embryonic death was also observed, as one dam showed only implantation sites. However, post-natal development was not affected by treatment with fenoxaprop-ethyl. Taken together, a NOAEL of 32 mg/kg bw/d can be established for maternal and fetal toxicity in the rat. No teratogenicity was observed.

Two developmental toxicity studies with different dose levels have been performed in Himalayan rabbits. In the first study, the dose levels were 12.5, 50 and 200 mg/kg bw/d, and in the second study 2, 10 and 50 mg/kg bw/d. At the highest dose level of 200 mg/kg, excessive maternal toxicity was observed, resulting in a reduced number of dams with live foetuses, an increase in abortions and early resorptions, and macroscopic enlargement and increased weights of the liver and spleen. A decreased number of resorption sites and of live foetuses per dam was observed at 50 mg/kg bw/d in the second rabbit study. These effects showed no statistical significant difference compared to concurrent controls, but were outside the range of previous studies. Additionally, a decrease in food consumption, a reduction in body weight during the treatment period, and decreased defecation were noted at 50 and 200 mg/kg bw/d. Embryonic death, reduced pup weight and reduced pup length were observed at 200 mg/kg bw/d, as well as an increased incidence of a 13th rib, all demonstrating embryotoxicity at this dose level. Furthermore, the incidence of diaphragmatic hernias was increased at 200 mg/kg bw/d (3 of 28 foetuses, 10.7 %). As maternal mortality at 200 mg/kg was greater than 10% (13.3%), maternal toxicity is considered excessive and according to the Guidance on the Application of the CLP Criteria, the data for that dose level 'shall not be considered for further evaluation'. A single case of diaphragmatic hernia was also observed in the second rabbit study at 50 mg/kg bw/d (1 of 40 foetuses, 2.5 %). It remains questionable whether this was related to treatment. In conclusion, in the first study, maternal NOAEL could be set at 12.5 mg/kg bw/d while the foetal NOAEL was 50 mg/kg bw/d. In the second study, the NOAEL for maternal and fetal toxicity was 10 mg/kg bw/d.

An embryotoxicity study was also performed in CD-1 mice. In this study, the only effect of maternal toxicity was an increased liver weight at 50 mg/kg. No foetotoxicity or teratogenicity was observed. The NOAEL for maternal toxicity is 10 mg/kg bw/d, while the NOAEL for foetal toxicity is 50 mg/kg bw/d.

A developmental toxicity study with fenoxaprop-ethyl in Cynomolgus monkeys (Osterburg, 1984) was of limited validity as no concurrent controls were used and the historical control data showed high variations for the incidence of abortion. Furthermore, the high dose employed in this study (50 mg/kg) was severely toxic to the dams, leading to mortality and abortions. As a result of maternal toxicity, only three foetuses were available in this dose group for evaluation of foetotoxicity or teratogenicity. Further maternal toxicity effects observed were slight diarrhoea and / or a reduction of food intake in both dose groups (10 and 50 mg/kg). Also, clinical chemistry was affected, showing a reduction in lipid parameters during the treatment period in all treated dams. In foetuses, relatively high rates of undeveloped or uneven thickening of the ribs were observed in both dose groups. Taken together, it is not possible to draw firm conclusions from this study to assess the maternal and foetal toxicity and teratogenicity of fenoxaprop-P-ethyl. Therefore, no NOAELs were established.

In conclusion, no classification for Reproductive toxicity is proposed.

Comments received during public consultation

Only one specific comment was received. The Spanish CA agreed with the use of the multi-generational study conducted with fenoxaprop-ethyl for the evaluation of the reproductive toxicity of fenoxaprop-P-ethyl due to their similar developmental toxicological profiles at comparable effect levels. The Spanish CA agreed with the proposal to not classify Fenoxaprop-P-ethyl for fertility and developmental effects under the CLP and DSD classification criteria.

Assessment and comparison with the classification criteria

Comparison with the criteria

Effects on fertility

With regard to the absence of effects on reproduction parameters and fertility in a multi-generation study on fenoxaprop-ethyl in Wistar rats and with regard to read across as proposed by the dossier submitter due to the similar toxic profiles with both substances, it is concluded that fenoxaprop-P-ethyl does not induce adverse effects on fertility.

The RAC noted that the Committees consideration the data in an efficient manner could have been facilitated if summary tables with details of all reproduction/fertility parameters of the multi-generation study had been included in the CLH dossier.

Developmental toxicity

Some developmental effects such as increased embryonic death, reduced pup weight and delayed skeletal ossifications in rats and increased incidences of a 13^{th} rib in rabbits were observed after prenatal treatment with fenoxaprop-P-ethyl. Effects occurred only at doses that caused maternal toxicity.

Overall effects in studies on fenoxaprop-P-ethyl were comparable to those seen in studies with fenoxaprop-ethyl. No developmental toxicity has been observed in the study on fenoxaprop-ethyl in mice. The information from the study on Cynomolgus monkeys is not valid for classification purposes.

For developmental effects that were seen only in association with maternal toxicity, classification is not appropriate 'if a test substance is so toxic that maternal death or severe inanition results, or the dams are prostate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects' (CLP guidance).

Maternal toxic effects were seen in three developmental studies at 100 mg/kg bw/d fenoxaprop-P-ethyl: In a first rat study at 100 mg/kg bw/d fenoxaprop-P-ethyl dams showed a lower body weight (-13%) and reduction in body weight gain of -27% on GD 21 (Baeder *et al*., 1985a). In the second rat (embryotoxicity/postnatal developmental) study a reduced body weight gain of – 16% (Pensler *et al*., 1987a) was observed at 100 mg/kg bw/d, while rabbits demonstrated body weight loss (Baeder *et al*., 1986a) at this dose. Reductions in body weight gain were associated with reduced food consumption. No clinical signs of toxicity or any abnormal maternal behaviour was reported. Reduced growth at this dose was a significant effect, in particular in the rabbits which lost body weight during the treatment period.

With regard to the rat developmental study of Baeder *et al*. (1985a) the mean pup weight in the 100 mg/kg dose group was -18% compared to the controls. The decrease could not be explained by a higher number of foetuses and appears to reflect the maternal reduction in body weight. Thus this foetotoxic effect is likely to be secondary to maternal toxicity. No foetotoxic effect was observed in the second rat and in the rabbit study.

No treatment-related malformations were observed in the rat studies. A higher number of skeletal variations (weak or no ossification of at least one cranial bone) were observed in all dose groups in the rat developmental study (Baeder *et al*., 1985a). Incidences at doses below 100 mg/kg bw/d (maternal toxic dose) were reported to be within the historical control range. The effect was not observed in rabbits. According to the CLP guidance delayed ossifications are considered to be minor developmental changes that do not justify classification.

The developmental study in rabbits (Baeder *et al*., 1986a), revealed a higher incidence of the anlage of a short or normally sized 13th rib (13.5% versus 2.1% in controls, Table 154 in the background document) in animals at 100 mg/kg bw/d. This dose was associated with body weight loss in the dams and slightly (non-significantly) lower mean pup weights. Previous control incidences of this anlage were cited to be 0-10.2%. A relationship of this effect to treatment at maternal toxic doses and with regard to the overall small increase compared to the historical control range was considered unlikely; a similar study on fenoxaprop-ethyl revealed incidences at doses of 2-50 mg/kg bw/d between 2.0 – 10% without any dose-relationship (Table 162 of the background document).

RAC noted the lack of indications of adverse effects on reproduction parameters and fertility from treatment with fenoxaprop-ethyl and the absence of adverse developmental effects of fenoxaprop-P-ethyl at maternally non-toxic doses. Adverse effects on pup development were only seen at doses of fenoxaprop-P-ethyl, which caused significant maternal toxicity and which were considered to be secondary to maternal toxicity. No treatment-related teratogenic effects were observed. RAC agreed with the proposal of the dossier submitter to not classify for fertility and developmental effects.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Fenoxaprop-P-ethyl currently does not have a harmonised classification. The dossier submitter proposed classification as Aquatic Acute 1, H400 (M=1) and Aquatic Chronic 1, H410 (M=1) according to CLP, and R50/53 according to DSD.

Degradation
One hydrolysis study was performed according to OECD 111 using fenoxaprop-P-ethyl and another one with its degradation product fenoxaprop-P. In the first study, the following DT_{50}'s have been estimated at 25 °C: pH 4 = 2.8 days, pH 5 = 19.2 days, pH 7 = 23.5 days, and pH 9 = 0.7 days. In the second study the hydrolytic stability of the degradation product fenoxaprop-P was determined (DT_{50} at 25°C: pH 5 = 26.8 days, pH 7 = 182.7 days, and pH 9 = 33.5 days).

No ready biodegradability test data were available. The substance is considered not readily biodegradable.

The behaviour of radio-labelled fenoxaprop-P-ethyl ([U-^{14}C-chlorophenyl] and [U-^{14}C-dioxyphenyl]) in a water/sediment system has been investigated in two studies. These studies show rapid primary degradation with formation of fenoxaprop-P AE F088406 and hydroxypropoxypropionic (HOPP) acid AE F096918 as major degradants. In the simulation test (according to German BBA Guideline) performed with [U-^{14}C-chlorophenyl]-labelled fenoxaprop-P-ethyl, two different water/sediment systems (sand and silt loam) were used. For fenoxaprop-P-ethyl, a DT_{50} (total system) of 0.1 days was reported. The DT_{50}-values for the degradation of the initial degradant fenoxaprop-P were 6.9 and 13.0 days (total system). 27.6% AR $^{14}CO_2$ was formed in the sand system after 199 days and 17.6% AR ^{14}CO2 was formed in the silt loam system after 120 days (NER formation in the sand system accounted for 54.9% at day 199, and in the silt loam system 75.5% at day 199). The second study (OECD 308) was performed with [U-^{14}C-dioxyphenyl]-labelled fenoxaprop-P-ethyl. The degradation has been investigated in a loamy sand system and a clay system. The DT_{50}-values for fenoxaprop-P-ethyl were 0.16 days and 0.29 days (total system). For the predominantly formed degradation product fenoxaprop-P DT_{50}-values for the degradation in total systems were 40 days and 39 days. Carbon dioxide

formation in the loamy sand system was 45.9% AR after 118 days and in the clay system 46.5% AR after 90 days (NER formation was 33.5% in the loamy sand system and 27.3% in the clay system at day 118). The geometric mean of the DT_{50}-values in total water/sediments systems was 0.2 days for fenoxaprop-P-ethyl and 19.3 days for fenoxaprop-P.

The aerobic biodegradation of fenoxaprop-P-ethyl in soil was tested in three laboratory studies. The results show rapid primary degradation in soil. Geometric mean DT_{50}-values (simple first order kinetics) were estimated to be 0.43 days for fenoxaprop-P-ethyl, 6.6 days for the transformation product fenoxaprop-P and 7.5 days for the transformation product benzoxazolone. The formation of CO_2 was too low to demonstrate 70% ultimate degradation in 28 days (^{14}C-chlorophenyl-label: 9.7 to 32.5% AR after 100 days; ^{14}C-dioxyphenyl-label: 45 to 55% after 64 days; NER (^{14}C-chlorophenyl-label) 49 to 70% after 100 days; NER (^{14}C-dioxyphenyl-label): 28 to 32% after 64 days.

In the overall conclusion for the rapid degradation, the dossier submitter states that no half-lives in abiotic tests are > 16 days. DT_{50} (whole system) in aerobic water-sediment system is <16 days, but the CO_2 formation demonstrates no ultimate degradation to a level of at least 70% within 28 days. Moreover, the dossier submitter considers the major degradation product fenoxaprop-P relevant for classification and labelling.

Bioaccumulation
In an OECD 117 test (HPLC method) a log Kow of 4.58 was measured at 30 °C.

A bioaccumulation study (OECD 305) in bluegill sunfish was performed with two nominal concentration levels of 0.001 mg/l and 0.01 mg/l under flow-through conditions. Concentration was determined based on radioactivity. The concentration of fenoxaprop-P-ethyl in water rapidly decreased to 38% (low treatment level) and 50% (high treatment level) after fish was added. As degradation products the free acid (49% and 45%) and benzoxazolone (< 5%) were measured. The same pattern was found in fish tissue. The mean lipid content (wet weight basis) was estimated to be 7.2% at study begin. During the whole test study the mean total lipid content was 9.0 ± 0.9% in the low treatment and 8.9 ± 1.1% in the high treatment.
After 27 days exposure and 14 days depuration, BCF values (whole fish) of 280 and 338 were obtained. In non-edible portions, BCF values of 548 and 619 were determined. The depuration half-life accounted for 0.4 days.

The dossier submitter concludes that the measured BCF is above the classification criterion of ≥ 500 (CLP) and below the classification criterion of ≥ 100 (DSD).

Aquatic toxicity
Studies on aquatic toxicity are available for fenoxaprop-P-ethyl and its degradant fenoxaprop-P.

The most sensitive species tested for acute toxicity of fenoxaprop-P-ethyl is the Bluegill sunfish with a LC_{50} (96h) of 0.19 mg/l based on mean measured concentrations. Regarding chronic toxicity of the substance, the lowest value has been obtained for *O. mykiss* with a 91d NOEC of 0.036 mg/l based on nominal concentrations for the endpoint mortality.

For the degradant fenoxaprop-P, two studies on acute aquatic toxicity have been conducted. The green algae *P. subcapitata* turned out to be more sensitive than *O. mykiss* with an EC_{50} of 34.2 mg/l based on biomass. *D. magna* showed the lowest value for chronic aquatic toxicity with a NOEC of 1 mg/l (based on nominal concentration) based on reproduction and weight.

When comparing with criteria for environmental hazards the dossier submitter proposes to classify fenoxaprop-P-ethyl as H400 (M=1) and H410 (M=1) based on the study results for the parent compound.

Table 1: Data element acute (short-term) aquatic toxicity of the active substance fenoxaprop-P-ethyl

	$L(E)C_{50}$ [mg/l]		Test guideline / design	GLP (y/n)	Reliability
Fish (96 hr LC_{50}):					
Oncorhynchus mykiss Rainbow trout	0.39 (m)		OECD 203, US EPA §72-1	y	n
Oncorhynchus mykiss Rainbow trout	0.46 (n)		US EPA §72-1	y	n
Lepomis macrochirus Bluegill sunfish	**0.19** (m)		OECD 203, US EPA §72-1	y	y
Crustacea (48 hr EC_{50}):					
Daphnia magna	> 1.06 (m)		OECD 202, US EPA §72-	y	n
Algae and water plants: (EC_{50})					
Pseudokirchn. subcapitata Green alga	0.54 (72h, m)	biomass	EPA 540/9-86-134	y	n
Anabaena flos-aquae Blue-green alga	>0.73 (im)	biomass growth rate	OECD 201, US EPA §122-2	y	n
Lemna gibba Duckweed	> 2.76 (im)	biomass growth rate	US EPA §122-2	y	n
Conclusion: Fenoxaprop-P-ethyl is very toxic to standard test species of fish and algae and toxic to aquatic invertebrates and higher plants. The most sensitive species is the Bluegill sunfish *Lepomis macrochirus* with an EC50 of 0.19 mg/l.					

Test concentration based on mean measured (m), initial measured (im) or nominal (n) concentration.

Table 2: Data element chronic (long-term) aquatic toxicity of the active substance fenoxaprop-P-ethyl

	NOEC [mg/l]		Test guideline / design	GLP (y/n)	Reliability
Fish (NOEC):					
Oncorhynchus mykiss Rainbow trout	0.1 (n)	mortality weight [1)]	OECD 204 flow-through	y	n
Oncorhynchus mykiss Rainbow trout (ELS)	**0.036** ≥ 0.1 (n)	mortality hatchability	US EPA §72-4 flow-through	y	y
Crustacea (21 d NOEC,):					
Daphnia magna	0.22 (m)	mortality reproduction	OECD 202, Part II 4 semi-static	y	n
Algae and water plants: (NOEC)					
Pseudokirchn. subcapitata Green alga	0.05 (m)	biomass	OECD 201	y	n
Skeletonema costatum Diatom (marin)	0.38 (im)	biomass growth rate	OECD 221 (Draft October 2000)	y	n

Other aquatic organisms (26 d NOEC)					
Chironomus riparius Midge	0.2 (im)	emergence development	BBA Guideline, OECD 219		
Conclusion: Fenoxaprop-P-ethyl is very toxic to fish, daphnids, algae and to *Chironomus riparius*. The most sensitive species is *Oncorhynchus mykiss* with a NOEC of 0.03628 mg/l.					

[1)] toxicity values based on mean measured concentration of dissolved test substance (sum of AE F046360 = fenoxaprop-P-ethyl (D-enantiomer)+ AE F053022 = fenoxaprop (racemic mixture)
Test concentration based on mean measured (m), initial measured (im) or nominal (n) concentration.

Table 3: Data element acute (short-term) aquatic toxicity of the major degradation product fenoxaprop-P

	L(E)C50 [mg/l]		**Test guideline / design**	**GLP (y/n)**	**Reliability**
Fish (96 hr LC_{50}):					
Oncorhynchus mykiss Rainbow trout	> 72.2 (m)		OECD 203, US EPA §72-1	y	n
Algae and water plants: (ErC50)					
Pseudokirchn. subcapitata Green alga	35.0 **34.2** (m)	biomass	EPA 540/9-86-134, 1986	y	y
Conclusion: The degradation product fenoxaprop-P is harmful to standard test species of fish and algae. The most sensitive species is the Green alga *Pseudokirchn. subcapitata* with an EC50 (only biomass data are available) of 34.2 mg/l.					

Test concentration based on mean measured (m), initial measured (im) or nominal (n) concentration.

Table 4: Data element chronic (long-term) aquatic toxicity of the degradation product fenoxaprop-P

	NOEC [mg/l]	**Test guideline / design**	**GLP (y/n)**	**Reliability**
Fish (NOEC):				
Oncorhynchus mykiss Rainbow trout	≥ 3.2 (n)	OECD 215	y	n
Crustacea (21 d NOEC):				
Daphnia magna Waterflea	**1.0** (n)	OECD 211, US EPA §72-4	y	y
Algae and water plants: (NOEC)				
Pseudokirchn. subcapitata Green alga	13.7 (n)	EPA 540/9-86-134, 1986	y	n
Conclusion: The degradation product fenoxaprop-P is chronic toxic to daphnids (*Daphnia magna*) and toxic to fish and algae. The most sensitive species is *Daphnia magna* with a NOEC = 1 mg/l.				

Test concentration based on mean measured (m), initial measured (im) or nominal (n) concentration.

Comments received during public consultation

Five member states (MS) and one industry representative (IND) contributed during public consultation. Three MS stated general agreement with the proposed classification including environmental hazards. One MS and IND limited their comments to health hazards. Another MS agreed to the proposed environmental classification while addressing specific arguments for support and asking why *Lemna gibba* is not considered as the most sensitive species for the

degradation product fenoxaprop-P. The dossier submitter has clarified that for *Lemna gibba* no study with fenoxaprop-P is available.

Assessment and comparison with the classification criteria

Degradation: For fenoxaprop-P-ethyl, no ready biodegradability test data are available.
The hydrolytic stability of fenoxaprop-P-ethyl was determined. The highest half-life in the pH range 4-9 was 23.2 days at pH 7. Fenoxaprop-P-ethyl does not undergo a fast primary abiotic degradation.

Two water/sediment simulation tests were carried out. The half-lives for fenoxaprop-P-ethyl were < 1 day and, therefore below the criterion for rapid primary degradation (< 16 days). The initial primary degradation indicated by ester hydrolysis of fenoxaprop-P-ethyl leads to the formation of the major degradant fenoxaprop-P. Moreover, in one of the water/sediment studies, benzoxazolone AE F054014 and phenol AE F040356 were referred to as minor degradants, whereas in the other study hydroxypropoxypropionic (HOPP) acid AE F096918 was identified as another degradant besides fenoxaprop-P. Information on the aquatic toxicity of the degradation products is provided for the degradation product fenoxaprop-P. A NOEC of 1.0 mg/l was obtained in *Daphnia magna*; thus fenoxaprop-P is classifiable. During both water/sediment studies the formation of $^{14}CO2$ was measured. In all cases the $^{14}CO2$ formation did not reach 70 % after 28 days. In the water/sediment system the highest $^{14}CO2$ formation was 46.5 % after 90 days.

In summary, fenoxaprop-P-ethyl does not undergo a fast primary hydrolysis. Under environmentally more realistic conditions in water/sediment studies, fast primary degradation was observed with formation of a classifiable degradation product. Ultimate degradation of >70% within 28 days was not observed. It can be concluded that fenoxaprop-P-ethyl is not rapidly degradable.

Bioaccumulation
A measured log Kow of 4.58 and whole body BCFs of 280 (low concentration) and 338 (high concentration) determined in a 56-day BCF study with bluegill sunfish indicate moderate bioaccumulation potential of fenoxaprop-P-ethyl.

However, the dossier submitter did not specify whether the BCF has been adjusted to a lipid content of 5%, although this would not affect the classification. When adjusting the reported BCFs to a lipid content of 5%, the values are below the decisive CLP criterion (BCF ≥ 500) and above the DSD criterion (BCF ≥ 100). The latter triggers a classification as R53 according to DSD, in line with the dossier submitter's proposal.

Aquatic Toxicity
Several studies on acute and chronic aquatic toxicity are available for fenoxaprop-P-ethyl and its degradant fenoxaprop-P. From the descriptions in the CLH report it is not entirely clear why the dossier submitter considers only some of these studies as reliable, however RAC noted that the dossier submitter confirms all key studies to be so, and that studies marked not reliable in the CLH report are considered reliable in the DAR. The purity of tested material ranged from 95.8 to 97.4% active ingredient. The assessment of the toxicity studies has to bear in mind fenoxaprop-P-ethyl's limited water solubility of 0.7 mg/l, whereas the higher solubility of the free acid fenoxaprop-P is not specified in the CLH report.

Acute Toxicity
RAC agreed with the dossier submitter to classify fenoxaprop-P-ethyl according to the lowest LC_{50} value of 0.19 mg/l from a 96h test with bluegill sunfish. Two other fish studies conducted with *O. mykiss* resulted in similar LC_{50} of 0.39 mg/l and 0.46 mg/l. In spite of the herbicidal use of fenoxaprop-P-ethyl, algae and duckweed studies did not show higher toxicities; water fleas were even less sensitive. For the degradation product fenoxaprop-P, available test results with fish and algae indicate a lower toxicity compared to the parent compound.

Chronic Toxicity

With regard to chronic toxicity of fenoxaprop-P-ethyl there is also a fish study resulting in the highest toxicity, i.e. a 91-day early life stage (ELS) test with rainbow trout giving a NOEC of 0.036 mg/l (nominal concentration, flow through regime, concentrations measured at the beginning of the test and weekly during the test duration accounted for 100-104% of nominal, calculated from 75-85% fenoxaprop-P-ethyl and 17-28% fenoxaprop-P). As for acute toxicity, the available algae and duckweed studies provided no evidence for a pronounced herbicidal toxicity profile. RAC noted some initial concerns regarding apparent uncertainties about real exposure concentrations or evaluation method (only biomass related EC-values). Chronic tests with invertebrates, i.e. water fleas and midget larvae resulted in similar NOEC values around 0.2 mg/l. RAC noted that the OECD TG 219 study with chironomids uses sediment and although introducing the test substance by spiking water, the strongly adsorbing properties of fenoxaprop-P-ethyl suggest that it significantly partitions to the sediment, thus preventing the test results from being conclusive for classification purposes. The fish NOEC of 0.036 mg/l and the algae NOEC of 0.05 mg/l (biomass) fulfil the ≤ 0.1 mg/l CLP criterion for Category Chronic 1 (non-rapidly degradable) with a corresponding M-factor of 1, as 0.01 < 0.036 ≤ 0.1 mg/l.

Chronic toxicity of the degradation product fenoxaprop-P is lower than that of the parent compound. A 21-day semi-static reproduction test with *Daphnia magna* resulted in a NOEC for reproduction and weight of 1.0 mg/l (LOEC 3.2 mg/l) based on nominal concentrations. An OECD 215 study with rainbow trout and an algae test resulted in higher NOECs of ≥ 3.2 and 13.7 mg/l, respectively.

Conclusion on classification

Aquatic acute classification according to CLP criteria

RAC agreed with the dossier submitter that fenoxaprop-P-ethyl fulfils the ≤ 1 mg/l CLP criterion for category **Acute 1 (H400)** based on the lowest LC_{50} value of 0.19 mg/l. As 0.1 mg/l < 0.19 mg/l ≤ 1 mg/l, a corresponding **M-factor = 1** should be applied.

Aquatic chronic classification according to CLP criteria

Fenoxaprop-P-ethyl undergoes fast primary degradation, but has to be considered non-rapidly degradable according to the classification criteria. Based on the lowest NOEC value of 0.036 mg/l from an ELS test with rainbow trout, RAC recommends to classify fenoxaprop-P-ethyl as **Chronic 1 (H410)** with a corresponding **M-factor = 1**. This is in line with the dossier submitter's proposal.

Aquatic hazard classification according to DSD criteria

Fenoxaprop-P-ethyl is not readily degradable and its measured BCF is >100. Following the DSD surrogate approach, the substance thus fulfils the criteria for R53 while the acute toxicity meets the ≤ 1mg/l DSD criterion for R50, thus RAC agreed with the dossier submitter's proposal that it should be classified as **R50/53**. The SCL corresponding to the decisive LC_{50} of 0.19 mg/l are:
N; R50-53: C ≥ 25%
N; R51-53: 2.5% ≤ C <25%
R52-53: 0.25% ≤ C < 2.5%

References (additional only; other references mentioned here are contained in the Background Document):

Muller A, Jacobsen H, Healy E, McMickan S, Istace F, Blaude M-N, Howden P, Fleig H, Schulte A (2006) Hazard classification of chemicals inducing haemlotic anaemia: An EU regulatory perspective. Reg Toxicol Pharmacol 45:229-241.

Sanders (2005), Fenoxaprop-P-ethyl technical Local Lymph Node Assay in the Mouse, SPL Project Number: 545/339 (for full reference, see RCOM table)

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and RAC (excl. confidential information)