Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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/A1

Adopted

7 March 2013

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Fenoxaprop-P-ethyl

EC Number: -

CAS Number: 71283-80-2

Index Number: -

Contact details for dossier submitter:

Version number: 2 **Date: 21 December 2011**

CONTENTS

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING 16

1.1 SUBSTANCE 16
1.2 HARMONISED CLASSIFICATION AND LABELLING PROPOSAL 16
1.3 PROPOSED HARMONISED CLASSIFICATION AND LABELLING BASED ON CLP REGULATION AND/OR DSD CRITERIA 17

2 BACKGROUND TO THE CLH PROPOSAL 12

2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING 12
2.2 SHORT SUMMARY OF THE SCIENTIFIC JUSTIFICATION FOR THE CLH PROPOSAL 12
2.3 CURRENT HARMONISED CLASSIFICATION AND LABELLING 12
2.4 CURRENT SELF-CLASSIFICATION AND LABELLING 13
2.4.1 Current self-classification and labelling based on the CLP Regulation criteria 13
2.4.2 Current self-classification and labelling based on DSD criteria 13

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL 13

SCIENTIFIC EVALUATION OF THE DATA 14

1 IDENTITY OF THE SUBSTANCE 14

1.1 NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE 14
1.2 COMPOSITION OF THE SUBSTANCE 11
1.2.1 Composition of test material 11
1.3 PHYSICO-CHEMICAL PROPERTIES 11

2 MANUFACTURE AND USES 22

2.1 MANUFACTURE 22
2.2 IDENTIFIED USES 22

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES 22

No classification required 22

4 HUMAN HEALTH HAZARD ASSESSMENT 22

4.1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) 25
4.1.1 Non-human information 25
Summary of ADME studies with Fenoxaprop-P-ethyl in rats 25
4.1.2 Human information 29
4.1.3 Summary and discussion on toxicokinetics 29
4.2 ACUTE TOXICITY 30
4.2.1 Non-human information 30
4.2.1.1 Acute toxicity: oral 30
4.2.1.2 Acute toxicity: inhalation 33
4.2.1.3 Acute toxicity: dermal 34
4.2.1.4 Acute toxicity: other routes 35
4.2.2 Human information 36
4.2.3 Summary and discussion of acute toxicity 37
4.2.4 Comparison with criteria 37
4.2.5 Conclusions on classification and labelling 37
4.3 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT SE) 38
4.4 IRRITATION 39

4.4.1 Skin irritation ... *39*
4.4.1.1 Non-human information ... 39
4.4.1.2 Human information ... 41
4.4.1.3 Summary and discussion of skin irritation ... 41
4.4.1.4 Comparison with criteria ... 41
4.4.1.5 Conclusions on classification and labelling ... 41
4.4.2 Eye irritation ... *42*
4.4.2.1 Non-human information ... 42
4.4.2.2 Human information ... 44
4.4.2.3 Summary and discussion of eye irritation ... 44
4.4.2.4 Comparison with criteria ... 44
4.4.2.5 Conclusions on classification and labelling ... 44
4.4.3 Respiratory tract irritation ... *45*
4.4.3.1 Non-human information ... 45
4.4.3.2 Human information ... 45
4.4.3.3 Conclusions on classification and labelling ... 45
4.5 CORROSIVITY ... 45
4.6 SENSITISATION ... 46
4.6.1 Skin sensititsation ... *46*
4.6.1.1 Non-human information ... 46
4.6.1.2 Human information ... 51
4.6.1.3 Summary and discussion of skin sensitisation ... 51
4.6.1.4 Comparison with criteria ... 51
4.6.1.5 Conclusions on classification and labelling ... 51
4.6.2 Respiratory sensitisation ... *52*
4.7 REPEATED DOSE TOXICITY ... 53
4.7.1 Non-human information ... *54*
4.7.1.1 Repeated dose toxicity: oral ... 54
4.7.1.2 Repeated dose toxicity: inhalation ... 100
4.7.1.3 Repeated dose toxicity: dermal ... 105
4.7.1.4 Repeated dose toxicity: other routes ... 109
4.7.1.5 Human information ... 109
4.7.1.6 Other relevant information ... 110
4.7.1.7 Summary and discussion of repeated dose toxicity ... 110
4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD ... 114
4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD ... 119
4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD ... 119
4.8 SPECIFIC TARGET ORGAN TOXICITY (CLP REGULATION) – REPEATED EXPOSURE (STOT RE) ... 120
4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation ... *120*
4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE ... *127*
4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE ... *127*
4.9 GERM CELL MUTAGENICITY (MUTAGENICITY) ... 135
4.9.1 Non-human information ... *135*
4.9.1.1 In vitro data ... 135
4.9.1.2 In vivo data ... 137
4.9.2 Human information ... *138*
4.9.3 Other relevant information ... *138*
4.9.4 Summary and discussion of mutagenicity ... *138*
4.9.5 Comparison with criteria ... *138*
4.9.6 Conclusions on classification and labelling ... *139*
4.10 CARCINOGENICITY ... 140
4.10.1 Non-human information ... *141*
4.10.1.1 Carcinogenicity: oral ... 141
4.10.1.2 Carcinogenicity: inhalation ... 181
4.10.1.3 Carcinogenicity: dermal ... 181
4.10.2 Human information ... *181*
4.10.3 Other relevant information ... *181*
4.10.4 Summary and discussion of carcinogenicity ... *181*
4.10.5 Comparison with criteria ... *182*
4.10.6 Conclusions on classification and labelling ... *184*

4.11 TOXICITY FOR REPRODUCTION 190
4.11.1 Effects on fertility *192*
4.11.1.1 Non-human information 192
4.11.1.2 Human information 192
4.11.2 Developmental toxicity *192*
4.11.2.1 Non-human information 192
4.11.2.2 Human information 218
4.11.3 Other relevant information *218*
4.11.4 Summary and discussion of reproductive toxicity *218*
4.11.5 Comparison with criteria *220*
4.11.6 Conclusions on classification and labelling *221*
4.12 OTHER EFFECTS 226
4.12.1 Non-human information *226*
4.12.1.1 Neurotoxicity 226
4.12.1.2 Immunotoxicity 226
4.12.1.3 Specific investigations: other studies 226
4.12.1.4 Human information 240
4.12.2 Summary and discussion *240*
4.12.3 Comparison with criteria *241*
4.12.4 Conclusions on classification and labelling *241*

5 ENVIRONMENTAL HAZARD ASSESSMENT 242

5.1 DEGRADATION 242
5.1.1 Stability *244*
5.1.2 Biodegradation *246*
5.1.2.1 Biodegradation estimation 246
5.1.2.2 Screening tests 246
5.1.2.3 Simulation tests 246
Biodegradation in water/sediment tests 246
Study 1 246
Biodegradation in soil 250
5.1.3 Summary and discussion of degradation *252*
Ready biodegradability 252
5.2 ENVIRONMENTAL DISTRIBUTION 254
5.2.1 Adsorption/Desorption *254*
5.2.2 Volatilisation *255*
5.2.3 Distribution modelling *255*
5.3 AQUATIC BIOACCUMULATION 256
5.3.1 Aquatic bioaccumulation *256*
5.3.1.1 Bioaccumulation estimation 256
5.3.1.2 Measured bioaccumulation data 256
5.3.2 Summary and discussion of aquatic bioaccumulation *258*
5.4 AQUATIC TOXICITY 259
5.4.1 Fish *261*
5.4.1.1 Short-term toxicity to fish 261
5.4.1.2 Long-term toxicity to fish 263
5.4.2 Aquatic invertebrates *266*
5.4.2.1 Short-term toxicity to aquatic invertebrates 266
5.4.2.2 Long-term toxicity to aquatic invertebrates 267
5.4.3 Algae and aquatic plants *268*
5.4.4 Other aquatic organisms (including sediment) *273*
5.5 COMPARISON WITH CRITERIA FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4) 277
5.6 CONCLUSIONS ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4) 279

6 OTHER INFORMATION 286

7 REFERENCES 287

7.1 PHYSICO-CHEMICAL PROPERTIES 287

8 ANNEXES 316

ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON FENOXAPROP-P-ETHYL

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Fenoxaprop-P-ethyl***
EC number:	**-**
CAS number:	***71283-80-2***
Annex VI Index number:	**-**
Degree of purity:	***≥ 920 g/kg***
Impurities:	***No relevant impurities (see inclusion directive 2008/66/EC)***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation (Regulation (EC) No 1272/2008)	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation		
Current proposal for consideration by RAC	Skin Sens. Cat. 1b H317 STOT-RE Cat. 2 H373 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410	R43 N; R50/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Sens. Cat. 1b H317 STOT-RE Cat. 2 H373 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410	R43 N; R50/53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation(EC) 1272/2008

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-			Conclusive but not sufficient for classification
2.2.	Flammable gases	-			Conclusive but not sufficient for classification
2.3.	Flammable aerosols	-			Conclusive but not sufficient for classification
2.4.	Oxidising gases	-			Conclusive but not sufficient for classification
2.5.	Gases under pressure	-			Conclusive but not sufficient for classification
2.6.	Flammable liquids	-			Conclusive but not sufficient for classification
2.7.	Flammable solids	-			Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-			Data lacking
2.9.	Pyrophoric liquids	-			Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	-			Inconclusive
2.11.	Self-heating substances and mixtures	-			Inconclusive
2.12.	Substances and mixtures which in contact with water emit flammable gases	-			Conclusive but not sufficient for classification
2.13.	Oxidising liquids	-			Conclusive but not sufficient for classification
2.14.	Oxidising solids	-			Conclusive but not sufficient for classification
2.15.	Organic peroxides	-			Conclusive but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.16.	Substance and mixtures corrosive to metals	-			Inconclusive
3.1.	Acute toxicity - oral	No classification	-	-	Conclusive but not sufficient for classification
	Acute toxicity - dermal	No classification	-	-	Conclusive but not sufficient for classification
	Acute toxicity - inhalation	No classification	-	-	Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	No classification	-	-	Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	No classification	-	-	Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	No data			Data lacking
3.4.	Skin sensitisation	H317	-	-	-
3.5.	Germ cell mutagenicity	No classification	-	-	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	No classification	-	-	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	No classification	-	-	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	No classification	-	-	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	H373	-	-	-
3.10.	Aspiration hazard	No classification	-	-	Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	H400 H410	M-factor: 1	-	-
5.1.	Hazardous to the ozone layer	No classification	-	-	Conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning
Hazard statements: H317, H373, H400, H410
Precautionary statements: P261, P272, P273, P280, P314, P302+P352, P333+P313, P321, P363, P391, P501

ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON FENOXAPROP-P-ETHYL

Proposed notes assigned to an entry: -

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	-	-	-	Conclusive but not sufficient for classification
Oxidising properties	-			Conclusive but not sufficient for classification
Flammability	-			Conclusive but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	-			-
Thermal stability	-	-	-	Conclusive but not sufficient for classification
Acute toxicity	No classification	-	-	Conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	No classification	-	-	Conclusive but not sufficient for classification
Repeated dose toxicity	No classification	-	-	Conclusive but not sufficient for classification
Irritation / Corrosion	No classification	-	-	Conclusive but not sufficient for classification
Sensitisation	R43	-	-	-
Carcinogenicity	No classification	-	-	Conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	No classification	-	-	Conclusive but not sufficient for classification
Toxicity to reproduction – fertility	No classification	-	-	Conclusive but not sufficient for classification
Toxicity to reproduction – development	No classification	-	-	Conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	No classification	-	-	Conclusive but not sufficient for classification
Environment	R50/53	-	-	-

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Harmful, Dangerous for the environment
R-phrases: R43, R50/53
S-phrases: S2, S13, S24, S29, S37, S46, S 56, S 57, S 60, S 61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Fenoxaprop-ethyl, CAS: 664441-23-4 was included in Annex I of Directive 67/548 with Directive 98/73/EC (ATP24) and in Annex VI of Regulation 1272/2008 with CLP00. Fenoxaprop-ethyl is classified with R43 and R50/53. R43 is based on test data performed with fenoxaprop-P-ethyl, which were discussed at ECB, Ispra by the Commission Working Group on the Classification and Labelling of Dangerous Substances in 1995.

Fenoxaprop-P, CAS: 113158-40-0 and Fenoxaprop-P-ethyl, CAS: 71283-80-2 are not included into Annex I of Directive 67/548 or Annex VI of Regulation 1272/2008 yet.

Fenoxaprop-P, CAS: 113158-40-0 and Fenoxaprop-P-ethyl, CAS: 71283-80-2 were subject to the pesticide risk assessment peer review in PRAPeR 19 (mammalian toxicology), whereby R43 and R63? were proposed by the experts. The respective proposal of the DAR was R43 and R50/53.

2.2 Short summary of the scientific justification for the CLH proposal

Human Health: No classification is required for acute toxicity as the respective LD_{50}s or LC_{50} were below the values set in Directive 67/548 or in Regulation (EU) No1272/2008. No evidence from acute studies was seen regarding specific target organ toxicity –single exposure. Slight irritating potential for skin and eyes could be found however, not leading to classification as the scores were below the ones set in Directive 67/548 or in Regulation (EU) No 1272/2008. An M&K test was positive leading to classification as skin sensitizer with R43 or Cat. 1b H317. No data are available regarding respiratory sensitization. Nephrotoxicity was seen in repeated dose studies in mice below the guidance value for STOT-RE set in Regulation (EU) No 1272/2008, but not below the cut off value for R48 set in Directive 67/548. Therefore classification with H373 STOT-RE Cat.2 is proposed. Fenoxaprop-P-ethyl was negative in a battery of *in vitro* and *in vivo* genotoxicity studies. It developed no carcinogenic potential in rats and dogs. In NMRI mice liver adenomas and carcinomas were seen due to a mechanism not relevant for humans (peroxisome proliferation). No impairment of fertility or adverse effects on or via lactation could be found in a multigeneration study conducted in rats. No teratogenic potential was found in rats and rabbits, however ossification was impaired. There was no indication for neurotoxic or immunotoxic potential according to the available acute, subchronic and chronic studies.

Regarding classification criteria for fenoxaprop-P-ethyl for **aquatic environment hazards** acute category 1, H400 (very toxic to aquatic life) and chronic category 2, H410 (very toxic to aquatic life with long lasting effects) is proposed based on classification criteria of CLP (Regulation (EC) No 1272/2008) and R50/53 based on Directive 67/548/EEC classification criteria.

2.3 Current harmonised classification and labelling

Fenoxaprop-P CAS: 113158-40-0 and Fenoxaprop-P-ethyl CAS: 71283-80-2 are as of yet not included in Annex I of Directive 67/548 or Annex VI of Regulation (EC) No 1272/2008.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

No information provided by the notifier.

2.4.2 Current self-classification and labelling based on DSD criteria

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

No need for justification for pesticides.

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.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

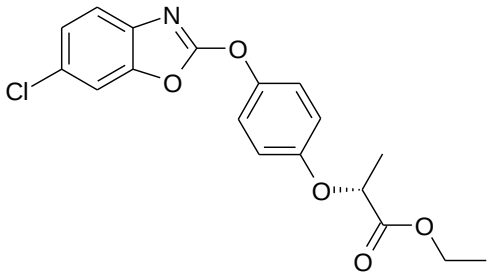
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	-
EC name:	-
CAS number (EC inventory):	-
CAS number: Fenoxaprop-P-ethyl	71283-80-2
CAS name:	-
IUPAC name:	(D+)-ethyl-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate
CLP Annex VI Index number:	
Molecular formula:	$C_{18}H_{16}ClNO_5$
Molecular weight range:	361.8

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Fenoxaprop-P-ethyl	≥ 92 %	No range, since minimal purity stated	-

Current Annex VI entry: -

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
No relevant impurities	-	-	-

Current Annex VI entry: -

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives	-	-	-	-

Current Annex VI entry: -

1.2.1 Composition of test material

Physico-chemical properties: see table 9 (purity of tested technical material in the range from 93.0% to 99.8%)

Human health hazard assessment: purity in the range from 95.6% to 99% for fenoxaprop-P-ethyl and in the range from 93% to 97.9% for fenoxaprop-ethyl.

Environmental hazard assessment: Purity of fenoxaprop-P-ethyl (sum of (D+) and (L-) enantiomers) is in the range from 95.8 to 97.4.

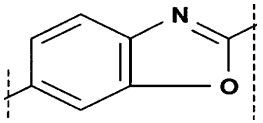
1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Study	Method	Results	Conclusion/Comment	Reference
B.2.1.1 Melting point, freezing point or solidification point (IIA 2.1.1)	EEC/A1 (Different scanning calorimetry method) GLP	Purified product [purity: 99.5% (w/w)] The melting point of pure Fenoxaprop-P-ethyl is 86.5 °C	Acceptable	Smeykal H. (1999w) (Document C004110)
B.2.1.2 Boiling point (IIA 2.1.2)			Not relevant as Fenoxaprop-P-ethyl is not a liquid	Rexer, K., Heinrich, (1988k) (Document A38754)
B.2.1.3 Temperature of decomposition or sublimation (IIA 2.1.3)	Differential thermal analysis (heating rate 10 °C/min) not GLP	Technical product [purity: ≈ 93.0% (w/w)] No exothermal decomposition up to 260 °C	Acceptable	Heinrich, Rexer K. (1987c) (Document A35719)
B.2.1.4 Relative density (IIA 2.2)	EEC/A3 (Pycnometer method) GLP	Purified product [purity: 98.2% (w/w)] The density of pure Fenoxaprop-P-ethyl is 1.32 g/cm^3 at 20 °C	Relative density is not reported	Bittner P., Rexer K. (1999cg) (Document C004890)
B.2.1.5 Vapour pressure (IIA 2.3.1)	OECD 104 (Vapour pressure balance) not GLP	Purified product [purity: 98.7% (w/w)] 5.3×10^{-7} Pa at 20°C 1.4×10^{-6} Pa at 25°C 1.1×10^{-4} Pa at 50°C	Acceptable	Roechling, Rexer K. (1987d) (Document A42898)
B.2.1.6 Volatility, Henry's law constant(IIA 2.3.2)	Calculation	Purified product [purity: 98.7% (w/w)] 2.739×10^{-4} $Pa \cdot m^3 \cdot mol^{-1}$ at 20°C Parameter used for calculation:	Acceptable	Schollmeier M. (1992ao) (Document A48206)

Study	Method	Results	Conclusion/Comment	Reference
		water solubility: 0.7 mg/L at 20 °C vapour pressure: 5.3 x 10^{-7} Pa at 20 °C		
B.2.1.7 Appearance: physical state (IIA 2.4.1)	Visual examination not GLP	Purified product [purity: 98.7% (w/w)] Solid		Heinrich, Rexer K. (1988o) (Document A38756)
	Visual examination	Technical product [purity: 96.3% (w/w)] Flakes; the physical form stated here describes only a single batch. The sales product also appears to be a coarse powder or solidified melt		Haase D., Rexer K. (2000l) (Document C008077
B.2.1.8 Appearance: colour (IIA 2.4.1)	Visual examination	Purified product [purity: 98.7% (w/w)] White		Heinrich, Rexer K. (1988n) (Document A38751)
	Visual examination	Technical product [purity: 96.3% (w/w)] Yellowish		Haase D., Rexer K. (2000j) (Document C008079)
B.2.1.9 Appearance: odour (IIA 2.4.2)	Organoleptic examination	Purified product [purity: 98.7% (w/w)] Practically odourless	Acceptable	Heinrich, Rexer K. (1988m) (Document A38752)
	Organoleptic examination	Technical product [purity: 96.3% (w/w)] Weak aromatic	Acceptable	Haase D., Rexer K. (2000k) (Document C008078)

Study	Method	Results		Conclusion/Comment	Reference
B.2.1.10 Spectra of the active substance (IIA 2.5.1)	OECD 101 UV/VIS spectroscopy GLP	Purified product [purity: 99.5% (w/w)] c = 9.785 mg/L in acetonitrile (to avoid transesterification with alcohol solvents) at ambient temperature		Acceptable	Kloeckner C., Weller O. (2000a) (Document C008445)
		λ_{max} [nm]	ε_{max} [L·mol^{-1}·cm^{-1}]		
		239 278 wavelength above 290 nm: 291	22862 7980 1488		
	FTIR measurement Direct application onto a diamond probe measured between 4000 and 600 cm^{-1}) GLP	Purified product [purity: 99.5% (w/w)]		Acceptable	Kloeckner C., Weller O. (2000a) (Document C008445)
		Wave number [cm^{-1}]	Assignment		
		3100-3000 3000-2900 1800-1700 1700-600	ν (C-H) (aromatic) ν (C-H) (aliphatic) ν (C=O) fingerprint		
		Spectrum is in agreement with the chemical structure			
	NMR spectroscopy ^{1}H-NMR ^{13}C-NMR GLP	Purified product [purity: 99.5% (w/w)] NMR spectra are in agreement with the chemical structure		Acceptable	Kloeckner C., Weller O. (2000a) (Document C008445)

<table>
<tr><th>Study</th><th>Method</th><th>Results</th><th>Conclusion/Comment</th><th>Reference</th></tr>
<tr><td></td><td>MS spectroscopy
Direct insert probe at 62 eV
Ionisation:
Electron impact (EI +)
GLP</td><td>Purified product [purity: 99.5% (w/w)]
<table><tr><th>m/z</th><th>Intensity approx.</th><th>Assignment</th></tr><tr><td>361</td><td>80</td><td>$[M]^+$</td></tr><tr><td>288</td><td>100</td><td>$[M - CO_2C_2H_5]^+$</td></tr><tr><td>261</td><td>23</td><td>$[M - C\text{–}CH_3 - CO_2C_2H_5]^+$</td></tr><tr><td>119</td><td>25</td><td>  </td></tr></table>Molecular ion (m/z = 361), fragmentation and isotop distribution pattern of chlorine confirm the chemical structure of Fenoxaprop-P-ethyl</td><td>Acceptable</td><td>Kloeckner C., Weller O. (2000a) (Document C008445)</td></tr>
<tr><td></td><td>AL63/88-1
GLP</td><td>Purified product [purity: 99.5% (w/w)]
sum of (D+) and (L-) enantiomers: 99.7% (w/w)
Fenoxaprop-P-ethyl: 99.5% (w/w)
Chromatograms for optical purity are submitted within the 5 – batch analysis</td><td>Acceptable</td><td>Weilbaecher R., Goerlitz G.(1998a) (Document C001123)
Cichy M., Perez-Diaz C. (1999o) (Document C003613)</td></tr>
<tr><td>B.2.1.11
Spectra of impurities
(IIA 2.5.2)</td><td></td><td></td><td>Not relevant as the technical material contains no toxicological or ecotoxicological</td><td>Wolf R., Le Gren I. (2004) (Document C044472)</td></tr>
</table>

Study	Method	Results		Conclusion/Comment	Reference
				relevant impurities	
B.2.1.12 Solubility in water (IIA 2.6)	OECD 105 Column elution method analog GLP[1)]	Purified product [purity: 98.7% (w/w)] 0.7 mg/L in bidistilled water (pH 5.8) at 20 °C		Acceptable Method OECD 105 is equivalent to EEC/A6	Goerlitz G., Eyrich U. (1987ad) (Document A36178) Weller O.(1990d) (Document A43650) (Addendum) Wolf R., (2004) (Document C045431)
B.2.1.13 Solubility in organic solvents (IIA 2.7)	OECD 105 Flask method analog GLP[1)]	Technical product [purity: 89.8% (w/w)]		Acceptable	Goerlitz, G. Rutz, U. (1989a) (Document A40979) Wolf R., (2004) (Document C045431)
		solvent	solubility at 20 °C [g/L]		
		n-hexane	7.0		
		acetone	> 400		
		toluene	> 480		
		dichloromethane	> 400		
		methanol	43.1		
		isopropanol	14.2		
		ethyl acetate	> 380		
		polyethylene glycol	18.2		
		dimethylsulfoxide	> 500		
B.2.1.14 Partition coefficient	OECD 117 HPLC method	Purified product [purity: 98.4% (w/w)] K_{OW} = 38000		Acceptable Method OECD 117 is	Schollmeier M., Eyrich U., Uhl A.

Study	Method	Results	Conclusion/Comment	Reference
n-octanol/water (IIA 2.8)	GLP	log K_{OW} = 4.58 at 30 °C neutral medium [water/methanol (70/30 v/v) without buffer]	equivalent to EEC/A8 HPLC method	(1992a) (Document A49082) Wolf R., Le Gren I. (2004) (Document C044472) Wolf R., (2004) (Document C045431)
	OECD 107 Shake flask method not GLP	Hoe 053022 (Fenoxaprop free acid) [purity: 98.1% (w/w)] K_{OW} (pH = 5) = 68.3 log K_{OW} = 1.81 K_{OW} (pH = 7) = 2.87 log K_{OW} = 0.46 K_{OW} (pH = 9) = 1.73 log K_{OW} = 0.24	Acceptable Method OECD 107 is equivalent to EEC/A8 shake flask method Hoe 053022 is a relevant metabolite	Goerlitz G., Eyrich U. (1985a) (Document A31446) Asshauer J. (1986) (Document 33108)
	OECD 117 HPLC method GLP	AE F054014 (6-chloro-2,3-dihydro-benzoxazol-2-one) [purity: 99.8% (w/w)] log K_{OW} = 1.9	Acceptable Method OECD 117 is equivalent to EEC/A8 HPLC method AE F054014 is a relevant metabolite	Tognucci A., (1999a) (Document C003620)
B.2.1.15 Hydrolysis rate (IIA 2.9.1)	OECD 111 GLP	^{14}C labelled Fenoxaprop-P-ethyl radiochemical purity: > 98.7 % First order kinetics at all pH values tested DT_{50} (25 °C) = 2.8 d at pH 4 DT_{50} (25 °C) > 19.2 d at pH 5	Acceptable For details see B 8.4 Fate and behaviour in water	Van der Gaauw A. (2002a) (Document C028353)

<table>
<tr><th>Study</th><th>Method</th><th>Results</th><th>Conclusion/Comment</th><th>Reference</th></tr>
<tr><td></td><td></td><td>DT_{50} (25 °C) > 23.2 d at pH 7
DT_{50} (25 °C) > 0.6 d at pH 9

DT_{50} (40 °C) = 0.8 d at pH 4
DT_{50} (40 °C) > 6.6 d at pH 5
DT_{50} (40 °C) > 5.1 d at pH 7
DT_{50} (40 °C) > 0.2 d at pH 9

Besides the parent compound, three major radioactive fractions were characterised as AE F054014 (6-chloro-2,3-dihydro-benzoxazol-2-one), AE F088406 (Fenoxaprop-P-acid) and AE F064124. (5-hydroxy-6-chloro-2,3-dihydro-benzoxazol-2-one).
^{14}C-Fenoxaprop-P-ethyl may be considered hydrolytically unstable under environmentally relevant acidic and neutral conditions, however with half-lives > 16 days at pH 5 and 7 hydrolysis is not taken into account for classification.</td><td></td><td></td></tr>
<tr><td>B.2.1.16
Direct phototrans-formation (IIA 2.9.2)</td><td>EPA N 161-2
OECD: Phototransfor-mation of Chemicals in Water (Part A)
ACIS-guideline,
GLP</td><td>^{14} C labelled Fenoxaprop-P-ethyl
radiochemical purity: > 98.0 %

Half-life (DT_{50}) and DT_{90} values were calculated assuming 1st order kinetics

In sterile buffer hydrolysis, Fenoxaprop-P-acid (AE F088406) was not formed. Since photolysis of AE F046360 was conducted at pH 5, hydrolysis to AE F088406 was slow and a majority of approx. 61 % was recovered as unchanged parent compound.

The results of the experiment in sterile buffer photolysis (pH 5) were summarised as follows:
<table>
<tr><th>Sun</th><th>Laboratory</th><th>x rel.</th><th>Sunlight</th></tr>
</table></td><td>Acceptable

For details see B 8.4 Fate and behaviour in water</td><td>Schwab W.; (1993e) (Document A51353)

Schwab W.; (1993c) (Document A51426)</td></tr>
</table>

Study	Method	Results	Conclusion/Comment	Reference
		- test No. | | **Inten -sity** | | |

Study	Method	Results	Conclusion/Comment	Reference
photochemical oxidative degradation (IIA 2.10)	Oxidation Program AOPWIN (based on Atkinson method, version 1.88)	atmosphere has been conducted according to the method of Atkinson. Overall OH rate constant: K_{OH} = 28.7039 x 10^{-12} cm^3 $molecule^{-1}$ sec^{-1} DT_{50} = 0.559 days (5 x 10^5 OH/cm^3 for 24 hrs per day) or DT_{50} = 0.373 days (1.5 x 10^6 OH/cm^3 for 12 hrs per day)		(Document C003258)
B.2.1.20 Flammability (IIA 2.11)	EEC/A10 GLP	Technical product [purity: 96.3% (w/w)] The result of the preliminary screening test was that Fenoxaprop-P-ethyl could not be ignited with a flame According EEC/A10 no further testing is required.	Technical Fenoxaprop-P-ethyl is not considered as highly flammable under test condition	Hoffmann H. (2000ac) (Document C009471)
B.2.1.21 Autoflammability (IIA 2.11.2)	EEC/A16 GLP	Technical product [purity: 96.3% (w/w)] No self ignition up to 401°C	Compound is not considered as auto-flammable under test condition	Hoffmann H. (2000ab) (Document C009473)
B.2.1.22 Flash point (IIA 2.12)			Not applicable as the melting point is > 40 °C	
B.2.1.23 Explosive properties (IIA 2.13)	EEC/A14 GLP	Technical product [purity: 96.3% (w/w)] <u>Thermal sensitivity test:</u> no explosion after 5 minutes (nozzle diameter: 2.0 mm) <u>Shock test:</u> no explosion occurred within 6 tests using a mass of 10 kg from a height of 0.4 m <u>Friction test:</u> no explosion occurred within 6 tests	Fenoxaprop-P-ethyl technical does not present a danger of explosion under test condition	Hoffmann H. (2000aa) (Document C009472)

Study	Method	Results	Conclusion/Comment	Reference
		using a 360 N loading		
B.2.1.24 Surface tension (IIA 2.14)	EEC/A5 Statement		Not applicable as the water solubility is <1mg/L	Rexer, K. (2001n) (Document C011094)
B.2.1.25 Oxidising properties (IIA 2.15)	EEC/A17 Statement	The molecule of Fenoxaprop-P-ethyl contains oxygen and chlorine, but bounded only to carbon.	Acceptable According the UN manual "Recommendations on the Transport of Dangerous Goods" (ST/SG/AC.10/11/Rev.3) Appendix 6: Fenoxaprop-P-ethyl is not considered to have oxidising properties.	Hoffmann H. (2000z) (Document C009474)

[1)] *analog GLP* means that in the laboratory conducting the study, GLP was implemented prior to 1990, but no certificate was available to this date, because no

GLP – authority inspections were conducted before German Chemical Act of 1990 came into force.

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for Classification and Labelling.

2.2 Identified uses

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

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

No classification required

4 HUMAN HEALTH HAZARD ASSESSMENT

Bridging statement for read across between fenoxaprop-P-ethyl and fenoxaprop-ethyl

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.

Comparison of ADME studies with Fenoxaprop-P-ethyl (Hoe 046360)and Fenoxaprop-ethyl (Hoe 033171)

Hoe 033171 and Hoe 046360. Comparison and evaluation of the metabolism and pharmacokinetics in rats

Reference: Schwalbe-Fehl M., 1988; Doc. No. A38647 / Hoechst, Report No. (B) 258/88

Guideline:not applicable

GLP: not applicable

In this report, the metabolism and pharmacokinetic behaviour of both Hoe 046360 (fenoxaprop-P-ethyl) and Hoe 033171 (fenoxaprop-ethyl) was summarized for male and female rats after oral administration of the radiolabelled test substances at two dose levels, 2 and 10 mg/kg bw. The frequency of application was single or repeated dose. Taken together, no significant difference in rat metabolism and kinetic studies was observed between Hoe 046360 and Hoe 033171.

Absorption: Both Hoe 046360 and Hoe 033171 were absorbed and excreted rapidly. Radioactivity was already found in the blood 15 min after oral application and reached a maximum concentration after 6 – 8 hours for both substances. The lowering of the blood concentration was biphasic with a shorter initial phase and a longer terminal phase and was comparable for the two substances (Hoe 046360: 9-11 h and 68-75 h, resp.; Hoe 033171; 6-14 h and 73-75 h, resp.). The minimum absorption rates were derived from addition of urinary

excretion, cage washes and residues in tissues and carcass. After oral administration, the rates were between 40 and 66 % for Hoe 046360 and between 48 and 74 % for Hoe 033171 (details can be found in Table 10).

Distribution: Following oral administration, radioactivity was widely distributed into the investigated organs and tissues for both substances. The total amount of residues 7 days after treatment was low, ranging from 0.7 – 2 % of the applied dose for Hoe 046360 and from 0.7 – 5 % for Hoe 033171. The highest concentrations of radioactivity were found in the kidneys, blood, fatty tissues (subcutaneous, peritoneal), lungs and the liver. The distribution profile was very similar for Hoe 046360 and Hoe 033171.

Excretion: Females generally excreted higher rates of radioactivity via urine than via faeces which was largely independent from dose level (2 or 10 mg/kg) or treatment frequency (single or repeated dose). The rates of excretion of radioactivity in urine (females) were 51 – 65 % (Hoe 046360) and 55 – 71 % (Hoe 033171) while the rates for faeces were 33 – 42 % (Hoe 046360) and 25 – 38 % (Hoe 033171). The males excreted more radioactivity via faeces than the females did. The rates for urinary excretion (males) were 35 – 54 % (Hoe 046360) and 44 – 54 % (Hoe 033171) and for faecal excretion 41 – 54 % (Hoe 046360) and 40 – 53 % (Hoe 033171). More than approximately 75 % of the administered dosed was excreted within the first 48 h after application of the test substances, indicating a rapid metabolism and excretion for both Hoe 046360 and Hoe 033171.

Table 10: overview on absorption and excretion profile of Hoe 046360 (fenoxaprop-P-ethyl) and Hoe 033171 (fenoxaprop-ethyl) after oral administration

Test substance	Dose (mg/kg bw)	Sex	% of administered dose		% enteral absorption[2)]	Reference
			in urine[1)]	in faeces		
Hoe 046360	1x 2	male female	42.76 56.86	53.06 37.14	44.4 58.4	Doc. A37450
Hoe 046360	1x 10	male female	44.98 59.38	52.33 38.47	46.4 61.0	Doc. A37448
Hoe 046360	15x 2[3)]	male female	54.10 64.99	40.63 32.74	55.6 66.3	Doc. A37449
Hoe 046360	1x 10	male female	44.0 52.2	50.0 42.2	44.8 53.0	Doc. A37324
Hoe 046360 + Hoe 107892 Hoe 046360	1x 10 + 1x 10 1x 10	male female male female	35.19 44.01 35.44 50.79	54.14 41.12 53.83 38.12	39.3 48.0 39.5 56.0	Doc. A49483
Hoe 033171	1x 2	male female	54.01 71.23	44.0 25.3	57.3 73.5	Doc. A24284
Hoe 033171	1x 2	- female	- 67.45	- 26.29	- 68.2	Doc. A32611
Hoe 033171	1x 10	male female	43.86 60.35	49.0 35.27	49.0 64.6	Doc. A30454

Test substance	Dose (mg/kg bw)	Sex	% of administered dose		% enteral absorption[2)]	Reference
			in urine[1)]	in faeces		
Hoe 033171	1x 10	- female	- 64.93	- 31.44	- 67.5	Doc. A32612
Hoe 033171	15x 2[3)]	male female	49.81 66.20	40.4 31.1	54.2 69.2	Doc. A30456
Hoe 033171	1x 10 1x 2	male female female	47.9 54.9 70.9	53.4 32.5 37.9	47.9[4)] 54.9[4)] 70.9[4)]	Doc. A30377

[1)] including cage washes
[2)] including urinary excretion, cage washes and residues in organs / tissues
[3)] 14 administrations of non-labelled test substance, 1 subsequent administration of labelled test substance
[4)] without cage washes and residues in organs / tissues

Metabolism: The optically active centre of Hoe 046460 and Hoe 033171 is located in the propionic acid fragment of the molecule. Consequently, racemate and isomers can be distinguished as long as the propionic acid fragment is connected with the radiolabel on the chlorophenyl ring. This applies both to the parent compound and its free acid which is formed after ester hydrolysis. The results of the investigations on the metabolism of Hoe 046360 proved that no racemisation of the parent compound and its free acid Hoe 088406 took place. Consequently, the optical activity is preserved in the animal body.

Comparison of the metabolism showed that the pathway is identical for both Hoe 046360 and Hoe 033171 (Doc. A37324 and Doc. A30490). The metabolism proceeds via hydrolysis of the parent compounds Hoe 046360 and Hoe 033171 to the free acids, Hoe 088406 and Hoe 053022, respectively. The free acid may be excreted following conjugation or further degradation via either of two pathways, both involving similar cleavage of the molecule. The predominant pathway involves cleavage and simultaneous attachment of the heterocycle to glutathione yielding a mercapturic acid which may be further transformed to a glucuronic acid conjugate. The alternate pathway involves cleavage and production of 6-chloro-2,3-dihydrobenzoxazol-2-one which is further degraded to 6-chloro-5-hydroxy-2,3-dihydro-benzoxazol-2-one which then is excreted with or without conjugation (metabolic pathway of Hoe 046360 see Figure 4.1).

The parent compound was not found in the urine but only in the faeces at a rate of 10 %. There was a slight sex dependent difference as only females excreted the free carboxylic acid in the urine indicating that females did not have the capacity to metabolize all the absorbed material beyond the free acid. The metabolites detected in blood, kidney and liver after administration of Hoe 046360 had the same structures as found in the excreta.

Comparison of the toxicological profile of Fenoxaprop-P-ethyl and Fenoxaprop-ethyl

An important aspect of the toxicological studies with fenoxaprop-P-ethyl was to establish whether there were differences between the toxicological profiles of fenoxaprop-P-ethyl and fenoxaprop-ethyl. Consequently, acute and subchronic, embryotoxicity and mutagenicity testing has been performed on both fenoxaprop-P-ethyl and fenoxaprop-ethyl. For this reason the study designs of the subchronic (4-week and 13-week) feeding studies in rats, mice and dogs and of the embryotoxicity studies in rats and rabbits with fenoxaprop-P-ethyl corresponded closely to those of fenoxaprop-ethyl.

Both fenoxaprop-P-ethyl and fenoxaprop-ethyl exhibited only slight toxic properties following acute oral and dermal treatment in rats and mice. Inhalational exposure to rats over

a period of 4 hours yielded an LC_{50} concentration higher than 0.475 mg/l of fenoxaprop-ethyl and 1.224 mg/l of fenoxaprop-P-ethyl, which were the highest technically feasible concentrations. The LD_{50} values and the clinical signs of intoxication of both compounds were similar.

Fenoxaprop-P-ethyl and fenoxaprop-ethyl proved to be non-irritating to slightly irritating to the skin and eye mucosa and showed no sensitising property in a test conducted by the epidermal method of Buehler.

Neither of the compounds was mutagenic in a variety of tests with different endpoints.

Repeated-dose (4-week) and subchronic (3-month) feeding studies in rat, mouse and dog indicated that the toxicological profiles of fenoxaprop-P-ethyl and fenoxaprop-ethyl were very similar.

Testing for embryotoxicity in rats and rabbits also indicated that fenoxaprop-P-ethyl and fenoxaprop-ethyl had an identical toxicological profile in both dams and in embryos and foetuses.

Based on this comparison of the toxicological data of fenoxaprop-P-ethyl and fenoxaprop-ethyl, it has to be concluded that the toxicological profile of fenoxaprop-P-ethyl is fully comparable to that of fenoxaprop-ethyl both in qualitative and quantitative terms. There was nothing to indicate any differences of toxicological significance between fenoxaprop-P-ethyl and fenoxaprop-ethyl. Thus from the toxicological point of view, it appears justified to base the evaluation of two generation reproductive toxicity, chronic toxicity and oncogenicity for fenoxaprop-P-ethyl on the corresponding long-term studies conducted with fenoxaprop-ethyl.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Summary of ADME studies with Fenoxaprop-P-ethyl in rats

Absorption: Fenoxaprop-P-ethyl was absorbed rapidly in male and female rats as the test substance was already found in the blood 15 min after single oral administration. The maximum concentration was reached 6 – 8 hours after application. Lowering of the blood concentrations was biphasic with half-lifes of 9 – 11 hours for the initial phase and half-lifes of 68 – 75 hours for the terminal phase. Pharmacokinetic investigation of blood levels revealed practically no difference between the dose levels of 2 and 10 mg/kg which were administered as a single dose by oral gavage. The minimum rate of absorption (urinary excretion including cages washes and residues in tissues/organs) was generally higher in females than in males and reached at least 40 % of the administered dose.

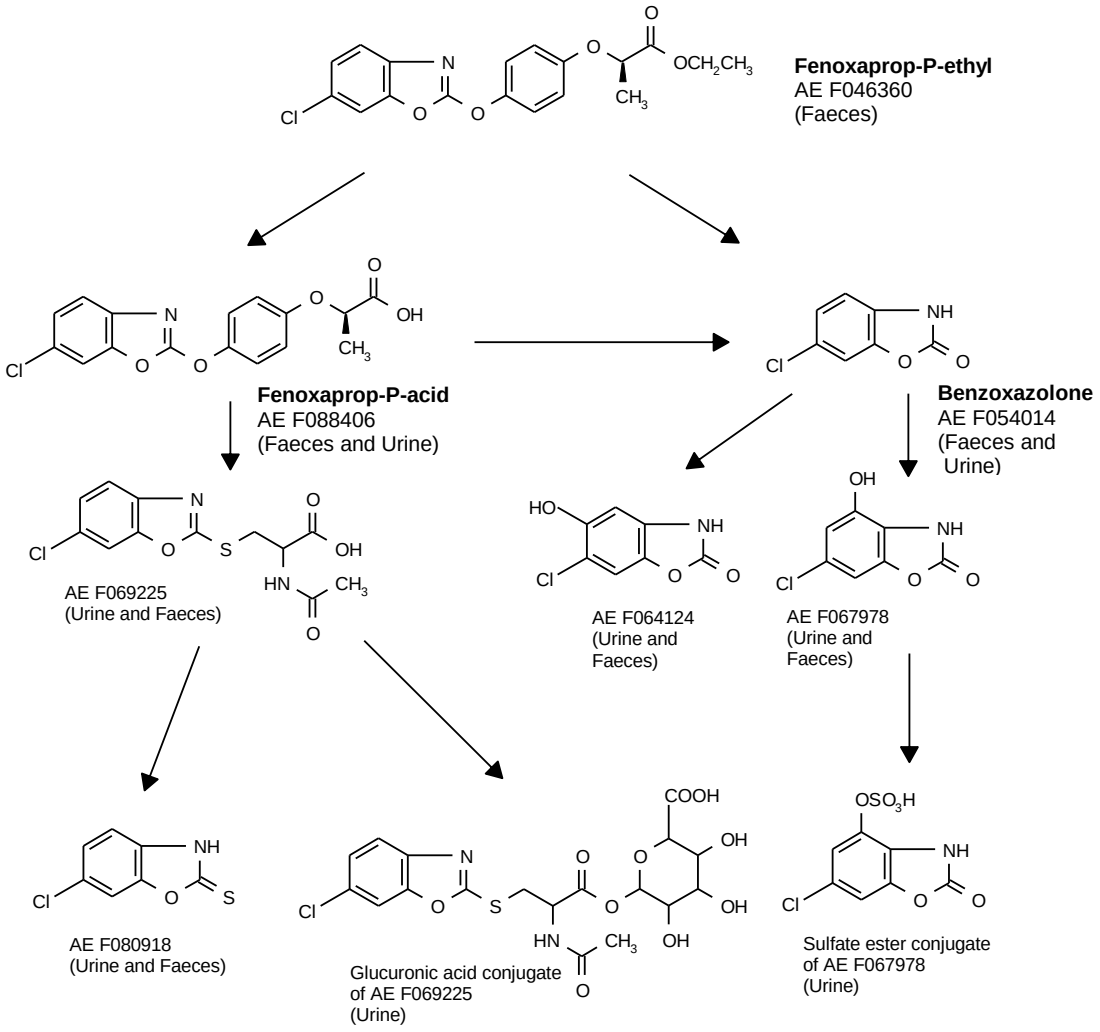
Distribution: Following oral administration of 2 or 10 mg/kg, radioactivity was widely distributed into the investigated organs and tissues. However, the amount of residues 7 days after treatment was rather low and varied between 0.7 and 2 % of the total applied dose even after repeated dosing. The highest concentrations were found in the kidneys, blood, fatty tissues (subcutaneous, retroperitoneal) and the liver. Administration of 2 mg/kg with intravenous injection showed similar results.

Excretion: After oral application, female rats generally excreted higher amounts of radioactivity via urine (51 – 65 %) than via faeces (33 – 42 %) which was independent from dose level (2 or 10 mg/kg) or application frequency (single or repeated dose). In contrast,

male rats generally excreted lower amounts of orally applied radioactivity with the urine (35 – 54 %) than with the faeces (41 – 54 %), with the exception of repeated dose application when higher amounts of radioactivity were excreted in the urine (54 %) than in the faeces (41 %). When the test substance was administered via intravenous injection, higher amounts of radioactivity were excreted renally (50 – 59 %) than via faeces (29 – 40 %) in both sexes. More than approximately 75 % of the administered dose was excreted within a time period of 48 hours, independent from route of application, dose level or sex.

Metabolism: No unchanged parent metabolite was found in the urine after oral administration of 10 mg/kg. The major metabolite in the urine of males was the mercapturic acid Hoe 069225. In the urine of females, the metabolite Hoe 069225 and also the free acid from the parent compound (Hoe 088406) appeared in a ratio of approximately 1:1. On average, 10 % of the applied dose was present in the faeces in the form of the intact parent compound Hoe 046360. Another major metabolite in the faeces was the free acid Hoe 088406, contributing to 9.5 – 13.5 % of the administered dose. Some other minor metabolites and their sulphate or glucuronic acid conjugates were found in the urine and faeces. The amounts of metabolites in blood, liver and kidneys were about 0.1 – 0.3 % of the applied dose. The metabolites had the same structures as found in the excreta. Based on the identified metabolites, a metabolic pathway was proposed (Figure 1).

Figure 1: Proposed metabolic pathway of Fenoxaprop-P-ethyl in rats



Supportive information

Summary of ADME studies with Fenoxaprop-ethyl in rats

Absorption: A rapid absorption was observed in both sexes after single oral administration of 2 mg/kg as radioactivity was already found in the blood 15 min after application. The maximum concentration was reached 8 h after treatment in both sexes. Half-lifes for the biphasic decline of blood levels were 6 – 14 h for the first phase and 73 – 75 h for the second phase. The minimum rate of absorption (urinary excretion including cages washes and residues in tissues/organs) was generally higher in females than in males and reached at least 49 % and more of the administered dose.

Distribution: Following oral administration of 2 mg/kg (single and repeated dose) or 10 mg/kg (single dose), radioactivity was widely distributed into the investigated organs and tissues. The amount of residues in the organs and tissues was between 0.7 and 5 % in both sexes 7 days after treatment. Highest concentrations of radioactivity were detected in kidneys, blood, fatty tissues (subcutaneous, retroperitoneal), lungs and liver.

Excretion: After oral application, female rats generally excreted higher amounts of radioactivity via urine (55 – 71 %) than via faeces (24 – 38 %) which was largely independent from dose level (2 or 10 mg/kg) or application frequency (single or repeated dose). Only in

the metabolism study when females were treated with 2 or 10 mg/kg, a higher urinary excretion was found at 2 mg/kg than at 10 mg/kg. In males, the picture was not so clear as higher urinary excretion was found after oral dosing with 10 mg/kg and higher faecal excretion was found after single and repeated oral doses and i.v. application of 2 mg/kg. More than approximately 80 % of the orally administered dose was excreted within a time period of 48 hours, independent from dose level or sex.

Metabolism: In the urine of males, the predominant metabolite was HPP-acid while in females HPP-acid and also the free acid were found in a ratio of 1:1 (high dose) and 2:1 (low dose). In faeces, the metabolite pattern was largely independent from sex, with the parent compound Hoe 033171 (fenoxaprop-ethyl) and the free acid appearing in the faeces of males and females. While the ratio between Hoe 033171 and the free acid was 1:1 in females of the high dose group, the ratio was 1:3 in females of the low dose group. Taken together, the renally excreted compounds were identified to an amount of 99 – 100 % while the fecally excreted metabolites were identified to 64 – 72 %.

Dermal absorption

One valid *in vivo* study has been performed with the undiluted formulation (69 g Fenoxaprop-P-ethyl/L) and its 1:250 spray dilution (0.276 g/L), which is analogue to the representative formulation PUMA S EW69. In the *in vivo* study, the maximum dermal penetration rate (systemic absorption, application site, adjacent skin) is concluded to be 2.7 % for the concentrate and 25 % for the spray dilution after an application period of 8 hours. An *in vitro* study was performed comparing the dermal penetration rates of human and rat skin with an undiluted formulation (Cheetah Super, 55 g/L Fenoxaprop-P-ethyl and 15 g/L Mefenpyr-diethyl) and its aqueous dilution (1:75; 0.73 g/L). For the concentrate, the worst case scenario is a maximum absorbed amount of 47.08 % for rat skin and 28.24 % for human skin resulting in a ratio of 1.7. For the dilution, a higher maximum absorbed dose was found for the human skin (64.32 %) than for the rat skin (46.06 %), leading to a ratio of 0.7.

The *in vivo* dermal absorption study in rats was performed with the representative formulation "PUMA S 69EW" (69 g/L a.i., Code no. Hoe 046360 24 EW 14 A7). However, the comparative *in vitro* dermal penetration study in human and rat skin was performed with a similar formulation "Cheetah Super, 55 g/L a.i., Code no. AE F046360 24 EW07 A5). Both compositions of the formulations ("Cheetah super" and "PUMA S 69EW", the latter being the representative formulation) have been provided by the notifier. From the toxicological point of view, they be regarded comparable. Furthermore, "Cheetah super" contains a lower concentration of the a.i. suggesting an even higher absorption rate compared to the lead formulation, representing a worst case scenario.

Conclusion for the concentrate: Considering 2.7 % for the maximum dermal penetration rate from the *in vivo* rat study and the correction factor of 1.7 from the comparative *in vitro* human and rat skin study results, an overall dermal absorption rate of 1.6 % for the concentrated formulation of Fenoxaprop-P-ethyl is proposed to be used for the purposes of exposure calculations and risk assessment.

Conclusion for the aqueous dilution: The maximum dermal penetration *in vivo* was found to be 25 %. The respective correction factor from the *in vitro* study comparing human and rat skin was calculated to be 0.7. This results in an overall dermal absorption rate of 36 % for the aqueous spray dilution of Fenoxaprop-P-ethyl in the representative formulation.

4.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.1.3 Summary and discussion on toxicokinetics

ADME: The rate and extent of absorption of fenoxaprop-P-ethyl is rapid and almost completely absorbed (>90%) after oral low dose application in rats, based on urinary and faecal (assumed biliary) excretion after oral and i.v. application. Highest concentrations after single and repeated doses have been found in kidneys, blood, fatty tissues and liver in a total amount after 7 days: 0.7-2%. Excretion was > 75 % within 48 hours, whereby males generally excreted lower amounts of radioactivity via urine (35-54%) than via faeces (41-54%) which is vice versa for females (urine: 51-65%; faeces: 33-42%). The amounts in bile were not available. Fenoxaprop-P-ethyl is extensively metabolised via hydrolysis into free acid and conjugation with glutathione resulting in mercapturic acid. Minor pathways of metabolism are excretion of free acid via faeces (both sexes) or urine (females only), or further degradation of the free acid with or without sulphate conjugation; 10 % of the parent substance is found in the faeces.

Dermal Absorption: The *in vivo* study was performed with Puma (representative formulation) while the *in vitro* study was performed with another formulation Cheetah. After comparison, the two formulations were considered sufficiently similar to allow a read-across of dermal absorption results. The dermal absorption values for the representative formulation were 1.6% for the concentrate and 36% for the dilution.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Acute oral toxicity (OECD 401)	Minimal: ♂/♀: 3150 < LD_{50} < 4000 mg/kg bw	Wistar rat	*Ehling, 1992*
Acute inhalative toxicity (OECD 403)	LC_{50} > 1.224 mg/L, technically highest administrable concentration	Wistar rat	*Hofmann, 1991*
Acute dermal toxicity (EPA Guideline 81-2)	LD_{50} > 2000 mg/kg bw	Wistar rat	*Diehl, 1985b*
Acute intraperitoneal toxicity	Minimal: ♂: LD_{50} = 1490 mg/kg bw	Wistar rat	*Diehl, 1985c*
Fenoxaprop-ethyl (supportive information)			
Acute oral toxicity (OECD 401)	Minimal: ♂: LD_{50} = 2357 mg/kg bw	Wistar rat	*Hollander, 1979a*
Acute inhalative toxicity (OECD 403)	LC_{50} > 0.475 mg/L, highest dose tested	Wistar rat	*Hollander, 1982*
Acute dermal toxicity (OECD 402)	LD_{50} > 2000 mg/kg bw	Wistar rat	*Hollander, 1978, 1979c*
Acute intraperitoneal toxicity	Minimal: ♂: LD_{50} = 739 mg/kg bw	Wistar rat	*Mayer, 1979c*

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Table 12: Acute oral toxicity studies with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute oral toxicity	Wistar rat	Sesame oil	♂/♀: 3150 < LD_{50} < 4000 mg/kg bw	*Ehling, 1992*
Acute oral toxicity	NMRI mouse	Sesame oil	♂/♀: LD_{50} > 5000 mg/kg bw	*Diehl, 1985a*

In the acute oral toxicity study in the rat, groups of 5 male and 5 female Wistar rats, were dosed at 2000, 3150, 4000 or 5000 mg/kg body weight Fenoxaprop-P-ethyl. Mortality rates and time course of mortality indicated no sex-specific differences. The lethally intoxicated animals died between 1 and 2 days after treatment. The clinical signs of toxicity included deterioration in general health condition, flanks drawn in, stilted gait, decreased spontaneous activity, squatting posture, coat bristling, and irregular breathing. The mortality rates are given in the Table 13 below.

Table 13: Fenoxaprop-P-ethyl - Acute oral toxicity study in rats - Mortality

Dose (mg/kg bw)	Mortality			Day of death (number of animals)
	Males	Females	Total	
2000	0/5	0/5	0/10	-
3150	1/5	1/5	2/10	Day 2 (1), Day 3 (1)

Dose (mg/kg bw)	Mortality			Day of death (number of animals)
	Males	Females	Total	
4000	5/5	5/5	10/10	Day 2 (10)
5000	5/5	5/5	10/10	Day 2 (6), day 3 (4)

Body weight was markedly impaired in both sexes of the two highest dose groups. Necropsy of the decedent animals revealed discoloration of the liver and haemorrhages in the stomach and intestinal tract. The animals sacrificed at the end of the observation period were free of visible changes.

In the acute oral toxicity study in the mouse, groups of 5 male and 5 female NMRI mice were dosed at 5000 mg/kg body weight Fenoxaprop-P-ethyl. Neither mortality nor clinical signs of toxicity were observed at any time during the study. Only a slight disturbance of body weight gain in the males was noted during the first study week. Necropsy of the animals killed at the end of the study revealed no pathomorphological changes.

Supportive information

Table 14: Acute oral toxicity studies with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute oral toxicity	Wistar rat	Sesame oil	♂: LD_{50} = 2357 mg/kg bw	*Hollander, 1979a*
Acute oral toxicity	Wistar rat	Sesame oil	♀: LD_{50} = 2500 mg/kg bw	*Hollander, 1979b*
Acute oral toxicity	NMRI mouse	Sesame oil	♂: LD_{50} = 4670 mg/kg bw	*Mayer, 1979a*
Acute oral toxicity	NMRI mouse	Sesame oil	♀: LD_{50} = 5490 mg/kg bw	*Mayer, 1979b*

In the acute oral toxicity studies in the rat, groups of 10 male Wistar-rats were dosed at 1600, 2000, 2250, 2500 and 5000 mg/kg bw, whilst groups of 10 female Wistar-rats were dosed at 2000, 2500, 3150, 4000 and 5000 mg/kg bw Fenoxaprop-ethyl.

In males, the mortality rates are presented in Table 15 below.

Table 15: Fenoxaprop-ethyl - Acute oral toxicity in male rats - Mortality

Dose (mg/kg bw)	Mortality	Day of death (number of animals)
1600	0/10	-
2000	0/10	-
2250	4/10	Day 2 (1), day 5 (1), day 6 (1), day 7 (1)
2500	7/10	Day 1-2 (2), day 2 (3), day 2-3 (2)
5000	10/10	Day 1-2 (9), day 2-3 (1)

Lethally intoxicated males died between 1 and 7 days after treatment. The following symptoms were observed: passiveness, disequilibrium, squatting, crawling or crouching, bristled hair, blepharophimosis, seromucous and sanguineous rhinorrhoea. Animals that had died had bright spots on the liver, lobular marking of the liver and diffuse reddening of the pancreas. Petechial haemorrhages in the gastric mucosa (fundic part) and in the duodenum a red-black liquid in the entire region of the small intestine were also seen.

The only finding in the animals killed at termination of the experiment was diffuse reddening of the abdominal viscera.

At the end of the 14-day observation period, the body weight gains of the surviving animals were normal.

In females, the mortally rates are given in Table 16 below.

Table 16: Fenoxaprop-ethyl - Acute oral toxicity in female rats - Mortality

Dose (mg/kg bw)	Mortality	Day of death (number of animals)
2000	1/10	Day 1-2 (1)
2500	5/10	Day 2 (2), day 2-3 (3)
3150	9/10	Day 1-2 (1), day 2 (3), day 2-3 (3), day 3 (2)
4000	10/10	Day 1/2 (2), day 2 (7), day 2/3 (1)
5000	9/10	Day 1/2 (4), day 2 (2), day 2/3 (2), day 3-4 (1)

Lethally intoxicated females died between 1 – 4 days after dosing. The following symptoms were observed: passiveness, disequilibrium, squatting, crawling or crouching, bristled hair, blepharophimosis, chromodacryorrhoea and increased respiratory rate.

Animals that had died had bright spots on the liver, lobular marking of the liver and diffuse reddening of small intestine and pancreas. Petechial haemorrhages in the gastric mucosa (fundic part) and in the duodenum, red-black liquid in the entire region of the small intestine and uterus reddened were also seen.

The body weight gains of the surviving animals were normal.

The only finding in the animals killed after termination of the experiment was a slight lobular marking of the liver.

In the acute oral toxicity studies in the mouse, groups of 10 Hoe:NMRKf(SPF71) male mice were dosed at 3150, 4000, 5000, 5600 and 6300 mg/kg bw Fenoxaprop-ethyl, whilst groups of 10 Hoe:NMRKf(SPF71) female mice were dosed at 2500, 3150, 4000, 5000, 5600 and 6300 mg/kg bw.

In males, the mortally rates are given in Table 17 below.

Table 17: Fenoxaprop-ethyl - Acute oral toxicity in male mice - Mortality

Dose (mg/kg bw)	Mortality	Day of death (number of animals)
3150	0/10	-
4000	4/10	Day 2-3 (2), day 3-4 (2)
5000	4/10	Day 2-3 (2), day 3 (1), day 4/5 (1)
5600	8/10	Day 1/2 (5), day 2 (1), day 2/3 (2)
6300	10/10	Day 1/2 (1), day 2/3 (6), day 3 (1), day 3-4 (1), day 4-5 (1)

Lethally intoxicated males died within one to five days after the treatment. The following clinical symptoms were observed: passiveness, increased respiratory rate, blepharophimosis, disequilibrium, abdominal position, drowsiness, increased lacrimation and jerky respiration. The surviving experimental animals were free from clinical symptoms within 48 or 72 hours

after the treatment. The behaviour and the body weight increments were normal during the follow-up period.

Animals from all dose groups which were found dead during the study developed advanced autolysis. Animals that had died at 6300 mg/kg bw had distention of the urinary bladder and marking of the hepaticlobules. There were no macroscopic post-mortem findings in animals killed at termination of the experiment.

In females, the mortally rates are given in Table 18 below.

Table 18: Fenoxaprop-ethyl - Acute oral toxicity in female mice - Mortality

Dose (mg/kg bw)	Mortality	Day of death (number of animals)
3100	0/10	-
2000	0/10	-
4000	0/10	-
5000	3/10	Day 4/5 (1), day 6-7 (2)
5600	8/10	Day 1-2 (5), day 2 (1), day 2-3 (2)
6300	6/10	Day 1/2 (2), day 2 (3), day 2/3 (1)

Lethally intoxicated females died within 1 to 7 days after the treatment. The following clinical symptoms were observed: passiveness, blepharophimosis, increased respiratory rate, disequilibrium, abdominal position, drowsiness, increased lacrimation and jerky respiration.

The surviving animals were free from clinical symptoms within 48 or 72 hours after dosing. The behaviour and the body weight increments were normal during the follow-up period.

The macroscopic post-mortem examination of the animals that had died or were sacrificed after termination of the experiment showed no findings.

4.2.1.2 Acute toxicity: inhalation

Table 19: Acute inhalative toxicity study with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute inhalative toxicity	Wistar rat	PEG 400	♂/♀: LC_{50} > 1.224* mg/L (analytical, aerosol, 4 h, nose only)	*Hofmann, 1991*

* reported to be the technically highest administrable concentration

In a nose-only inhalation LC_{50} study, a group of 5 male and 5 female Wistar rats, was dosed with Fenoxaprop-P-ethyl at a concentration of 1.224 mg/l of air, the highest technically applicable concentration, for 4 hours.

No mortality occurred. Non-specific clinical signs such as impairment of respiration and motility or ruffled coat were observed for the first 5 days after exposure. Animals were free of any clinical signs thereafter.

Body weight remained unaffected by the treatment and no macroscopic changes were observed at necropsy.

Supportive information

Table 20: Acute inhalative toxicity study with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute inhalative toxicity	Wistar rat	Ethanol / polyglycol 1:1	♂/♀: LC_{50} > 0.475 mg/L (analytical, aerosol, 4 h, nose only)	*Hollander, 1982*

In a nose-only inhalation LC_{50} study, a two groups of 6 male and 6 female Wistar rats, were dosed with Fenoxaprop-ethyl at nominal concentrations of 151 and 511 mg/m^3 of air, for 4 hours.

Fenoxaprop-ethyl (Code Hoe 33171 0 H AT204, purity 93%, AZ No.: 01783) was tested for acute inhalation toxicity (nose only) in rats by means of an aerosol spray disperser over 4 hours. The test compound was a light-brown crystalline powder and was used as a 5% dilution in ethanol/ polyglycol (1:1) to determine the LC_{50}. Actual analytically determined concentrations were 140 and 475 mg/m^3 of air.

No treatment-related clinical signs were observed. One male animal from the highest dosage group died between day 1 and 2 following treatment. During the 14-day follow-up period, the surviving animals of both the experimental and control groups gained significant body weight after an initial weight loss. No findings were seen macroscoipically at the end of the study.

4.2.1.3 Acute toxicity: dermal

Table 21: Acute dermal toxicity study with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute dermal toxicity	Wistar rat	Moistened with PEG 400	♂/♀: LD_{50} > 2000 mg/kg bw	*Diehl, 1985b*

A group of five male and five female Wistar rats were each given a single 24-hour dermal application of 2000 mg/kg body weight Fenoxaprop-P-ethyl moistened with PEG 400.

Neither mortality nor clinical signs of toxicity were observed at any time during the study. The body weight remained unaffected and necropsy of the rats killed at the end of the study revealed no pathomorphological changes.

Examination of the treated skin revealed partial scaling of the skin in all of the males between days 1 and 4, and in 3 females from days 1 to 3.

Supportive information

Table 22: Acute dermal toxicity studies with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute dermal toxicity	Wistar rat	Sesame oil	♀: LD_{50} > 2000 mg/kg bw	*Hollander, 1978*
Acute dermal toxicity	Wistar rat	Sesame oil	♀: LD_{50} > 2000 mg/kg bw	*Hollander, 1979c*

In two separate studies, a group of 6 female SPF-Wistar-rats each received a single 24-hour dermal application of 2000 mg/kg body weight of 2000 mg/kg bw Fenoxaprop-ethyl applied as a 40 % (w/v) suspension in sesame oil.

No mortality was observed in either study. Slight passiveness, ruffled pelage and blepharophimosis in the first 24 hours after treatment were the only clinical signs observed. Macroscopic postmortem examination of the animals sacrificed at study termination revealed no specific findings in either study.

4.2.1.4 Acute toxicity: other routes

Table 23: Acute intraperitoneal toxicity study with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute intraperitoneal toxicity	Wistar rat	Sesame oil	♂: LD_{50} = 1490 mg/kg bw; ♀: LD_{50} > 2000 mg/kg bw	*Diehl, 1985c*

Groups of five male and five female Wistar rats were given a single intraperitoneal injection at dose levels of 1000, 1600 or 2000 mg/kg body weight Fenoxaprop-P-ethyl.

Males reacted more sensitively than the females. Mortality occurred in a dose-related manner between 1 and 3 days after administration. The mortality rates are given in the Table 24 below.

Table 24: Acute i.p. toxicity study in rats - Mortality

Dose (mg/kg bw)	Mortality			Day of death (number of animals)
	Males	Females	Total	
1000	0/5	0/5	0/10	-
1600	4/5	-	4/5	Day 1/2 (2), Day 2 (1), Day 2/3 (1)
2000	4/5	2/5	6/10	Day 1/2 (6)

Non-specific symptoms comprising of reduced spontaneous activity, drawn flanks, ataxic gait and mucous faeces were seen. The surviving animals were free of clinical signs 14 days after treatment. The body weights of some animals were impaired during the first week.

Necropsy of the decedent animals revealed a number of findings in the abdominal cavity including clear yellowish fluid in the intestine, oily fluid in the abdominal cavity and abdominal organs coated with a white-grey film and blood in the urine. All animals sacrificed at the end of the observation period were free of macroscopically visible changes with the exception of one female of the high dose group which showed a grey-white film over parts of the liver and deposits of test substance in the mesentery.

Supportive information

Table 25: Acute intraperitoneal toxicity studies with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Acute intraperitoneal toxicity	Wistar rat	Sesame oil	♂: LD_{50} = 739 mg/kg bw	*Mayer, 1979c*
Acute intraperitoneal toxicity	Wistar rat	Sesame oil	♀: LD_{50} = 864 mg/kg bw	*Mayer, 1979d*

Fenoxaprop-ethyl was administered once by intraperitoneal injection at dose levels of 500, 800, 1250, 2000, 3150 and 5000 mg/kg to groups of 10 male Wistar rats and in a separate study to groups of 10 female Wistar rats at dose levels of 315, 500, 800, 1250, 2000 and 3150 mg/kg bw.

Decedent males died between 1 and 6 days after treatment. Clinical symptoms were: squatting, piloerection, abdominal position and passiveness. Marked decrease in weight was recorded after 7 days in some of the animals dosed with 1250, 2000 and 3100 mg/kg bw. At the end of the study the body weights of all surviving animals were back to normal.

Autopsy of animals that died during the study showed extreme filling of the stomach with mashy feed and autolysis. The animals killed after termination of the experiment showed deposits of substance in the abdominal cavity and on the organs. Punctiform white spots were seen on the liver, kidneys, intestine and diaphragm. In addition, liver and suprarenal glands were partly light-brown discoloured and the liver showed slight marking.

The mortality rates for males are given in the Table 26 below.

Table 26: Acute i.p. toxicity study in male rats - Mortality

Dose (mg/kg bw)	**Mortality**	**Day of death (number of animals)**
500	2/10	Day 5/6 (2)
800	8/10	Day 2/3 (8)
1250	7/10	Day 1/2 (7)
2000	7/10	Day 1/2 (7)
3150	8/10	Day 1-2 (8)
5000	10/10	Day 1/2 (10)

Decedent females died between 1 and 3 days after the treatment with the following clinical symptoms: squatting, piloerection, abdominal position and passiveness. Slight to marked decrease in weight was recorded 7 days after treatment in some animals dosed with 315, 600, 800, 1250 and 3150 mg/kg body weight. At the end of the study bodyweight gain of all animals was normal again.

The mortality rates in females are given in the Table 27 below.

Table 27: Acute i.p. toxicity study in female rats - Mortality

Dose (mg/kg bw)	**Mortality**	**Day of death (number of animals)**
315	0/10	-
500	0/10	-
800	6/10	Day 1/2 (1), Day 2/3 (4), Day 3/4 (1)
1250	9/10	Day 1/2 (9)
2000	10/10	Day 1-2 (10)
3150	9/10	Day 1/2 (9)

Autopsy of animals that died during the study showed extreme filling of the stomach with mashy feed and autolysis. The animals killed after termination of the experiment showed deposits of substance in the abdominal cavity and on the organs. Punctiform white spots or a film-like, thin-layered coat were seen on the liver, spleen and kidneys. In addition, the liver was partly light-brown discoloured and showed slight marking.

4.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.2.3 Summary and discussion of acute toxicity

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 inhalative toxicity is assumed to be low.

Supportive information

Fenoxaprop-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, 1 of 6 male animals died at the highest concentration of 0.475 mg/L (analytical). No definitive conclusions on the acute inhalative toxicity of Fenoxaprop-ethyl can be made with this study.

4.2.4 Comparison with criteria

All estimated LD_{50} and LC_{50} values are above the criteria for triggering classification and labelling (both DSD and CLP).

4.2.5 Conclusions on classification and labelling

No classification is proposed for acute toxicity.

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.

4.3 Specific target organ toxicity – single exposure (STOT SE)

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 to fenoxaprop-P-ethyl, 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 proposed.

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.

4.4 Irritation

4.4.1 Skin irritation

Table 28: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Acute Dermal Irritation/Corrosion (EPA Guideline 81-5)	Slightly irritating (no classification)	Rabbit NZW	*Diehl, 1985d*
Fenoxaprop-ethyl (supportive information)			
Acute Dermal Irritation/Corrosion (EPA Guideline 81-5)	Slightly irritating (no classification)	Albino-Himalayan rabbits	*Hollander, 1979d*

4.4.1.1 Non-human information

Table 29: Skin irritation study with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Dermal irritation study	Rabbit NZW	PEG 400	Slightly irritating (no classification)	*Diehl, 1985d*

A 500 mg quantity of Fenoxaprop-P-ethyl was moistened with 0.55 ml PEG 400 and administered for 4 hours to an area (2.5 cm x 2.5 cm) of intact, clipped, dorsal-lumbar skin of 6 adult New Zealand White rabbits under a semi-occlusive dressing. The rabbits were observed daily for clinical signs and mortality. Skin responses were evaluated 30 - 60 minutes, and 24, 48 and 72 hours after the end of the exposure period according to the technique of Draize.

Very slight erythema was observed in all 6 animals 30 – 60 minutes after the exposure period, after 24 hours this finding was noted in only two animals and by 48 post exposure, this finding was completely reversible. No edema was observed throughout the study.

Based on the system of evaluation defined by the EEC, the following overall group mean scores for dermal irritation after 24, 48 and 72 hours are presented in Table 30 below.

Table 30: Primary dermal irritation in rabbit - Individual and mean score after a 24 hours application of Fenoxaprop-P-ethyl

	30 - 60 minutes							**24h**							**48h**							**72h**						**Mean score*** **
Animal N°	1	2	3	4	5	6		1	2	3	4	5	6		1	2	3	4	5	6		1	2	3	4	5	6	
Erythema*	1	1	1	1	1	1		0	1	0	0	0	1		0	0	0	0	0	0		0	0	0	0	0	0	**0.11**
Oedema**	0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0	**0.00**

* Score for erythema : 0 = no erythema; 1 = very slight, barely perceptible erythema; 2 = well-defined erythema; 3 = moderate to severe erythema; 4 = severe erythema to slight eschar formation
** Score for oedema: 0 = no oedema; 1 = very slight, barely perceptible oedema; 2 = slight oedema, edges of area well defined by definite raising; 3 = moderate oedema, raised approx. 1 mm; 4 = severe oedema, raised more than 1 mm and extending beyond the area of exposure
*** mean of scores of 24, 48 and 72 hours (according to EEC criteria)

Supportive information

Table 31: Skin irritation study with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Dermal irritation study	Albino-Himalayan rabbits	PEG 400	Slightly irritating (no classification)	*Hollander, 1979d*

A quantity of 500 mg fenoxaprop-ethyl which was premixed with 0.3 ml polyethylene glycol 400, was applied to gauze patches measuring 2.5 x 2.5 cm each which were placed on the flank of 6 Albino-Himalayan-rabbits for a period of exposure of 24 hours. At least 6 x 8 cm of the flank skin of each animal was clipped free of hair. One half of the shorn area was additionally scarified. Evaluation of irritant effects was made immediately after removal of the dressing and subsequently 48 and 72 hours after the application.

Details of the skin scores are presented in Table 32 below.

Table 32: Skin irritation (individual and mean values)

Animal No		24 hours		48 hours		72 hours	
		Erythema*	Oedema**	Erythema*	Oedema**	Erythema*	Oedema**
1	Intact	1	2	1	0	0	0
	Scarified	*1*	*2*	*1*	*0*	*0*	*0*
2	Intact	3	2	1	0	0	0
	Scarified	*3*	*2*	*1*	*1*	*0*	*0*
3	Intact	3	2	2	0	0	0
	Scarified	*2*	*2*	*1*	*0*	*0*	*0*
4	Intact	2	1	1	0	0	0
	Scarified	*2*	*1*	*1*	*0*	*0*	*0*
5	Intact	2	1	1	0	0	0
	Scarified	*2*	*1*	*1*	*0*	*0*	*0*
6	Intact	1	1	2	0	1	0
	Scarified	*2*	*1*	*2*	*0*	*1*	*0*
Mean score (intact skin)		**2.0**	**1.5**	**1.25**	**0.08**	**0.16**	**0.0**

* Score for erythema: 0 = no erythema; 1 = very slight, barely perceptible erythema; 2 = well-defined erythema; 3 = moderate to severe erythema; 4 = severe erythema to slight eschar formation
** Score for oedema: 0 = no oedema; 1 = very slight, barely perceptible oedema; 2 = slight oedema, edges of area well defined by definite raising; 3 = moderate oedema, raised approx. 1 mm; 4 = severe oedema, raised more than 1 mm and extending beyond the area of exposure

Based on the system of evaluation defined by the EEC, the following overall group mean scores for dermal irritation after 24, 48 and 72 hours were calculated:

Table 33: Overall group mean score (intact skin)

	Erythema	Oedema
Mean score (24, 48 and 72h)	1.14	0.53

4.4.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.1.3 Summary and discussion of skin irritation

For fenoxaprop-P-ethyl the mean value for erythema within 72 hours was 0.11. No edemas were observed.

Supportive information

The average score for erythema for fenoxaprop-ethyl within 72 hours was 1.14, and 0.53 for edema.

4.4.1.4 Comparison with criteria

Estimated skin irritation scores are below the criteria for triggering classification and labelling (according to both DSD and CLP).

4.4.1.5 Conclusions on classification and labelling

No classification is proposed for skin irritation.

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.

4.4.2 Eye irritation

Table 34: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Acute Eye Irritation/Corrosion (EPA Guideline 81-4)	Slightly irritating (no classification)	Rabbit NZW	*Diehl, 1985e*
Fenoxaprop-ethyl (supportive information)			
Acute Eye Irritation/Corrosion (EPA Guideline 81-4)	Slightly irritating (no classification)	Albino-Himalayan rabbits	*Hollander, 1979d*

4.4.2.1 Non-human information

Table 35: Eye irritation study with Fenoxaprop-P-ethyl

Type of study	Species	Vehicle	Results	Reference
Eye irritation study	Rabbit NZW	undiluted	Slightly irritating (no classification)	*Diehl, 1985e*

A 100 mg quantity of Fenoxaprop-P-ethyl was applied to the conjunctival sac of the left eye of six female New Zealand White rabbits. In each case the untreated eye served as a control.

After 24 hours the treated eyes were washed out and were examined for ocular reactions at 1, 24, 48 and 72 hours after treatment. In addition, 3 animals were treated analogously but the eyes were washed out 1 minute after treatment.

When applied for 24 hours before washing, the test substance caused mild eye irritation in the form of conjunctival reddening, chemosis and discharge which subsided completely by day 2 after treatment. All signs of irritation were completely reversible within 3 days.

The following group mean scores (within 72 hours after treatment) were calculated:

Table 36: Eye irritation study in rabbits - Individual and mean score after a 24 hours application of fenoxaprop-P-ethyl

Time after application	1h							24h							48h							72h						Mean Score*
Animal N°	1	2	3	4	5	6		1	2	3	4	5	6		1	2	3	4	5	6		1	2	3	4	5	6	
Discharge	2	2	2	2	2	3		1	1	1	1	1	2		0	0	0	0	1	1		0	0	0	0	0	0	
Conjuntivae																												
Chemosis	1	1	1	1	2	1		0	0	1	0	1	2		0	0	0	0	0	0		0	0	0	0	0	0	**0.22**
Redness	1	2	2	2	2	2		1	2	2	2	2	2		0	0	0	0	0	0		0	0	0	0	0	0	**0.61**
Inflammation of iris	0	0	0	0	0	0		0	0	0	0	0	1		0	0	0	0	0	0		0	0	0	0	0	0	**0.06**
Cornea																												
Opacity	0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0	**0.00**
Translucency (fluorescein test)	0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	0	0	0	

* Mean of scores after 24, 48 and 72 hours

When the test material was applied for 1 minute before washing, signs of irritation were limited to slight chemosis and redness 1 hour after exposure. Except for slight discharge

which was observed at 24 hours, all animals were free of any signs 24 hours after application of the test substance.

Supportive information

Table 37: Eye irritation study with Fenoxaprop-ethyl

Type of study	Species	Vehicle	Results	Reference
Eye irritation study	Albino-Himalayan rabbits	undiluted	Slightly irritating (no classification)	*Hollander, 1979d*

Single doses of 100 mg Fenoxaprop-ethyl premixed with 0.08 ml polyethylene glycol 400, were applied to the conjunctival sac of the left eye of 9 Albino – Himalayan rabbits. The right eye remained untreated for control purposes. One minute after the application of the substance the eye of 3 animals was flushed with sodium chloride solution. The eyes of the remaining 6 animals were not flushed out. The irritant effects were evaluated at 1, 7, 24, 48 and 72 hours after application. The 48 -and 72-hour values were recorded after the instillation of one drop of fluorescein-sodium dilution.
A classification of irritancy potential was performed according to the classification system from "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics", FDA, Austin,Texas, p 51, 1978.

There were no deaths or clinical signs of systemic toxicity. The test substance caused mild eye irritation in the form of conjunctival reddening, chemosis and discharge which subsided completely by 2 days after treatment.

The following group mean scores (within 72 hours after treatment) were calculated:

Table 38: Fenoxaprop-ethyl - Eye irritation - Individual and mean values

Animal No	24 hours			48 hours			72 hours		
	Cornea	Conjuntivae		Cornea	Conjuntivae		Cornea	Conjuntivae	
	Opacity	Redness	Chemosis	Opacity	Redness	Chemosis	Opacity	Redness	Chemosis
1*	1	2	0	0	0	0	0	0	0
2*	0	2	0	0	0	0	0	0	0
3*	0	2	0	0	1	0	0	1	0
4	1	2	1	1	1	0	1	1	0
5	1	2	1	0	0	0	0	0	0
6	0	2	1	0	1	0	0	0	0
7	0	2	1	0	1	0	0	1	0
8	1	2	1	1	2	0	0	1	0
9	0	2	1	0	1	0	0	0	0
Mean score	**0.44**	**2.0**	**0.66**	**0.22**	**0.77**	**0.0**	**0.11**	**0.44**	**0.0**

* Eyes of this animals were flushed with sodium chloride solution

Table 39: Fenoxaprop-ethyl - Irritation indices (group mean scores) according to EEC criteria

Group mean score within 72 hours after treatment				
Ocular lesion	**Cornea opacity**	**Iris**	**Conjunctiva redness**	**Conjunctiva chemosis**
Test substance	0.26	0.00	1.07	0.22

4.4.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.2.3 Summary and discussion of eye irritation

For fenoxaprop-P-ethyl the average scores after 24, 48 and 72 hours were 0.61 for conjunctivae redness, 0.22 for conjunctivae 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).

Supportive information

For fenoxaprop-ethyl the average scores after 24, 48 and 72 hours were 0.83 for conjunctivae redness, 0.16 for conjunctivae 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 animal 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 regarding 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.

4.4.2.4 Comparison with criteria

Estimated eye irritation scores (24 – 72 hours; 0.22 (conjunctival chemosis), 0.61 (conjunctival redness), 0.06 (iritis) and 0.0 (corneal opacity) are below the criteria for triggering classification and labelling (according to both DSD and CLP).

4.4.2.5 Conclusions on classification and labelling

No classification is proposed for eye irritation.

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.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

There is no specific information regarding the ability of fenoxaprop-P-ethyl to cause irritation to the respiratory tract during the acute inhalation toxicity study.

4.4.3.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.3.3 Conclusions on classification and labelling

No classification is proposed for respiratory tract irritation.

4.5 Corrosivity

Based on the data from the skin and eye irritation studies it can be concluded that fenoxaprop-P-ethyl is not corrosive.

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 40: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Dermal sensitization Maximisation Test (EPA guideline 81-6, compliant with OECD guideline 406 (1992))	Sensitizing	Guinea pig (♀) (Pirbright-White)	*Diehl, 1986a*
Dermal sensitization Buehler Test (OECD 406)	Not sensitizing	Guinea pig (♀) (Pirbright-White)	*Hack, 1992*
Fenoxaprop-ethyl (supportive information)			
Dermal sensitization Buehler Test (OECD 406)	Not sensitizing	Guinea pig (♀) (Pirbright-White)	*Jung, Weigand, 1982*

4.6.1.1 Non-human information

Skin sensitization with Fenoxaprop-P-ethyl

Testing for sensitizing properties in the Pirbright-White guinea pig in a maximisation test

Reference: *Diehl K.-H., Leist K.-H.; 1986a;* Doc.No. A37243 / Hoechst Report No. 86.0003

Guideline: EPA Guideline 81-6 (1982), compliant with OECD guideline 406 (1992)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Female Pirbright-White guinea pigs (strain: DHPK, source: Hoechst) with body weights between 209 and 304 g (about 10 weeks old) were given Fenoxaprop-P-ethyl (Hoe 046360 0H ZC96 0002, purity 95.6%) in the maximisation test. The number of animals was 20 in the treatment group and 10 in the control group. Further animals served for the determination of the primary non-irritating concentration (6) and the intradermic tolerance (3). As treatment with Freund´s Adjuvant can lower the threshold value for primary irritation, an escort group (5) was additionally used for the determination of the concentration of the test substance used for challenge treatment.

On day 0 body weights of animals were recorded and guinea pigs were shaved mechanically over a dorsal area of 4 x 6 cm.

Based on preliminary tests, 5 % Fenoxaprop-P-ethyl in vaseline was selected as a suitable intradermal induction concentration. During the intradermal induction treatment (day 1), each animal received 0.1 ml injections of 50 % Freund´s Adjuvant, 5 % solution of test substance in vaseline, and 5 % solution of test substance in 50 % Freund´s Adjuvant. Controls and escort groups received the same treatment excluding the test substance.

For dermal induction (day 9), 50 % Fenoxaprop-P-ethyl in vaseline was fixed occlusively for 48 hours on the area where the intradermal injection had been placed. Control and escort groups received vaseline only.

On days 15 – 18, the escort groups received a challenge treatment carried out in the same way as that of control and treated groups (days 22 – 25).

On day 22, two areas (5 x 5 cm) were shaved on the left and right flank of the animals. Challenge was conducted with 50 % Fenoxaprop-P-ethyl in vaseline on the left flanks and vaseline alone on the right flanks of all animals. The occlusive bandage was removed on day 23, and skin was examined on days 24 and 25. Body weight was recorded on day 26.

Findings:

In the primary non-irritant concentration test, 12.5 %, 25 % or 50 % preparations of test substance in vaseline were applied occlusively to the left flank of the guinea pigs for 24 hours. There were no signs of irritation observed. Also, the animals of the escort group treated with 50 % test substance did not develop any signs of irritation. The concentration of 50 % was selected for the main test.

Preliminary studies on intradermic injections showed more or less equally marked redness and swelling after application of 0.2, 1 and 5 % preparations, therefore 5 % were chosen for the main test.

In the main study, the intradermic injections of Freund´s Adjuvant (with and without test substance) caused clearly marked redness and swelling of the injection sites. Intradermic injections with vaseline caused slight edema and in some cases very slight erythema. No information is presented if any irritation was observed after topical induction treatment with 50 % test substance. Challenge treatment led to slight to severe erythema (up to grade 3) in 19/20 animals, slight edema (grade 1) in 14/20 animals, and to scab formation in 2/20 animals 48 hours after treatment. 72 hours after treatment slight to severe erythema (up to grade 3) was noted in 20/20 animals, slight edema (grade 1) in 11/20 animals and scab formation in 3/20 animals. None of the control animals showed any signs of skin effects.

There were no clinical signs of systemic toxicity and no impairment of body weight gains observed.

Conclusion:

Under the conditions of this study, Fenoxaprop-P-ethyl demonstrated sensitizing effects in 100 % of the treated guinea-pigs, though dermal induction treatment probably took place under non-irritating conditions. The results of this study indicate classification of Fenoxaprop-P-ethyl for skin sensitization.

Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler

Reference: *Diehl K.-H., Leist K.-H.; 1986b;* Doc.No. A36040 / Hoechst Report No. 86.0466

Guideline: EPA Guideline 81-6 (1982)

GLP: yes

Deviations: the induction phase was performed under non-irritating conditions.

This study is of limited validity due to technical reasons.

Material and Methods:

Female Pirbright-White guinea pigs (strain: DHPK, source: Hoechst) with body weights between 140 and 267 g (about 10 weeks old) were given Fenoxaprop-P-ethyl (Hoe 046360 0H ZC96 0002, purity 95.6%) in the Buehler test. The number of animals was 20 in the treatment group and 10 in the control group. Further 6 animals served for the determination of the primary non-irritating concentration.

On day 1 body weights of animals were recorded and guinea pigs were shaved mechanically over the left flank. The animals received a total of nine topical induction applications (days 1, 3, 5, 8, 10, 12, 15, 17 and 19) of 0.5 ml test substance (50 % in vasline) on the shaved left flank. After an exposure period of 6 hours the occlusive bandage was removed and the flank skin washed. All clinical signs and irritant effects were recorded approximately 24 hours after each induction application. The control group was treated the same way with vehicle alone.

On day 36 the first challenge was performed with a 25 % preparation in vaseline on the shaven right flank of the guinea pigs. The occlusive bandage was removed after 6 hours and any remnants were washed off with warm water. The flank was then reshaved with the clipper. On day 37 the skin was examined macroscopically and then reshaved in the late afternoon. On day 38 skin was re-examined. Further challenges were carried out in the same procedure as the first challenge. The second challenge (day 43) was performed with 10 % test substance in vaseline, and the third and fourth challenge (days 51 and 58, resp.) with 2 % test substance in vaseline.

For all challenges, skin reactions were scored approximately 24 and 48 hours after the challenge and re-challenge treatment.

Findings:

In the preliminary non-irritant concentration test, 12.5, 25 and 50 % Fenoxaprop-P-ethyl did not cause any signs of irritation after an occlusive bandage for 24 hours. However 50 % were selected for the induction phase of this study.

In the main test, no irritation occurred on the treated skin during induction phase. The first three challenge treatments (25 %, 10 %, and 2 %, resp.) lead to skin reactions evidenced by slight, barely perceptible erythema (grade 1) in some of the animals in both the control and the treatment group. These skin reactions were reported to be probably due to a technical factor (clipping). For this reason, the animals were not reshaved after the fourth challenge with a 2 % preparation. No skin reactions were observed after the fourth challenge.

There were no clinical signs of systemic toxicity and no impairment of body weight gains observed. One animal of the treatment group died during the study between induction and challenge period, but there was no apparent connection with application of the test substance. Autopsy revealed the following clinical signs: pericardium filled with large quantities of fluid; lungs congested; abdominal cavity filled with blood-coloured fluid; liver with light-coloured patches, spongy and with an uneven surface; gastro-intestinal tract reddened; intestine inflated and filled with blood.

Conclusion:

The results of this study are inconclusive. It is reported that technical reasons (clipping) might have lead to slight skin reactions in both the control and the treatment group. Furthermore, the induction phase was conducted under non-irritating conditions. Therefore this study is of

limited validity and supplementary information only. Another test according to Buehler was performed in 1992 and is evaluated in this chapter.

Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler

Reference: *Hack R., Leist K.-H.; 1992;* Doc.No. A47403 / Hoechst Report No. 91.1199

Guideline: EPA Guideline 81-6 (revised 1984), OECD Guideline 406 (adopted 1987), MAFF (1985)

GLP: yes

Deviations: the induction phase was performed under non-irritating conditions.

The study is scientific valid and acceptable.

Material and Methods:

Female Pirbright-White guinea pigs (strain: DHPK, source: Hoechst) with body weights between 236 and 291 g (about 10 weeks old) were given Fenoxaprop-P-ethyl (Hoe 046360 00 ZC97 0002, purity 90.0%, sum of (D+)- and (L-)-isomer 97.7%) in the Buehler test. The number of animals was 20 in the treatment group and 10 in the control group. Further 6 animals served for the determination of the primary non-irritating concentration.

The animals received a total of nine topical induction applications of the test material (75 % in PEG 400) with an occlusive bandage on the shaven left flank on study days 1, 3, 5, 8, 10, 12, 15, 17 and 19. After an exposure period of 6 hours the flank skin was washed and clinical signs and irritant effects were recorded. The control animals were treated analogously with 0.5 ml PEG 400 alone.

Challenge took place on day 36 with 75 % Fenoxaprop-P-ethyl in PEG 400. The test substance was applied to the right flank of the animals for 6 hours under an occlusive bandage. After removal the preparation was washed off with warm water and skin was examined on day 37 and 38. A second challenge was performed on day 43 with skin examinations 24 and 48 hours later.

Findings:

In a preliminary test for primary skin irritation, 25, 50 and 75 % preparations of Fenoxaprop-P-ethyl in PEG 400 did not cause any signs of irritation, however the highest concentration (75 %) of Fenoxaprop-P-ethyl was selected for induction and challenge treatment. In the main test, no signs of irritation were observed during induction treatment with the exception of one single animal which developed a dry and rough skin surface after the fifth and sixth treatment. After challenge treatment none of the animals neither in the treatment group nor in the control group exhibited any effects on the skin. The results of the rechallenge are not reported.

There were no clinical signs of systemic toxicity and no effects on body weight gains observed.

Conclusion:

Fenoxaprop-P-ethyl did not induce skin sensitization in a test according to Buehler in guinea-pigs. However, the induction phase was conducted under non-irritating conditions.

Supportive information

Skin sensitization with Fenoxaprop-ethyl

Testing for sensitizing properties of Hoe 33171 0H AS201 in the guinea pig according to Buehler

Reference: *Jung, Weigand; 1982;* Doc.No. A30110 / Hoechst Report No. 573/82

Guideline: corresponding to OECD Guideline 406 (adopted 1987)

GLP: yes

Deviation: reduced number of animals (10 treatment, 5 controls)

The study is of supplementary information due to reduced animal number.

Material and Methods:

Female Pirbright-White guinea pigs (strain: DHPK(SPCLac), source: Hoechst) with body weights between 247 and 320 g were given Fenoxaprop-ethyl (Hoe 33171 0H AS201) in the Buehler test. Information on the purity of the test substance (Hoe 33171 0H AS201) is not included in the study report, but presented by the notifier in a separate report (A36866) where the purity was 94.0 %. The number of animals was 10 in the treatment group and 5 in the control group. Further 1 and 5 animals served for the determination of the primary non-irritating concentration in a first and second preliminary test, respectively. Treatments were made on the shaven flanks of the guinea pigs. In the first preliminary test 1, 10 or 25 % test substance in PEG 400 or in starch mucilage were tested during a 24 hours exposure period. Irritation effects were evaluated after 24 and 48 hours. In the second preliminary test, the guinea pigs received 1, 5 or 10 % test substance in PEG 400. In the main study the animals were treated with 9 topical applications of 10 % Fenoxaprop-ethyl in PEG 400 during 3 weeks. The test area was covered with cellulose patches for 6 hours. The dermal reactions were determined 24 hours after application. Controls were treated with PEG 400 alone. After the last application the animals remained untreated for 16 days. Challenge and re-challenge then took place at an interval of 48 hours in both treatment and control group. Challenge and re-challenge were performed by the administration of 5 % test substance in PEG 400. Dermal reactions were assessed after 6, 24 and 48 hours.

Findings:

The first preliminary test showed a slight reddening over the whole flank after the application of 10 and 25 % Fenoxaprop-ethyl in PEG 400 but not at 1 %. All irritation disappeared after 24 hours. In the second preliminary test slight reddening was observed only at the highest dose of 10 % in PEG 400 while no skin effects were recorded after 1 and 5 %. The main test was conducted with 9 topical applications of a 10 % preparation in PEG 400 and induced slight to marked reddening of the treated flank. During challenge and re-challenge of the previously untreated flanks with a 5 % preparation in PEG 400 no skin reactions were observed in treatment and control animals. The body weight gains of the animals were normal and no macroscopic findings were noted at autopsy.

Conclusion:

Fenoxaprop-ethyl did not induce skin sensitization in a test according to Buehler in guinea-pigs. However, only a reduced number of animals was used in this study which limits the validity of this study.

4.6.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.6.1.3 Summary and discussion of skin sensitisation

A Magnusson & Kligman assay was performed only with Fenoxaprop-P-ethyl resulting in sensitizing effects on the skin of guinea pigs. However, in sensitization tests according to Buehler, both Fenoxaprop-P-ethyl and Fenoxaprop-ethyl (in a Buehler test with limited validity) did not show sensitizing effects on the skin of guinea pigs.

4.6.1.4 Comparison with criteria

A Magnusson & Kligman assay demonstrated skin sensitizing effects of Fenoxaprop-P-ethyl in guinea pigs. 5 % Fenoxaprop-P-ethyl in vaseline was selected as a suitable intradermal induction dose. All of the animals treated (100%) showed a positive dermal reaction during the observation period after the challenge treatment. In a test according to Buehler, no sensitizing properties of Fenoxaprop-P-ethyl were noticed under non-irritating conditions.

4.6.1.5 Conclusions on classification and labelling

Fenoxaprop-P-ethyl should be classified regarding skin sensitizing effects with the risk phrase R43 (Irritant; May cause sensitization by skin contact) according to Annex VI of the EC Council Directive 67/548/EEC and as skin sensitizing Category 1b with the hazard statement H317 (May cause an allergic skin reaction) according to Annex I of Regulation (EC) No 1272/2008.

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).

4.6.2 Respiratory sensitisation

No data.

4.7 Repeated dose toxicity

Table 41: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Wistar rat 13 weeks oral (OECD 408)	NOAEL: 10 ppm (♂: 0.7 mg/kg bw/d; ♀: 0.8 mg/kg bw/d) overall subchronic NOAEL in rats = 2 mg/kg bw/d	- haematology, clinical chemistry and urinalysis findings - increased organ weights (liver, kidney) - macroscopically enlarged kidneys	*Tennekes H. et al., 1987*
NMRI mouse 13 weeks oral (OECD 408)	NOAEL: 10 ppm (♂: 1.4 mg/kg bw/d; ♀: 2.0 mg/kg bw/d) overall subchronic NOAEL in mice = 5.5 mg/kg bw/d	- increased organ weights (liver) - histopathological findings (tubular injury)	*Suter P. and Luetkemeier H., 1987a*
Beagle dog 13 weeks oral (EPA guideline 82-1)	NOAEL: 400 ppm (♂: 15.6 mg/kg bw/d; ♀: 16.2 mg/kg bw/d)	- decreased body weight gain - clinical chemistry findings	*Sachsse K. et al., 1987b*
Wistar rat 28 day inhalation (OECD 412)	NOAEL: 0.015 mg/L	- haematology and clinical chemistry findings - increased organ weights (liver)	*Hofmann T. et al., 1989*
Wistar rat 21 day dermal application (OECD 410)	NOAEL: 20 mg/kg bw/d	- haematology and clinical chemistry findings - increased organ weights (liver, kidney)	*Ebert E. et al., 1988*
Fenoxaprop-ethyl (supportive information)			
Wistar rat 32 days oral	NOAEL: < 80 ppm	- clinical chemistry findings - increased organ weights (kidney)	*Leist et al., 1980a*
Wistar rat 3 months oral (OECD 408)	NOAEL: 20 ppm (♂: 1.57 mg/kg bw/d; ♀: 1.74 mg/kg bw/d)	- clinical chemistry findings - increased organ weights (adrenals)	*Donaubauer et al., 1981*
NMRI mouse 32 days oral	NOAEL: < 80 ppm	- increased organ weights (liver) - histopathological findings (liver)	*Leist et al., 1980b*
NMRI mouse 30 days oral	NOAEL: 10 ppm (♂: 1.82 mg/kg bw/d; ♀: 1.85 mg/kg bw/d)	- clinical chemistry findings - increased organ weights (liver) - histopathological findings (liver)	*Leist et al., 1981*
NMRI mouse	NOAEL: < 320 ppm	- haematology findings	*Ehling G., 1993a*

Method	Results	Remarks	Reference
13 weeks oral (EPA guideline 82-1)		- clinical chemistry findings - increased organ weights (liver, kidney, spleen, adrenals) - histopathological findings (liver, kidney, spleen) - electron microscopy and special biochemistry findings (peroxisome proliferation)	
Beagle dog 3 months oral	NOAEL: 16 ppm	- histopathology findings (interstitial pyelonephritis)	*Brunk et al., 1981a*
Beagle dog 1 year oral (OECD 409)	NOAEL: > 75 ppm	No treatment-related effects could be identified in any of the dose groups.	*Brunk et al., 1984*

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Table 42: Repeated dose toxicity: oral with Fenoxaprop-P-ethyl

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Wistar rat 28 days oral *Suter P. et al., 1987a*	0, 20, 80, 320, 1280 and 5120 ppm / diet (equivalent to 0, 2, 6, 26, 95 and 126 mg/kg bw/d in males; 0, 2, 6, 28, 94 and 144 mg/kg bw in females)	20 ppm (♂ and ♀: 2 mg/kg bw/d) <u>Supplementary information only</u>	**- haematology, clinical chemistry and urinalysis findings** 5120 ppm group terminated on treatment day 9 due to severe impairment of food consumption, resulting in stagnation of growth <u>Remaining dose levels</u> - ≥ 80 ppm: ↓ phospholipid levels, shorter thromboplastin time (F), ketonuria - ≥ 320 ppm: ↓ in body weight gain and food consumption, ↓ cholesterol, ↑ triglycerides kidney and liver weights -1280 ppm only: ↑ leucine aminopeptidase and alkaline phosphatase – indicative of hepatotoxicity, prolonged thromboplastin and partial thromboplastin times (M)

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Wistar rat 13 weeks oral *Tennekes H. et al., 1987*	0, 10, 80 and 640 ppm / diet (equivalent to 0, 0.7, 5.8 and 49.0 mg/kg bw/d in males; 0, 0.8, 6.3 and 51.8 mg/kg bw/d in females)	10 ppm (♂: 0.7 mg/kg bw/d; ♀: 0.8 mg/kg bw/d)	**-clinical chemistry and urinalysis findings** **- increased organ weights (liver, kidney)** **- macroscopically enlarged kidneys** - ≥ 80 ppm: changes in lipid metabolism, ↑ in liver and kidney weights, ketonuria, urobili- and bilirubinuria - 640 ppm only: ↓ in body weight and food consumption. ↓ haemoglobin, haematocrit, MCV, ↑ MCHC, alkaline phosphatase, , prolonged thromboplastin and partial thromboplastin times (M), shorter thromboplastin time (F), centrilobular hepatocellular hypertrophy
NMRI mouse 28 days oral *Suter P. et al., 1987b*	0, 20, 80, 320 and 1280 ppm / diet (equivalent to 0, 3, 14, 56 and 260 mg/kg bw/d in males; 0, 4, 16, 61 and 280 mg/kg bw/d in females)	80 ppm (♂: 14 mg/kg bw/d; ♀: 16 mg/kg bw/d) Supplementary information only	**- clinical chemistry findings** **- increased liver weight** **- histopathological findings (tubular injury, hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes)** - ≥ 320 ppm: changes in lipid metabolism, ↑ liver weight associated with hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes, tubular injury in the kidney - 1280 ppm only: ↑ aspartate and alkaline aminotransferase, alkaline phosphatase, albumin and protein levels,↑ kidney weights
NMRI mouse 13 weeks oral *Suter P. and Luetkemeier H., 1987a*	0, 10, 80 and 640 ppm / diet (equivalent to 0, 1.4, 11.9, 100.8 mg/kg bw/d in males; 0, 2.0, 16.5 and 122.4 mg/kg bw/d in females)	10 ppm (♂: 1.4 mg/kg bw/d; ♀: 2.0 mg/kg bw/d)	**- increased liver weight** **- histopathological findings (tubular injury)** - ≥ 80 ppm: ↑ liver weight, tubular injury in the kidney - 640 ppm only: changes in lipid metabolism, ↑ liver enzymes associated with hepatocellular hypertrophy, ↑ total protein, albumin and urea, ↑ kidney weight

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Beagle dog 28 days oral *Sachsse K. et al., 1987a*	0, 80, 320 and 1280 ppm / diet (equivalent to 0, 3.3, 13.0 and 67.9 mg/kg bw/d in males; 0, 3.7, 14.9 and 56.1 mg/kg bw/d in females)	NOAEL could not be established Supplementary information only	No treatment-related effects could be identified in any of the dose groups (only 1 animal/sex/group).
Beagle dog 13 weeks oral *Sachsse K. et al., 1987b*	0, 80, 400 and 2000 ppm / diet (equivalent to 0, 3.0, 15.6 and 77.7 mg/kg bw/d in males; 0, 3.2, 16.2 and 83.4 mg/kg bw/d in females)	400 ppm (♂: 15.6 mg/kg bw/d; ♀: 16.2 mg/kg bw/d)	**- decreased body weight gain** **- clinical chemistry findings** - 2000 ppm only: ↓ body weight gain, ↑ aspartate aminotransferase, lactate dehydrogenase and total protein (M), ↓ alkaline aminotransferase (M + F),

All studies with Fenoxaprop-P-ethyl were conducted according to GLP and most of the studies also according to OECD and/or EPA Guidelines. However, the subacute 28- or 30-day dose findings studies had some limits in study design and are of supplementary information only.

Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in rats

Reference: *Suter P.* et al.; 1987a; Doc. No. A36568 / RCC Project No. 060636
Addendum to final report, *Suter P.* et al., 1990, Doc. No. A42820

Guideline: OECD Guideline 407 (1981), deviation: according to current standards, limited organ weight analysis and very limited histopathology have been performed.

GLP: yes, deviation: the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.

The study was conducted as a dose finding study for a 13 week toxicity study. Due to limited pathology investigations the study is of supplementary information only.

Material and Methods:

Groups of 5 male and 5 female Wistar rats (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 20, 80, 320, 1280 or 5120 ppm Fenoxaprop-P-ethyl equivalent to 0, 2, 6, 26, 95 or 126 mg/kg bw/d in males and 0, 2, 6, 28, 94 or 144 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the rats were about 6 weeks old and weighed 138 – 167 g (males) and 130 – 145 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption and body weight were recorded weekly. After 28 days blood and urine samples were taken after a fasting period of 24 hours. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count, red cell morphology, thromboplastin time and partial thromboplastin time. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, total bilirubin, total cholesterol, triglycerides, HDL-cholesterol, HDL-phospholipids, ASAT, ALAT, LDH, ALP, LAP, calcium, phosphorus, sodium,

potassium, chloride, albumin and total protein. Urinanalyis included 18-hour volume, specific gravity, color, appearance, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen, urine sediment, total protein, creatinine, creatinine clearance, LDH, GGT, LAP, sodium and potassium.

All animals of the highest dose group were killed in extremis on treatment day 9 and discarded. All remaining animals were necropsied and macroscopic changes were recorded for controls and 1280 ppm treatment group. The following organ weights of all animals necropsied at study termination were recorded: adrenal glands, liver, thyroids, kidneys and testes. Histopathological examinations were performed on the liver and kidneys from animals of the control and the 1280 ppm treatment group.

Findings:

Mortality / Clinical Signs: All animals of the highest dose group (5120 ppm) were sacrificed in extremis on treatment day 9 as they displayed severe signs of toxicity like emaciation, ruffled fur and a curved position. No signs of toxicity were seen in other treatment groups.

Food consumption: Food consumption was dramatically reduced to approximately 20 % of control levels on average for both sexes at 5120 ppm. Furthermore it was reduced to approximately 80 % of control levels for both sexes at 1280 ppm.

Body weight: Stagnant growth was noted for both sexes at 5210 ppm. Body weight was significantly reduced at 1280 ppm in males and females.

Table 43: 28 day feeding study in rats with Fenoxaprop-P-ethyl
Group food consumption and mean body weight

	Dose group level (ppm)											
	Males						Females					
	0	20	80	320	1280	5210[1]	0	20	80	320	1280	5210[1]
Food consumption (g/d)	22	22	22	20	17	41	14	14	15	16	12	31
Body weight on day 1 (g)	158	148	154	147	162	1581	136	137	139	139	140	1381
Terminal body weight (g)	285	289	298	265	220**	-1	180	183	186	181	160*	-1

* ($p< 0.05$); ** ($p< 0.01$); significantly different from controls (Dunnett-test)
[1] animals sacrificed in extremis on study day 9

Hematology: Slightly prolonged thromboplastin times and partial thromboplastin times were observed in males at 1280 ppm, whereas slightly shorter thromboplastin times were noticed in females at 80, 320 and 1280 ppm. The effects in females showed a clear dose-dependency, therefore a relation to treatment with the test substance cannot be excluded.

Table 44: 28 day feeding study in rats with Fenoxaprop-P-ethyl
Relevant haematology findings after 28 days

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1280	0	20	80	320	1280
Thromboplastin times (s)	12.3	12.4	12.6	12.8	13.6*	12.8	12.6	12.2*	12.0*	11.5*
Partial thromboplastin times (s)	22.5	22.6	23.4	25.3	28.4*	18.5	20.7	20.4	21.3	17.9

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

Clinical chemistry: An assessment of clinical chemistry data revealed changes in the lipid status as evidenced by lower total cholesterol and HDL-cholesterol levels in males at 320 and 1280 ppm, and decreased HDL-phospholipid levels in males at 80 ppm and above. Furthermore, slightly increased triglyceride levels were noticed in females at 320 and 1280 ppm and in males at 1280 ppm. These effects on lipid metabolism were dose-related and considered to reflect alterations in the liver. Regarding liver enzymes, increased activity was observed for ALP in both sexes at 1280 ppm and for LAP in females at 1280 ppm, which could be signs of liver toxicity at high doses. Male rats developed slightly decreased calcium levels (at 320 ppm and 1280 ppm) and phosphorus levels (at 1280 ppm). Slightly increased albumin levels were noticed in males at 320 and 1280 ppm and females at 1280 ppm. All other differences were considered to be incidental and of normal biological variation.

Table 45: 28 day feeding study in rats with Fenoxaprop-P-ethyl
Relevant clinical chemistry findings after 28 days

	Dose group level (ppm)									
	Males					**Females**				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Total cholesterol (mmol/L)	2.02	1.77	1.78	1.39*	1.05*	1.78	1.57	1.83	1.54	1.90
HDL-cholesterol (mmol/L)	1.06	0.95	0.85	0.53*	0.27*	1.14	0.99	1.10	0.96	1.05
HDL-phospholipid (mmol/L)	1.01	0.96	0.83*	0.73*	0.58*	1.13	1.03	1.07	1.01	1.25
Triglycerides (mmol/L)	0.31	0.32	0.33	0.40	0.71*	0.17	0.16	0.19	0.25*	0.43*
ALP (ukat/L)	4.04	4.03	4.27	5.16	6.54*	1.90	2.62	2.17	2.58	3.83*
LAP (ukat/L)	23.65	23.54	25.16	26.84	27.10	21.65	23.78	22.99	24.62	28.08*
Calcium (mmol/L)	2.57	2.55	2.53	2.45*	2.44*	2.51	2.50	2.55	2.50	2.45
Phosphorus (mmol/L)	2.21	2.12	2.23	2.17	1.84*	1.52	1.71	1.85*	1.57	1.49
Albumin (g/L)	28.8	29.6	29.6	32.2*	34.1*	33.0	32.9	32.7	32.2	34.8*

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

Urinalysis: Slight ketonuria was seen in males at 80 ppm and in both sexes at 320 and 1280 ppm. Slight bilirubinuria and urobilinogenuria was observed in males only at 320 an 1280 ppm. Further observations in males at 1280 ppm were slightly decreased creatinine level, a decreasing trend for creatinine clearance, markedly decreased GGT and LAP, and a moderately decreased potassium level. In females only, a slightly increased LDH activity was noted at 1280 ppm. The ketonuria was considered a reflection of enhanced lipid catabolism, whereas the urobilinogenuria, bilirubinuria, decreased creatinine and creatinine clearance, GGT, LAP and potassium levels might reflect changes in liver and kidney function. Slight hematuria was reported in males at 1280 ppm in the original study report. However, in the addendum to the final report (Suter et al., 1990; Doc. A42820) hematuria was not reported any more.

Table 46: 28 day feeding study in rats with Fenoxaprop-P-ethyl
Relevant urinalysis findings after 28 days

	Dose group level (ppm)									
	Males					**Females**				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Ketone (score 0/3)[1]	0	0	1+	1+	2	0	0	0	1	1
Bilirubin (score 0/3)[2]	0	0	0	1+	1+	1	1	1	1	1
Urobilinogen (score 0/4)[3]	0	0	1	1+	1+	1	0	0	1	0
Creatinine (mmol/24h)	74.2	80.9	72.2	66.3	52.5*	41.1	43.4	43.9	39.4	35.6
Creatinine Clearance (ml/min)	0.82	0.95	0.90	0.71	0.54	0.37	0.41	0.43	0.43	0.36
LDH (nkat/24h)	5.93	8.32	7.70	7.92	9.66	1.27	1.98	2.76	2.60	4.08*
GGT (nkat/24h)	321.7	355.0	342.6	311.2	107.1**	30.0	33.8	41.0	25.8	25.2
LAP (nkat/24h)	87.4	82.7	89.4	76.6	29.4**	9.5	11.7	9.7	5.4	3.6
Potassium (mmol/24h)	1.34	1.49	1.42	1.18	0.79*	0.66	0.69	0.83	0.60	0.64

* ($p < 0.05$); significantly different from controls (Dunnett-test)
+ ($p < 0.05$); significantly different from controls (Steel-test)
[1] Scores: 0 = negative – 0.5 mmol/L; 1 = 1.5 mmol/L; 2 = 3.9 mmol/L; 3 ≥ 7.8 mmol/L
[2] Scores: 0 = negative; 1 = small; 2 = moderate; 3= large
[3] Scores: 0 = 1.6 µmol/L; 1 = 16 µmol/L; 2 = 33 µmol/L; 3 = 66 µmol/L; 4 ≥ 131 µmol/L

Organ weight analysis: Statistically significant increases in the absolute and relative liver weights were observed in males and females at 320 ppm and above. Slight trends towards an increased absolute and relative liver weight were already observed at 80 ppm. The relative kidney weights were increased in males at 1280 ppm and females at 320 and 1280 ppm.

Table 47: 28 day feeding study in rats with Fenoxaprop-P-ethyl
Relevant organ weight findings after 28 days

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Liver weight										
absolute (g)	8.26	7.99	9.44	9.83	10.88	5.25	5.42	5.83	6.73**	6.42**
relative (% bw)	2.89	2.76	3.17	3.72**	4.93**	2.92	2.96	3.13	3.74**	4.01**
Kidney weight										
absolute (g)	1.86	1.83	1.97	1.94	1.72	1.13	1.13	1.23	1.28	1.21
relative (% bw)	0.66	0.63	0.66	0.73	0.78**	0.63	0.62	0.66	0.71*	0.76**

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

Macroscopic examination: No macroscopic findings were noted at necropsy of the control and the 1280 ppm treatment group.

Histopathological examination: No treatment-related findings were observed at the histopathological examination of the control and the 1280 ppm group.

Conclusion:

Fenoxaprop-P-ethyl demonstrated excessive toxicity at 5120 ppm so that animals had to be sacrificed in extremis on treatment day 9. There was a significantly decreased body weight at 1280 ppm in both sexes. The target organs identified were the liver (metabolic changes, enzyme release, increased absolute and relative weight) and the kidney (excretion, relative kidney weights). First effects on the target organs (haematology, lipid metabolism, ketonuria, trends to an increased absolute and relative liver weight) were already observed at a dose level of 80 ppm.

In this dose finding study, the NOAEL is considered to be 20 ppm (equivalent to 2 mg/kg bw/d in males and females). Due to a limited study design, the study is of supplementary information.

Hoe 046360 Technical. Subchronic oral toxicity 13-week feeding study in rats

Reference: *Tennekes H. et al.; 1987;* Doc. No. A36566 / RCC Project No. 060671

Guideline: OECD Guideline 408 (1981), EPA Guideline 82-1 (adopted 1982)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 10 male and 10 female Wistar rats (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 10, 80 or 640 ppm Fenoxaprop-P-ethyl equivalent to 0, 0.7, 5.8 or 49.0 mg/kg bw/d in males and 0, 0.8, 6.3 or 51.8 mg/kg bw/d in females over a period of 13 weeks. The reversibility of treatment-related changes was studied with 10 additional animals/sex in the control and the 80 ppm and 640 ppm treatment groups over a 4-week recovery period. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the rats were about 6 weeks old and weighed 143 – 172 g (males) and 128 – 153 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption and body weight were recorded weekly. Ophthalmoscopic examinations were performed prior to treatment, at week 13 of treatment and at the end of the recovery period.

At the end of treatment (13 weeks) and recovery period (17 weeks), blood samples were taken after a fasting period of 18 hours. At the same points of time urine was collected over an 18-hour period using a metabolism cage. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count, red cell morphology, thromboplastin time and partial thromboplastin time. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, total bilirubin, total cholesterol, triglycerides, HDL-cholesterol, HDL-phospholipids, ASAT, ALAT, LDH, ALP, LAP, calcium, phosphorus, sodium, potassium, chloride, albumin, total protein and protein electrophoresis. Urinalysis included 18-hour volume, specific gravity, color, appearance, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen and urine sediment. Descriptions of all macroscopic findings were recorded. The following organ weights were recorded: adrenal glands, liver, thyroids, kidneys and testes. Histopathological examinations were performed on several organs of the control and 640 ppm dose group, and of all animals which died or were killed in extremis: adrenal glands, aorta, brain (cerebrum, cerebellum, brainstem), esophagus, heart, kidneys, large intestine (colon, cecum, rectum), liver, lungs, lymph nodes (mesenteric), pancreas, parathyroid glands, pituitary gland, salivary glands (mandibular, sublingual), sciatic nerve, small intestine (duodenum, jejunum, ileum), spleen, stomach, testes, thymus, thyroid glands, urinary bladder, uterus and all gross lesions. Only lungs, livers, kidneys, adrenal glands and thyroid glands were examined in the animals which were sacrificed after 13 weeks in groups 10 and 80 ppm. No microscopic examination was performed on the animals which had undergone recovery, except for the livers of dose group 640 ppm.

Findings:

Mortality / Clinical Signs: One control male died during anesthesia (blood sampling) after 13 weeks of treatment. No clinical signs of toxicity were seen during the study.

Food consumption: After 13 weeks of treatment, food consumption was slightly reduced for both sexes at the highest dose group of 640 ppm. After recovery period, food consumption remained slightly reduced for males at the highest dose group but not for females.

Body weight: At 640 ppm, body weight was significantly reduced relative to controls in males and slightly reduced in females after the treatment period of 13 weeks. The reduction of body weight was still significant in males after the recovery period.

Table 48: 13 week feeding study in rats with Fenoxaprop-P-ethyl
Group food consumption and mean body weight after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Food consumption (g/d)								
13 weeks	22.3	22.2	23.0	20.3	17.5	17.0	16.8	15.9
17 weeks	24.3	-	25.0	22.9	18.3	-	16.8	17.9
Body weight on day 1 (g)	155	154	155	154	140	140	142	140
Terminal body weight (g)								
13 weeks	367.1	375.0	384.8	310.2**	225.8	230.5	224.7	206.0
17 weeks	387.2	-	411.1	332.6*	236.2	-	242.6	230.3

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

Ophthalmoscopic examinations: The findings noted at ophthalmoscopic examinations (e.g. lens turbidity, pale and/or granulated ocular fundus) were observed in controls and treated animals and therefore considered to be unrelated to treatment.

Hematology: A marginal decrease in the hemoglobin concentration, hematocrit value and mean corpuscular volume, and a marginal increase in the mean corpuscular haemoglobin concentration were observed in male rats at 80 and/or 640 ppm. Similar marginal changes in mean corpuscular haemoglobin concentration were also observed in females at 640 ppm. In addition, slightly prolonged thromboplastin time and partial thromboplastin time were noted in males at 640 ppm while a slightly shorter thromboplastin time was observed in females at 640 ppm. Most of the findings recovered during the 4 week recovery period, while hemoglobin concentration and hematocrit value remained slightly decreased. Other statistical differences were considered to be incidental and of normal biological variation.

Table 49: 13 week feeding study in rats with Fenoxaprop-P-ethyl
Relevant haematology findings after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Hemoglobin (mmol/L)								
13 weeks	10.0	9.8	9.9	9.7*	9.8	9.8	9.8	9.8
17 weeks	10.1	-	10.0	9.6*	10.0	-	10.1	9.8
Hematocrit (l/L)								
13 weeks	0.43	0.42	0.42*	0.41*	0.42	0.42	0.42	0.42
17 weeks	0.43	-	0.43	0.41*	0.43	-	0.43	0.42

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Mean corpuscular volume (fL)								
13 weeks	45.0	44.8	45.4	43.8*	47.8	47.3	48.3	46.8
17 weeks	45.2	-	45.7	44.6	48.0	-	49.2*	48.6
Mean corpuscular hemoglobin concentration (mmol/L)								
13 weeks	23.2	23.4	23.6*	23.7*	23.2	23.3	23.2	23.7*
17 weeks	23.6	-	23.5	23.3	23.6	-	23.5	23.5
Thromboplastin time (sec)								
13 weeks	13.5	13.4	13.5	14.0*	13.6	13.3*	13.4	12.8*
17 weeks	13.2	-	13.1	12.8*	13.1	-	12.7*	12.9
Partial Thromboplastin time (sec)								
13 weeks	22.6	22.8	22.5	24.6*	21.0	19.7	21.6	21.0
17 weeks	22.9	-	22.5	20.0*	20.4	-	19.2	20.6

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

Clinical chemistry: The following effects were reported: slightly decreased glucose levels for males at 80 and 640 ppm, slightly increased urea levels for males at 640 ppm, moderately decreased total cholesterol levels for males at 640 ppm, slightly to moderately increased triglyceride levels for females at 80 and 640 ppm, slightly to moderately decreased HDL-cholesterol level for both sexes at 640 ppm and moderately decreased HDL-phospholipid levels for males at 640 ppm, slightly to moderately increased ALP for both sexes at 640 ppm, slightly decreased calcium level for females at 80 ppm and both sexes at 640 ppm, slightly increased sodium levels for both sexes at 80 and 640 ppm, and slightly decreased total protein level for males at 640 ppm. The reported effects were found to be reversible at the end of the 4-week recovery period with the exception of total protein levels. Other statistical differences in the results of the clinical chemistry parameters were considered to be incidental and of normal biological variation.

Table 50: 13 week feeding study in rats with Fenoxaprop-P-ethyl
Relevant clinical chemistry findings after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Glucose (mmol/L)								
13 weeks	6.00	6.00	5.56*	5.55*	5.57	5.54	5.37	5.58
17 weeks	6.21	-	5.88	5.30	5.40	-	5.21	5.59
Urea (mmol/L)								
13 weeks	7.23	7.41	7.22	8.32*	8.53	8.42	8.84	8.83
17 weeks	6.79	-	7.47	6.81	8.64	-	8.92	9.21
Total cholesterol (mmol/L)								
13 weeks	2.32	2.20	2.10	1.46*	2.23	2.32	2.20	2.03
17 weeks	2.35	-	2.67	2.39	2.25	-	2.55	2.36
Trigylcerides (mmol/L)								
13 weeks	0.57	0.54	0.62	0.57	0.42	0.40	0.48*	0.57*
17 weeks	0.69	-	0.70	0.69	0.60	-	0.65	0.64
HDL cholesterol (mmol/L)								
13 weeks	1.06	1.08	1.00	0.41*	1.20	1.37	1.22	1.05*
17 weeks	1.14	-	1.24	1.12	1.37	-	1.67*	1.48
HDL phospholipid (mmol/L)								
13 weeks	1.06	1.06	1.02	0.72*	1.29	1.51*	1.30	1.23
17 weeks	1.10	-	1.16	1.12	1.44	-	1.68	1.54

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
ALP (ukat/L)								
13 weeks	2.74	2.74	2.39	4.47*	1.37	1.01*	1.26*	1.68*
17 weeks	2.43	-	2.52	2.83	1.24	-	1.15	1.30
Calcium (mmol/L)								
13 weeks	2.44	2.41	2.42	2.33*	2.56	2.60	2.50*	2.44*
17 weeks	2.40	-	2.44	2.40	2.45	-	2.52*	2.44
Sodium (mmol/L)								
13 weeks	144.1	144.5	145.5*	146.4*	143.1	143.6	144.4*	145.2*
17 weeks	141.3	-	141.6	142.2	141.1	-	141.0	143.1
Total protein (g/L)								
13 weeks	65.6	63.3	65.0	60.3*	63.4	64.0	63.4	62.9
17 weeks	67.2	-	69.9*	65.1*	70.6	-	70.8	69.0

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

Urinalysis: Slight to moderate ketonuria was noted for males at 80 and 640 ppm and was considered to be related to the intermediary metabolism of fatty acids and therefore a secondary effect of the treatment and not of biological relevance. Slight urobilinogenuria was found in males at 80 and 640 ppm and slight bilirubinuria in males at 640 ppm. Both findings were within the normal range of biological variation and the significance remains unclear. Other differences were considered to be incidental and of normal biological variation. All observed effects were found to be reversible at termination of recovery period.

Table 51: 13 week feeding study in rats with Fenoxaprop-P-ethyl
Relevant urinalysis findings after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Ketone (score 0/3)[1]								
13 weeks	0	0	1^+	2^+	0	0	0	0
17 weeks	0	-	0	0	0	-	0	0
Bilirubin (score 0/3)[2]								
13 weeks	0	1	1	1^+	0	0	0	0
17 weeks	1	-	1	1	1	-	1	1
Urobilinogen (Score 0/4)[3]								
13 weeks	0	0	1^+	1^+	0	0	0	0
17 weeks	0	-	1	1	1	-	1	0

$^+$ ($p < 0.05$); significantly different from controls (Steel-test)
[1] 0 = negative; 1 = 1.5 mmol/L; 2 = 3.9 mmol/L; 3 ≥ 7.8 mmol/L
[2] 0 = negative; 1 = small; 2 = moderate; 3 = large
[3] 0 = 1.6 µmol/L; 1 = 16 µmol/L; 2 = 33 µmol/L; 3 = 66 µmol/L; 4 ≥ 131 µmol/L

Organ weight analysis: Absolute and relative liver weights were markedly increased in males and females at 640 ppm. A slight but statistically significant increment in relative liver weights was also noted for females at 80 ppm. Absolute and relative kidney weights were increased in females at 80 and 640 ppm. In males, an increase of relative kidney and testes weight was noted at 640 ppm, which probably was related to reduced terminal bodyweight. A slight increase in absolute and relative adrenals weights observed in females at 80 ppm was considered to be an incidental finding within the normal range of biological variation. After recovery period, the effects were found to be reversible with the exception of absolute and relative liver weight in females at 640 ppm and relative kidney weight in males at 640 ppm.

Table 52: 13 week feeding study in rats with Fenoxaprop-P-ethyl
Organ weight findings after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Liver weight Week 13								
absolute (g)	9.54	9.44	10.21	11.77*	6.11	6.58	6.71	7.36**
relative (% bw)	2.59	2.52	2.65	3.78**	2.70	2.87	2.99**	3.57**
Liver weight Week 17								
absolute (g)	9.59	-	10.35	8.89	6.69	-	7.23	7.66**
relative (% bw)	2.49		2.51	2.67	2.83		2.98	3.33**
Kidney weight Week 13								
absolute (g)	2.07	2.15	2.21	2.17	1.29	1.39	1.49**	1.46*
relative (% bw)	0.57	0.57	0.58	0.70**	0.57	0.61	0.66**	0.71**
Kidney weight Week 17								
absolute (g)	2.09	-	2.25	2.05	1.50	-	1.45	1.51
relative (% bw)	0.54		0.55	0.62*	0.64		0.60	0.66
Testes weight Week 13								
absolute (g)	3.35	3.29	3.56	3.28	-	-	-	-
relative (% bw)	0.92	0.88	0.93	1.07**				
Testes weight Week 17								
absolute (g)	3.43	-	3.49	3.18	-	-	-	-
relative (% bw)	0.89		0.85	0.96				

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

Macroscopic examination: The livers were enlarged in both sexes at 640 ppm. Furthermore, enlargement of the kidneys was observed in females at 80 and 640 ppm.

Histopathological examination: After 13 weeks, minimal centrilobular hypertrophy was observed in the livers of 5/10 males and 1/10 females of the 640 ppm dose group. No such findings were noted after recovery period in this dose group.

Table 53 13 week feeding study in rats with Fenoxaprop-P-ethyl
Microscopic findings after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Histopathological examination								
Liver Week 13 Hepatocellular hypertrophy: - centrilobular	-	-	-	5/10	-	-	-	1/10
Liver Week 17 Hepatocellular hypertrophy: - centrilobular	-	-	-	-	-	-	-	-

* ($p < 0.05$); ** ($p < 0.01$); significantly different from controls (Fischer´s Exact-test)

Conclusion:

Clear signs of treatment-related effects on liver and kidneys were observed at 80 and 640 ppm. While body weight reduction and histopathological findings were noted only in the highest dose group of 640 ppm, effects on haematological, clinical chemistry and urinalysis parameters as well as increased organ weights (liver, kidney) and macroscopic findings (enlargement of kidneys) were already observed at a dose level of 80 ppm. The majority of effects was reversible during a recovery period of 4 weeks.

The NOAEL is considered to be 10 ppm (equivalent to 0.7 mg/kg bw/d in males and 0.8 mg/kg bw/d in females).

Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in mice

Reference: *Suter P. et al*.; 1987b; Doc. No. A36557 / RCC Project No. 060647

Guideline: OECD Guideline 407 (1981), deviation: No haematology and limited organ weight analysis and very limited histopathology have been performed.

GLP: yes, deviation: the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.

The study was conducted as a dose finding study for a 13 week toxicity study. Due to missing haematology and limited pathology investigations the study is of supplementary information only.

Material and Methods:

Groups of 5 male and 5 female NMRI mice (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 20, 80, 320 or 1280 ppm Fenoxaprop-P-ethyl equivalent to 0, 3, 14, 56 or 260 mg/kg bw/d in males and 0, 4, 16, 61 or 280 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the mice were about 6 weeks old and weighed 25 - 30 g (males) and 20 - 25 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption and body weight were recorded weekly. After 28 days blood samples were taken after a fasting period of 18 hours. Clinical chemistry included: glucose, urea, creatinine, total cholesterol, triglycerides, total phospholipids, ASAT, ALAT, ALP, sodium, potassium, albumin and total protein. Hematology and urinalyis were not performed in this study.

All remaining animals were necropsied and macroscopic changes were recorded. The following organ weights of all animals necropsied at study termination were determined: adrenal glands, liver with gall bladder, thyroids, kidneys, and testes. Histopathological examinations were performed on the liver and kidneys from all animals.

Findings:

Mortality / Clinical Signs: All animals survived to scheduled necropsy. No signs of toxicity were seen during the study.

Food consumption: Food consumption was increased by approximately 25 % on average for males at the highest dose group of 1280 ppm.

Body weight: There was a trend towards higher body weight at 1280 ppm. However, this was only statistically significant for females. Body weights were comparable in other groups. The higher body weights at the top dose could be a result of the markedly increased absolute liver weights in this dose group.

Table 54: 28 day feeding study in mice with Fenoxaprop-P-ethyl
Group food consumption and mean body weight

	Dose group level (ppm)

	Males					Females				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Food consumption (g/d)	5.8	5.9	6.4	6.6	7.3	5.7	5.4	5.5	5.3	6.2
Body weight on day 1 (g)	27	27	28	28	27	22	21	23	23	21
Terminal body weight (g)	33.5	33.6	35.1	35.5	37.2	24.6	22.2*	26.3	24.5	28.2**

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

Clinical chemistry: An assessment of clinical chemistry data reflects toxicological alterations in the liver. The effects included slightly increased total cholesterol and total phospholipids levels in females at 320 ppm, and markedly increased ALAT, ASAT and ALP activities in both sexes at 1280 ppm. Slightly increased sodium levels were found in males and females, which showed no dose-dependency up to 320 ppm. A statistically significant increase was noted in albumin for both sexes at 1280 ppm and in total protein for males at 1280 ppm.

Table 55: 28 day feeding study in mice with Fenoxaprop-P-ethyl
Relevant clinical chemistry findings after 28 days

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Total cholesterol (mmol/L)	4.30	4.84	5.20	4.41	3.39	3.72	3.73	3.88	5.29*	3.07
Phospholipids (mmol/L)	3.88	3.97	4.18	3.42	2.92	2.78	2.87	2.99	3.56*	2.44
ASAT (ukat/L)	1.10	1.14	1.47	1.15	5.02*	1.54	1.66	1.25	1.38	2.88*
ALAT (ukat/L)	0.78	0.80	0.76	0.92	8.56*	0.95	0.71	0.75	0.86	4.71*
ALP (ukat/L)	3.59	3.09	3.31	4.48	19.80*	5.30	5.03	4.55	4.76	8.73*
Sodium (mmol/L)	139.3	150.2*	149.3*	151.8*	153.5*	145.6	145.7	149.1	150.0	153.4*
Albumin (g/L)	26.6	27.9	28.9	27.5	35.3*	29.7	30.1	30.3	31.2	34.7*
Protein (g/L)	54.6	57.9	61.2	56.5	68.2*	60.5	61.8	62.2	63.3	65.3

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

Organ weight analysis: Absolute and relative liver weights were markedly increased in both sexes at 320 and 640 ppm. Slight trends towards an increased absolute and relative liver weight were already observed at 80 ppm. In females, absolute kidney weights were increased at 80 and 1280 ppm and relative kidney weights at 1280 ppm. In males, only absolute kidney weights were increased at 1280 ppm. Furthermore, a decrease in relative testes weight was noted at 1280 ppm.

Table 56 28 day feeding study in mice with Fenoxaprop-P-ethyl
Relevant organ weight findings after 28 days

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Liver weight										
absolute (g)	1.48	1.52	1.73	2.74**	5.40**	1.19	1.05	1.41	1.59	3.73**
relative (% bw)	4.44	4.55	4.92	7.71**	14.51**	4.84	4.73	5.34	6.49**	13.15**

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1280	0	20	80	320	1280
Kidney weight										
absolute (g)	0.560	0.553	0.528	0.605	0.665*	0.347	0.339	0.396*	0.370	0.469**
relative (% bw)	1.678	1.646	1.518	1.707	* 1.792	0.417	1.524	1.506	1.514	1.661**
Testes weight										
absolute (g)	0.240	0.240	0.245	0.236	0.204	-	-	-	-	-
relative (% bw)	0.720	0.713	0.703	0.667	0.549*					

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

Macroscopic examination: No treatment-related changes were found at macroscopic examination.

Histopathological examination: Moderate hepatocellular hypertrophy was seen in all males at 320 ppm and all animals at 1280 ppm. Furthermore, single cell necrosis and increased mitotic activity in the liver were observed in some of the animals receiving 320 and 1280 ppm. Treatment-related minimal tubular injury was noted in the kidneys of 1/5 males and 4/5 females receiving 320 ppm. In these cases only very few tubules were affected by necrosis of isolated tubular epithelial cells. Slight tubular injury was seen in the kidneys of 1/3 males and moderate to marked tubular injury was noted in all females in the 1280 ppm group. In moderate to marked cases injury mainly affected the straight portion of the proximal tubules and was characterized by unicellular or multicellular necrosis of the epithelial lining, by increased basophilia, tubular swelling, and sloughed epithelial fragments in the lumen.

Table 57: 28 day feeding study in mice with Fenoxaprop-P-ethyl
Relevant histopathological findings after 28 days

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1280	0	20	80	320	1280
Liver										
- hepatocellular	0/5	0/5	0/5	5/5	5/5	0/5	0/5	0/5	0/4	5/5
hypertrophy	0/5	0/5	0/5	2/5	5/5	0/5	0/5	0/5	0/4	2/5
- single cell necrosis	0/5	0/5	0/5	1/5	3/5	0/5	0/5	0/5	0/4	2/5
- mitotic hepatocytes										
Kidney										
- tubular injury	0/5	0/5	0/5	1/5	1/3	0/5	0/5	0/5	4/5	5/5

Conclusion:

Clear signs of treatment-related effects on the liver and kidneys were observed in both sexes. Slight effects on lipid metabolism were observed at 320 ppm. Liver toxicity was demonstrated by markedly increased levels of liver enzymes (ALP, ALAT, ASAT) in both sexes receiving 1280 ppm. Furthermore, increased absolute and relative liver weights were noted, together with histopathological findings of hepatocellular hypertrophy, single cell necrosis and mitotic hepatocytes in both sexes receiving 320 and 1280 ppm. The effects on the liver were more distinct in males than in females. Absolute kidney weight was increased in females at 80 ppm and in both sexes at 1280 ppm, while relative kidney weight was only increased at 1280 ppm in females. Histopathological examination of the kidneys revealed tubular injury in males and females at 320 and 640 ppm, with effects being more marked in females than in males.

In this dose finding study, the NOAEL is considered to be 80 ppm (equivalent to 14 mg/kg bw/d in males and 16 mg/kg bw/d in females). Due to a limited study design, the study is of supplementary information.

Hoe 046360 Technical. Subchronic oral toxicity 13-week feeding study in mice

Reference: *Suter P. and Luetkemeier H.*; 1987a; Doc. No. A36567 / RCC Project No. 060660

Guideline: OECD Guideline 408 (1981), EPA Guideline 82-1 (adopted 1982). There were some minor deviations in pathology compared to current guidelines.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 10 male and 10 female NMRI mice (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 10, 80 or 640 ppm Fenoxaprop-P-ethyl equivalent to 0, 1.4, 11.9 or 100.8 mg/kg bw/d in males and 0, 2.0, 16.5 or 122.4 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the mice were about 6 weeks old and weighed 26 – 32 g (males) and 22 – 30 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption and body weight were recorded weekly.

At the end of treatment (13 weeks), blood samples were taken after a fasting period of 18 hours. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count and red cell morphology. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, total bilirubin, total cholesterol, triglycerides, phospholipids, ASAT, ALAT, ALP, sodium, potassium, albumin and total protein. Descriptions of all macroscopic findings were recorded. The following organ weights were recorded: adrenal glands, liver with gall bladder, thyroids, kidneys and testes. Histopathological examinations were performed on several organs of the control and the highest dose group (640 ppm) and of all animals which died during study: adrenal glands, aorta, brain, esophagus, heart, gallbladder, kidneys, large intestine (cecum, colon, rectum), liver, lungs, mesenteric lymph node, pancreas, parathyroid glands, pituitary gland, salivary glands (mandibular, sublingual), sciatic nerve, small intestine (duodenum, jejunum, ileum), spleen, stomach, testes, thymus, thyroid glands, urinary bladder, uterus and all gross lesions. In animals receiving 10 or 80 ppm, the following tissues were examined: adrenal glands, kidneys, liver lung, thyroid gland and all gross lesions.

Findings:

Mortality / Clinical Signs: Two males and one female receiving 80 ppm and one male receiving 640 ppm died after blood sampling on the day of scheduled necropsy. These intercurrent deaths were not related to treatment. No signs of toxicity were observed during the study.

Food consumption: Feed intake was similar in all groups.

Body weight: Body weight gains and terminal body weights were similar in all groups of males and females.

Hematology: In the highest dose group of 640 ppm, slight increases in MCV and reticulocyte counts were noted in males. In females receiving 640 ppm, the number of platelets was slightly increased.

Table 58: 13 week feeding study in mice with Fenoxaprop-P-ethyl
Relevant haematology findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Mean corpuscular volume (fL)	42.2	42.4	42.8	44.6*	44.6	43.4	43.8	44.2
Platelets (g/L)	1407	1376	1235	1294	1101	1086	1115	1260*
Reticulocytes (1)	0.024	0.025	0.024	0.031*	0.029	0.028	0.030	0.026

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

Clinical chemistry: Treatment-related effects were noted at 640 ppm in male and female mice. The effects were indicative of changes in lipid metabolism (total cholesterol, phospholipids) and liver toxicity (ALAT, ALP, albumin). Furthermore, an increase of urea in females suggested changes in kidney function. All other statistical differences were considered to be incidental and of normal biological variation.

Table 59: 13 week feeding study in mice with Fenoxaprop-P-ethyl
Relevant clinical chemistry findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Urea (mmol/L)	8.36	8.25	9.26	9.01	7.21	7.34	5.72	13.78*
Total cholesterol (mmol/L)	4.97	4.42	4.63	3.84*	3.66	3.97	4.55	4.60*
Phospholipids (mmol/L)	3.61	3.42	3.65	2.68*	2.53	2.77	3.00	2.98
ALAT (ukat/L)	0.90	1.27	0.85	1.82*	1.03	1.29	0.98	1.08
ALP (ukat/L)	2.56	2.45	2.44	6.95*	3.54	3.29	3.88	4.79
Albumin (g/L)	27.3	27.5	28.0	30.8*	29.4	27.0	29.8	31.0

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

Organ weight analysis:

Absolute and relative liver weights were markedly increased in both sexes at 640 ppm. An increase in relative liver weight was already observed in males receiving 80 ppm. In females, absolute kidney weights were increased at 640 ppm.

Table 60: 13 week feeding study in mice with Fenoxaprop-P-ethyl
Relevant organ weight findings after 3 weeks

	Dose group level (ppm)							
	Males				Females			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Liver weight								
absolute (g)	1.81	1.73	2.00	4.28*	1.40	1.33	1.49	2.80**
relative (% bw)	4.36	4.31	5.03**	10.46**	4.83	4.79	5.30	9.30**

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Kidney weight								
absolute (g)	0.708	0.700	0.676	0.724	0.449	0.428	0.450	0.525**
relative (% bw)	1.721	1.741	1.716	1.771	1.553	1.545	1.617	1.745

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

Macroscopic examination: In the highest dose group (640 ppm), enlarged livers (10/10 males, 7/10 females) and irregular kidney surface (2/10 females) were observed.

Histopathological examination: Moderate to marked diffuse hepatocellular hypertrophy in males and slight to moderate hepatocellular hypertrophy in females were observed at 640 ppm. This finding was characterized by a generalized increase in cell size and cytoplasm with a characteristic "ground-glass" appearance.

Minimal renal unilateral tubular injury was noted in one female receiving 80 ppm, and moderate (7 females: grade 3) to marked (3 females: grade 4) tubular injury was noted in all females receiving 640 ppm. In five males receiving 640 ppm minimal (4 males: grade 1) to slight (1male: grade 2) tubular injury was observed. The tubular injury mainly affected the straight portion of the proximal tubule and was characterized mainly by necrosis and degeneration of the tubular lining cells with concomitant epithelial regeneration. The affected tubules were hypercellular and lined with variably sized and shaped epithelial cells which characteristically had a high nucleocytoplasmic ratio, basophilic cytoplasm, and large vesicular nuclei. The nuclei of these cells were occasionally observed in mitosis and there was frequently mild multifocal tubular calcification at the corticomedullary junction. A mild to moderate chronic interstitial inflammatory response and thickened tubular basement membranes were seen in association with this lesion in the more severely affected kidneys. When tubular injury was scored minimal, only one or two affected tubules were found per kidney section. When tubular injury was scored moderate to severe, major parts of the inner cortex were affected.

The type and incidence of other findings were considered to be similar in the treatment and control groups.

Table 61: 13 week feeding study in mice with Fenoxaprop-P-ethyl
Relevant histopathological findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Liver								
- hepatocellular hypertrophy	0/10	0/10	0/10	10/10	0/10	0/10	0/10	10/10
Kidney								
- tubular injury	0/10	0/10	0/10	5/10	0/10	0/10	1/10	10/10

Conclusion:

The target organs identified in this study were the liver and the kidney which were affected at doses of 80 ppm and above. Effects in the liver (lipid metabolism, enzyme release, increased organ weight, hepatocellular hypertrophy) were more pronounced in males than in females. On the other hand, treatment-related effects on the kidney (urea in blood, increased organ weight, tubular injury) were more prominent in females than in males.

The NOAEL is considered to be 10 ppm (equivalent to 1.4 mg/kg bw/d in males and 2.0 mg/kg bw/d in females).

Hoe 046360 Technical. Repeated-dose oral toxicity 28-day feeding study in dogs

Reference: *Sachsse K. et al.*; 1987a; Doc. No. A36558 / RCC Project No. 060658

Guideline: -

GLP: yes, deviation: the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.

This study was conducted as a dose finding study for a 13-week toxicity study with only one animal per dose group. Therefore this study is considered of supplementary information only.

Material and Methods:

One male and one female Beagle dog (source: Kleintierfarm Madoerin AG, CH) per dose group were administered Fenoxaprop-P-ethyl in the diet for 4 weeks. The dose groups were 0, 80, 320 and 1280 ppm which was equivalent to 0, 3.3, 13.0 and 67.9 mg/kg bw/d in males and 0, 3.7, 14.9 and 56.1 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At delivery from the breeder the dogs were about 4 – 5 months old and weighed 4.4 – 7.2 kg (males) and 4.8 – 5.4 kg (females). The acclimation period was 4 weeks and 4 days under test conditions after veterinary examination. Diets were prepared at the beginning of the study and after 2 weeks, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption was recorded daily. Body weights were recorded weekly. Each animal was examined for changes in the eyes at pretest and at 4 weeks of treatment. After 28 days blood samples were taken after a fasting period of 18 hours. Urine was collected for a period of 24 hours. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count, red cell morphology, thromboplastin time and partial thromboplastin time. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, total bilirubin, total cholesterol, triglycerides, HDL-cholesterol, HDL-phospholipids, ASAT, ALAT, LDH, ALP, GGT, ornithine-carbamyl-transferase (OCT), leucine-aminopeptidase (LAP), calcium, phosphorus, sodium, potassium, chloride, total protein and protein electrophoresis. Urinalysis included 24-hour volume, specific gravity, color, appearance, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen, urine sediment, creatinine, creatinine clearance, LDH, GGT, LAP, sodium and potassium. Descriptions of all macroscopic findings were recorded. The following organ weights were recorded: adrenals, brain, kidneys, liver, pituitary, ovaries, testes, thyroids and thymus. Histopathological examinations were performed on the following organs of all animals: adrenal glands, aorta, brain (cerebrum, cerebellum, medulla oblongata/pons), cecum, colon, duodenum, esophagus, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical, mesenteric), pancreas, pituitary gland, rectum, salivary glands (mandibular, zygomatic), sciatic nerve, spleen, stomach, testes, thymus, thyroid / parathyroid glands, urinary bladder, uterus and all gross lesions.

Findings:

Mortality / Clinical Signs: No animal died. Incidents of diarrhea were spontaneously observed in animals receiving 0, 80 and 320 ppm during pretest and treatment period. The female receiving 320 ppm showed vomiting on treatment day 9.

Food consumption: The food consumption was occasionally slightly to moderately decreased in all three treated females, particularly at 80 and 1280 ppm during the first two weeks of treatment. However the females allocated to treatment already showed a decreased food intake during the pretest period.

Body weight: Body weight gain was slightly increased in all treated males when compared to the control male which must be seen in perspective of the lower initial bodyweight of the treated males. In the treated females body weight gain was slightly reduced at 80 and 1280 ppm when compared to control and 320 ppm animals.

Table 62: 28 days feeding study in dogs with Fenoxaprop-P-ethyl
Body weights of single animals

	Dose group level (ppm)							
	Males				Females			
	0	80	320	1280	0	80	320	1280
Initial body weight (g)	7924	6755	6825	5115	6118	5337	5668	5541
Body weight day 28 (g)	8388	7454	7558	6052	7213	6114	6695	6276
Body weight gain	464	699	733	937	1095	777	1027	735

Ophthalmoscopic examinations: No treatment-related effects were observed in the animals.

Hematology, clinical chemistry, urinalysis: No statistical analysis could be performed due to low animal number (1 dog/sex/treatment group). No treatment-related effects could be identified.

Macroscopic examination, organ weights and histopathological examination: No macroscopic findings related to treatment were observed. No effect on organ weights and their ratios could be identified. No treatment-related microscopic findings were recorded.

Table 63: 28 days feeding study in dogs with Fenoxaprop-P-ethyl
Organ weights of single animals after 28 days

	Dose group level (ppm)							
	Males				Females			
	0	80	320	1280	0	80	320	1280
Liver weight								
absolute (g)	305.2	276.8	264.0	253.7	222.7	212.8	241.0	214.2
relative (% bw)	3.8	4.0	3.7	4.7	3.4	3.9	4.1	3.8
relative (% brain weight)	373.2	338.0	384.4	333.9	312.1	281.9	364.5	327.0
Kidney weight								
absolute (g)	50.28	41.28	43.52	34.19	33.35	31.78	33.16	30.09
relative (% bw)	0.62	0.59	0.61	0.63	0.50	0.58	0.56	0.53
relative (% brain weight)	61.48	50.41	63.38	45.00	46.73	42.10	50.16	45.94

Conclusion:

Due to the low animal number (1 dog/sex/dose group) the study is of supplementary information only. No NOAEL could be established.

Hoe 046360 Technical. Sub-chronic oral toxicity 13 week-feeding study in Beagle dogs

Reference: *Sachsse K. et al.*; 1987b; Doc. No. A36617 / RCC Project No. 060682

Guideline: EPA Guideline 82-1 (1982). There were some minor deviations in pathology compared to current guidelines.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Four Beagle dogs/sex/dose group (source: Kleintierfarm Madoerin AG, CH) were administered Fenoxaprop-P-ethyl in the diet for 13 weeks. The dose groups were 0, 80, 400 and 2000 ppm which was equivalent to 0, 3.0, 15.6 and 77.7 mg/kg bw/d in males and 0, 3.2, 16.2 and 83.4 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At delivery from the breeder the dogs were about 4 – 6 months old and weighed 4.1 – 8.6 kg (males) and 4.2 – 6.8 kg (females). The acclimation period was 5 weeks and 4 days under test conditions. Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Viability and clinical signs were checked twice daily. Food consumption was recorded daily. Body weights were recorded weekly. Each animal was tested for hearing impairment using a simple noise test at pretest and after 4 and 13 weeks of treatment. Furthermore ophthalmoscopic examinations were performed in each animal at pretest and after 4 and 13 weeks of treatment. Blood and urine samples were taken at pretest and after 4 and 13 weeks of treatment. Animals were fasted for 18 hours before blood samples were collected. Urine samples were taken using a catheter. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count, red cell morphology, thromboplastin time and partial thromboplastin time. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, total bilirubin, total cholesterol, triglycerides, HDL-cholesterol, HDL-phospholipids, ASAT, ALAT, LDH, creatine kinase (CK), alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), ornithine-carbamyl-transferase (OCT), leucine-aminopeptidase (LAP), calcium, phosphorus, sodium, potassium, chloride, total protein and protein electrophoresis. Urinalysis included specific gravity, color, appearance, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen and urine sediment. Complete necropsy was performed on all dogs. The following organ weights were recorded: brain, pituitary, liver, thyroids, kidneys, adrenals, thymus, testes and ovaries. Histopathological examinations were performed on the following organs of all dogs: adrenal glands, aorta, brain (cerebrum, cerebellum, medulla oblongata/pons), cecum, colon, duodenum, esophagus, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (cervical, mesenteric), pancreas, pituitary gland, rectum, salivary glands (mandibular, zygomatic), sciatic nerve, spleen, stomach, testes, thymus, thyroid / parathyroid glands, urinary bladder, uterus and all gross lesions.

Findings:

Mortality / Clinical Signs: No animal died and no treatment-related signs of toxicity were observed during the study. Incidences of diarrhea (all groups), feces containing traces of

mucous or blood (0, 80 ppm) and spontaneous vomiting (all groups) were noted in some animals on occasional treatment days.

Food consumption: The mean food consumption was slightly decreased in females at the highest dose group of 2000 ppm during the first half of the treatment (statistically significant only between days 36 and 42).

Body weight: The mean percentage of body weight gain was significantly reduced in males receiving 2000 ppm.

Table 64: 13 week feeding study in dogs with Fenoxaprop-P-ethyl
Food consumption and body weights after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	**80**	**320**	**1280**	**0**	**80**	**320**	**1280**
Food consumption (g/day)	298	300	300	300	294	299	291	289
Initial body weight (g)	5971	6807	6583	6956	6277	6166	6123	5836
Body weight day 90 (g)	8524	8910	8755	8456	8644	8685	7962	7881
Body weight gain (%)	43.0	32.0	33.4	22.2*	37.6	41.0	30.9	34.9

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

Hearing tests and ophthalmoscopic examinations: No impairment of auditory perception and no treatment-related effects on eyes were observed.

Hematology: All statistically significant findings were within biological variance and without dose-dependency and are therefore considered not to be related to treatment.

Clinical chemistry: ASAT and LDH were slightly but statistically significant increased in males receiving 2000 ppm after 13 weeks, while ALAT was slightly decreased after 4 weeks in males (2000 ppm) and females (400 and 2000 ppm), and after 13 weeks in both sexes (2000 ppm). Total protein levels were increased in males (2000 ppm) 4 and 13 weeks after treatment. Further statistically significant changes in clinical chemistry values were within the normal range of biological variation and showed no dose-relation, and were therefore considered to be of no toxicological relevance.

Table 65: 13 week feeding study in dogs with Fenoxaprop-P-ethyl
Relevant clinical chemistry findings after 4 and 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	**80**	**400**	**2000**	**0**	**80**	**400**	**2000**
ASAT (ukat/L)								
4 weeks	0.78	0.80	0.85	0.91	0.85	0.90	0.83	0.94
13 weeks	0.67	0.74	0.75	0.82*	0.71	0.82	0.79	0.79
ALAT (ukat/L)								
4 weeks	0.67	0.62	0.66	0.53*	0.69	0.67	0.56*	0.49*
13 weeks	0.54	0.51	0.50	0.37*	0.51	0.52	0.46	0.38*
LDH (ukat/L)								
4 weeks	2.57	2.93	3.12	3.32	3.23	3.66	3.02	3.61
13 weeks	2.67	3.19	3.02	3.80*	3.18	3.76	3.14	3.72
Total protein (g/L)								
4 weeks	49.5	52.2	53.6	54.6*	51.0	53.1	50.9	52.1
13 weeks	54.1	56.0	55.6	58.4*	55.6	56.1	54.4	55.6

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

Urinalysis: No treatment-related effects were observed at urinalysis.

Organ weight analysis: No statistically significant changes were found at organ weight analysis. However, there was a tendency towards slightly increased relative liver and kidney weights (% brain weight) in males at 2000 ppm and to slightly increased relative liver weights (% brain weight) in females at 2000 ppm.

Table 66: 13 weeks feeding study in dogs with Fenoxaprop-P-ethyl Organ weight findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	80	400	2000	0	80	400	2000
Liver weight								
absolute (g)	282.5	278.4	272.9	290.1	257.1	236.2	244.9	276.6
relative (% bw)	3.6	3.4	3.4	3.7	3.2	3.0	3.3	3.9
relative (% brain weight)	374.2	383.5	380.4	405.9	344.5	333.5	343.0	385.2
Kidney weight								
absolute (g)	40.15	41.83	39.38	43.34	37.55	36.75	34.12	36.43
relative (% bw)	0.50	0.52	0.49	0.56	0.47	0.46	0.47	0.51
relative (% brain weight)	53.11	57.90	54.88	60.51	50.27	51.85	47.79	50.53

Macroscopic examination / Histopathological examination: No treatment-related macroscopic or microscopic findings were recorded. All gross lesions and various spontaneous findings were within the normal range observed in this age and strain of dog.

Conclusion:

In the highest dose group (2000 ppm), a decrease in body weight gain was noted in males. Furthermore, clinical chemistry findings indicating effects on the liver were observed in both sexes. Organ weight analysis showed a slight trend to increased organ weights of liver and kidney.

The NOAEL is considered to be 400ppm (equivalent to 15.6 mg/kg bw/d in males and 16.2 mg/kg bw/d in females).

Supportive information

Table 67: Repeated dose toxicity: oral with Fenoxaprop–ethyl

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Wistar rat 32 days oral *Leist et al., 1980a*	0, 80, 315, 1250 and 5000 ppm / diet (values in mg/kg bw/d are not presented in the study report)	< 80 ppm	**- clinical chemistry findings** **- increased organ weights (kidney)** 5000 ppm group terminated after 1 week of treatment as this dose level clearly exceeded the MTD <u>Remaining dose levels</u> - ≥ 80 ppm: hypolipidaemia, ↑ kidney weight - ≥ 315 ppm: ↑ liver weight correlated with histopathology changes including enlarged hepatocytes, ↓ phosphorus (males only) - 1250 ppm only: clinical signs including reduced activity and shallow breathing, ↓ body weight gain and food consumption, ↑ alkaline phosphatase, ↓ phosphorus (both species)
Wistar rat 3 months oral *Donaubauer et al., 1981*	0, 20, 80 and 320 ppm / diet (equivalent to 0, 1.57, 6.29 and 25.27 mg/kg bw/d in males; 0, 1.74, 6.93 and 27.53 mg/kg bw/d in females)	20 ppm (♂: 1.57 mg/kg bw/d; ♀: 1.74 mg/kg bw/d)	**- clinical chemistry findings** - ≥ 20 ppm: hypolipidaemia - ≥ 80 ppm: ↑ adrenal weights - 320 ppm only: ↓ water consumption, slight anaemia, liver toxicity consisting of ↑ alkaline phosphatase and liver weight with hepatocyte enlargement, ↑ kidney and thyroid weight

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
NMRI mouse 32 days oral *Leist et al., 1980b*	0, 80, 315, 1250 and 5000 ppm / diet (equivalent to 0, 14.6, 56.7, 215.0 and 556.7 mg/kg bw/d in males; 0, 14.9, 58.6, 222.7 and 463.6 mg/kg bw/d in females).	< 80 ppm	**- increased organ weights (liver)** **- histopathological findings (liver)** 5000 ppm group terminated after 1 week of treatment as this dose level clearly exceeded the MTD <u>Remaining dose levels</u> - ≥ 80 ppm: ↑ liver weight correlated with hepatocyte enlargement - ≥ 315 ppm: ↑ kidney weight correlated with tubular lesions, ↑ alkaline phosphatase - 1250 ppm only: ↓ haemoglobin, ↑ alanine aminotransferase
NMRI mouse 30 days oral *Leist et al., 1981*	0, 5, 10, 20 and 80 ppm / diet (equivalent to 0, 0.87, 1.82, 3.52 and 14.35 mg/kg bw/d in males; 0, 0.96, 1.85, 3.52 or 15.35 mg/kg bw/d in females)	10 ppm (♂: 1.82 mg/kg bw/d; ♀: 1.85 mg/kg bw/d)	- **clinical chemistry findings** **- increased organ weights (liver)** **- histopathological findings (liver)** - ≥ 20 ppm: ↑ total lipids, ↑ liver weight correlated with enlarged hepatic epithelia, large nuclei and dense eosinophilic cytoplasm - 80 ppm only: ↑ cholesterol

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
NMRI mouse 13 weeks oral *Ehling G., 1993a*	0, 320, 640 and 1280 ppm / diet (equivalent to 0, 51.6, 100.7 and 211.9 mg/kg bw/d in males; 0, 54.4, 113.8 or 230.0 mg/kg bw/d in females)	< 320 ppm	**- haematology findings** **- clinical chemistry findings** **- increased organ weights (liver, kidney, spleen, adrenals)** **- histopathological findings (liver, kidney, spleen)** **- electron microscopy and special biochemistry findings (peroxisome proliferation)** - ≥ 320 ppm: ↓ erythrocytes, ↑ reticulocytes (F) liver – impaired liver erythropoiesis, ↑ bilirubin, albumin, ↑ liver weight, hepatocellular hypertrophy due to peroxisome proliferation and single cell necrosis. Kidney - ↑ kidney weight and tubular vacuolation (F) Spleen - extramedullary erythropoiesis (M) Adrenals - ↑ adrenal weight (M) - ≥ 640 ppm: ↑ leucocytes (F), ↑ total protein, trigylcerides, ↑ enzymic activity in the liver Kidney – tubular atrophy and cell necrosis (F) - 1280 ppm only: ↑ spleen weight (M), ↓ thrombocytes (F), ↑ reticulocytes (M)
Beagle dog 30 days oral *Brunk et al., 1980*	0, 80, 400 and 2000 ppm / diet (values in mg/kg bw/d are not presented in the study report-	Supplementary information only, dose finding study with two animals per group	-2000 ppm: excessive toxicity leading to premature sacrifice by treatment day 3 (2M, 1F) or 5 (1F) - 400 ppm: only finding was ↑ adrenal weights with no corresponding histopathology - 80 ppm: no findings
Beagle dog 3 months oral *Brunk et al., 1981a*	0, 16, 80 and 400 ppm / diet (values in mg/kg bw/d are not presented in the study report)	16 ppm	**- interstitial pyelonephritis** -≥ 80 ppm: chronic interstitial pyelonephritis - 400 ppm only: ↑ relative pituitary weight with no corresponding histopathology
Beagle dog 1 year oral *Brunk et al., 1984*	0, 3, 15 and 75 ppm / diet (values in mg/kg bw/d are not presented in the study report)	> 75 ppm	No treatment-related effects could be identified in any of the dose groups.

The studies conducted with Fenoxaprop-ethyl were conducted according to GLP. In most of the study reports there is no reference to international toxicity testing guidelines. However, with the exception of a dose finding study in dogs which is of supplementary information only, the study designs come close to the corresponding international guidelines.

Range-finding-test with Hoe 33171 0H AT203 in a 32-day study with SPF-Wistar-rats

Reference: *Leist et al.*; 1980a; Doc. No. A26171 / Hoechst Report No. 164/80

Guideline: No guideline is mentioned in the study report. However, the study design is comes close to OECD Guideline 407.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 10 male and 10 female Wistar rats (strain: WISKf(SPF 71), source: Hoechst) received a diet containing 0, 80, 315, 1250 or 5000 ppm Fenoxaprop-ethyl for 32 days (the daily test substance intake in mg/kg bw/d is not presented in the study report). Prior to the beginning of the study the rats were 36 – 38 days old and the body weights were 95 – 98 g for males and 89 – 91 for females. The purity of the test substance (Hoe 33171 0H AT203) was 97 % (according to certificate of analysis No. 00792). Diets were prepared at the beginning of the study and on days 13 and 24 of the experiment. Samples of each preparation were analyzed for their content of the test substance.

Behaviour and general state of health (clinical signs) were assessed on 5 days per week. Food consumption and body weight were recorded twice weekly, while water consumption was controlled weekly. In hematology the following parameters were assessed: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count, reticulocytes, thrombocytes and coagulation time. Clinical chemistry included sodium, potassium, inorganic phosphorus, uric acid, bilirubin, creatinine, glucose, urea nitrogen, calcium, chloride, ASAT, ALAT, ALP, cholesterol and total lipids. At urinanalyis the following parameters were determined: appearance, colour, protein, glucose, haemoglobin, bilirubin, pH and sediment. The urine of the watered but fasted animals was collected overnight in diuresis cages. All animals were necropsied and macroscopic changes were recorded. The following organ weights of all animals were determined: heart, lungs, liver, kidneys, spleen, testes, ovaries, adrenals, thyroid, brain and pituitary. Histopathological examinations were performed in all animals on heart, lungs, liver, kidneys, spleen, stomach, small intestine, large intestine, urinary bladder, testes, epididymes, prostate, seminal vesicles, ovaries, uterus, thyroid, pancreas, adrenals, thymus, pituitary, brain, eyes with optical nerve and bone marrow. Statistical evaluation was performed on body weights and weight changes, haematological and clinical chemistry parameters and relative organ weights.

Findings:

Mortality / Clinical Signs: All animals of the highest dose group (5000 ppm) were killed and examined prematurely on treatment day 7 or 8 because of poor general condition, refusal of food and marked decrease in body weight. The male and female rats in the 1250 ppm group showed markedly passive behaviour on treatment days 4 and 5. At the same time shallow and irregular respiration was observed. Though these symptoms were no longer seen after day 15

or 16, the animals showed markedly bristed hair during the further course of the study. No signs of toxicity were seen in other treatment groups.

Food and water consumption: Very marked reduction in food consumption was seen in the 5000 ppm dosage group until the time of premature autopsy. At 1250 ppm, food intake was reduced at the beginning of study but returned to normal during the course of the study, while water consumption remained increased throughout the study in this dose group.

Body weight: Marked decrease in body weight was registered for all animals in the 5000 ppm dosage group until premature necropsy. A significant reduction in body weight gain was observed in male and female rats of the 1250 ppm dose group.

Table 68: 32 day feeding study in rats with Fenoxaprop-ethyl
Food and water consumption, body weight

	Dose group level (ppm)									
	Males					Females				
	0	80	315	1250	5000[1]	0	80	315	1250	5000[1]
Food consumption[2] (g/100g), days 1 - 33	9.23	9.02	8.87	8.26	3.611	9.31	8.64	8.64	7.57	3.241
Water consumption[2] (g/100g), day 29	11.83	12.38	12.51	17.36	-1	11.99	10.02	12.85	16.17	-1
Body weight gain (g)	148	148	134	83*	-1	74	71	67	45*	-1
Terminal body weight (g)	255	261	241	194*	751	180	175	170	148*	751

* ($p < 0.05$); significantly different from controls
[1] animals were killed prematurely on treatment days 7 and 8 due to excessive toxicity
[2] statistical analysis have not been performed on this parameter

Hematology: Only two changes were observed which were considered not to be of toxicological relevance. Males receiving 1250 ppm showed a decrease in the number of leucocytes without changes of the differential blood count. The females of the 315 ppm dose group developed a slight increase in the number of erythrocytes without dose-dependency.

Clinical chemistry: A lipid-lowering effect of Fenoxaprop-ethyl was observed in both sexes (reduced cholesterol in all dose groups, reduced total lipids at 315 ppm and above). The increase in ALP (males and females at 1250 ppm) and the decrease in serum phosphorus (males: 315 ppm and above; females: 1250 ppm) were judged to be signs of a substance-related toxic effect. The clinical relevance of the other observed changes could not be determined definitely (increased urea nitrogen in males at 1250 ppm; decreased uric acid in females at 315 and 1250 ppm; decreased potassium in females at 1250 ppm).

Table 69: 32 day feeding study in rats with Fenoxaprop-ethyl
Statistically significant clinical chemistry findings after 32 days

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Cholesterol (mmol/L)	1.84	1.36*	1.24*	0.85*	1.75	1.45*	1.39*	1.23*
Total lipids (mmol/L)	4.01	3.65	2.84*	3.06*	4.07	3.37	3.25*	3.23*
ALP (U/L)	339	336	360	415*	237	255	267	325*
Phosphorus (mmol/L)	2.79	2.42	2.06*	1.90*	2.18	1.96	2.19	1.70*

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Urea nitrogen (mmol/L)	7.74	7.78	8.07	9.30*	8.36	9.42	8.11	7.39
Uric acid (mmol/L)	126	58	68	107	104	109	64*	75*
Potassium (mmol/L)	7.0	6.1	6.6	6.4	6.1	5.6	6.1	5.3*

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

Urinalysis: No statistical analysis was performed on urinalysis results. However, no treatment-related effects were obvious.

Organ weight analysis: No statistical analysis was performed on absolute organ weights (g) but only on relative organ weights. Relative liver weights were significantly increased in males and females at 315 and 1250 ppm. A dose-dependent increase in relative kidney weight was observed in females at 80 ppm and above, while the increase in males was statistically significant only at 80 and 1250 ppm and no dose correlation was noted. Further changes in relative organ weights (increased brain weight in males and females, decreased adrenals weight in females, increased testes weight) were only observed in the highest dose group and were considered to be of no toxicological relevance but rather a result of decreased body weight at this dose group.

Table 70: 32 day feeding study in rats with Fenoxaprop-ethyl Statistically significant organ weight findings after 32 days

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Liver weight								
absolute (g)[1]	10.02	10.82	11.99	11.52	7.32	7.19	7.66	8.32
relative (% bw)	3.933	4.147	4.956*	5.926*	4.074	4.119	4.516*	5.632*
Kidney weight								
absolute (g)[1]	1.74	2.25	1.78	1.63	1.19	1.34	1.33	1.20
relative (% bw)	0.683	0.858*	0.739	0.840*	0.666	0.768*	0.782*	0.818*
Brain weight								
absolute (g)[1]	1.99	2.03	1.96	1.89	1.85	1.90	1.89	1.79
relative (% bw)	0.784	0.782	0.816	0.987*	1.034	1.092	1.116	1.216*
Adrenals weight								
absolute (g)[1]	0.0431	0.0519	0.0402	0.0368	0.0578	0.0503	0.0517	0,0378
relative (% bw)	0.0170	0.0199	0.0167	0.0190	0.0322	0.0288	0.0305	0.0256*
Testes weight								
absolute (g)[1]	2.98	3.07	2.81	2.72	-	-	-	-
relative (% bw)	1.173	1.182	1.164	1.410*				

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: No findings were recorded which could be attributed to treatment with the test substance.

Histopathological examination: Dose-dependent findings in the liver were observed at 315 and 1250 ppm in all animals, with effects being more marked in males than in females. Livers showed a fine-granulated eosinophil staining of the cytoplasm of hepatocytes in many or all parts of the hepatic lobules and an enlargement of hepatocytes. Other findings were not considered to be substance-induced.

Conclusion:

Fenoxaprop-ethyl demonstrated excessive toxicity at 5000 ppm so that animals had to be sacrificed prematurely on treatment days 7 and 8. Body weight gain was impaired only in the highest dose group, while effects on lipid metabolism were already observed at 80 ppm and above. Liver toxicity demonstrated by increased ALP and decreased phosphorus levels was noted in the highest dose group in both males and females. Clear effects on the liver were seen at necropsy when an increased organ weight and histopathological findings (fine-granulated eosinophil staining, enlargement of hepatocytes) were observed. Also, relative kidney weights were increased in both sexes at 80 ppm and above.

The NOAEL is considered to be smaller than 80 ppm.

Repeated-dose (3 months) oral toxicity study of the active substance Hoe 33171 (Code: Hoe 33171 0H AT204) administered in the feed to rats

Reference: *Donaubauer et al.*; 1981; Doc. No. A35788 / Hoechst Report No. 695/81
Addendum to Report No. 695/81, *Thier W., 1986,* Doc. No. A32985

Guideline: No guideline is mentioned in the study report. However, the study design is close to OECD Guideline 408.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 30 male and 30 female Wistar rats (strain: WISKf(SPF 71), source: Hoechst) received a diet containing 0, 20, 80 or 320 ppm Fenoxaprop-ethyl which is equivalent to 0, 1.57, 6.29 and 25.27 mg/kg bw/d in males and 0, 1.74, 6.93 and 27.53 mg/kg bw/d in females for 3 months. The reversibility of treatment-related effects was studied with 10 additional animals/sex in the control and treatment groups over a 4-week observation period. Prior to the study the rats were approximately 5 weeks old and had a mean body weight of 128 g (males) or 121 g (females). The purity of the test substance (Hoe 33171 0H AT204) was 96 % (according to certificate of analysis No. 01514). Diets were prepared at 14-day intervals. The stability and homogeneity of the test substance in the diet were controlled by analytical examinations.

Behaviour and general state of health (clinical signs) were assessed daily. Food consumption and body weight were recorded once weekly, while water consumption was determined at 14-day intervals. Hematological examinations were made prior to the beginning of the study (initial value), at week 6 (intermediate value) and at week 13 (final value) of the study, but not after the recovery period. The following parameters were assessed: hemoglobin, erythrocytes, hematocrit, MCV, MCH, MCHC, reticulocytes, Heinz bodies, leukocytes, thrombocytes, coagulation time and differential blood count. Clinical chemistry was performed in 10 non-fasted rats/sex/group prior to the beginning of the study and at week 6, while the final values at week 13 were determined from 20 rats/sex/group. After the observation period of 4 weeks, clinical chemistry was examined from the recovery groups. At the beginning of the study, clinical chemistry included glucose, urea-nitrogen, ASAT, ALAT and ALP. At the following examinations a larger number of parameters was assessed: sodium, potassium, inorganic phosphorus, uric acid, total bilirubin, glucose, creatinine, urea nitrogen, calcium, chloride, ASAT, ALAT, ALP, total protein, total lipids, cholesterol, LDH, direct bilirubin and electrophoresis. After the animals were deprived of food and drinking water, their urine was collected overnight in diuresis cages. Urinalysis was performed in 10 rats/sex/dose at the

beginning of study (initial value), at week 6 (intermediate value) and at week 13 of study (final value). The following parameters were determined: appearance, colour, protein, glucose, haemoglobin, bilirubin, pH, sediment, specific weight, ketone bodies and urobilinogen. All animals were necropsied and macroscopic changes were recorded. The following organ weights were determined in all animals: heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, adrenals, pituitary, seminal vesicle and thyroid. Histopathological examination was performed in all animals and included heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, adrenals, pituitary, seminal vesicle, thyroid, thymus, salivary glands (parotis and mandibularis), trachea, esophagus, stomach (fundus and prepyloric region), intestine (duodenum, jejunum, ileum, doecum, colon, rectum), urinary bladder, prostate, epididymes, uterus, pancreas, abdominal aorta, diaphragm, eyes with optic nerves, skeletal muscle, marrow of the femur, 1. lubar vertebra, lymph nodes (hilus and iliacus), skin with mammary gland, tumors (if any) and spinal marrow with sciatic nerve. Statistical evaluation was performed on body weights, haematological and clinical chemistry parameters, and relative organ weights.

Findings:

Mortality / Clinical Signs: No mortality occurred and no treatment-related effects were observed.

Food and water consumption: Food consumption showed no differences between treated and untreated animals, while the relative water consumption of males and females receiving 320 ppm was slightly lower throughout the study.

Body weight: The body weight gains were normal and not influenced by administration of the test substance.

Hematology: A significant decrease in haemoglobin and erythrocyte values was observed in male rats at the top dose at week 6 and 13 of the study. A transient decrease in the number of thrombocytes was noted in females of the top dose only during week 6 of the study. According to the study report both results were within normal range of biological variation of the strain of rats used for this study.

Clinical chemistry: At various times of measuring several parameters differed statistically significant from that of the controls. A substance-induced change in the lipid status was demonstrated by decreased cholesterol levels in males (80, 320 ppm) and females (320 ppm) and by decreased total lipid levels in females (20 ppm and above). These effects were largely reversible after 4 weeks. The significant increase in ALP in males receiving 320 ppm was considered the first sign of a substance-induced toxic effect. Other changes were judged to be of no toxicological relevance as on the one side all values were within the normal range of biological variation and on the other side there was no histopathological correlation detectable. These changes included sodium levels (decreased in males at 80 and 320 ppm; increased in females at 320 ppm), potassium (decreased in males at 320 ppm), inorganic phosphorus (increased in males at 20, 80 and 320 ppm and in females at 80 and 320 ppm), bilirubin (increased in males at 320 ppm), uric acid (decreased in males at 320 ppm; increased in females at 320 ppm), creatinine (increased in males at 320 ppm and in females at 20, 80 and 320 ppm), urea-nitrogen (decreased in males at 320 ppm) and some changes in the electrophoresis pattern.

Urinalysis: No statistical analysis was performed on urinalysis results. However, the urinalysis findings are not indicative of a harmful effect of the test-substance on the urinary tract.

Table 71: 3 months feeding study in rat with Fenoxaprop-ethyl
Relevant haematology and clinical chemistry findings after 3 months (final values)

	Dose group level (ppm)							
	Males				Females			
	0	20	80	320	0	20	80	320
Hematology								
Hemoglobin (g/L)	166	158	157	154*	156	156	152	149
Erythrocytes (10^{12}/L)	8.35	8.14	8.07	7.75*	7.70	7.88	7.50	7.44
Clinical chemistry								
Cholesterol (mmol/L)	2.07	1.86	1.63*	1.68*	1.76	1.65	1.62	1.51*
Total lipids (g/L)	3.55	3.19	3.41	3.28	5.02	4.27*	3.67*	3.61*
ALP (U/L)	254	248	251	302*	184	174	171	178

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

Organ weight analysis: No statistical analysis was performed on absolute organ weights (g) but only on relative organ weights. Relative liver weight was increased in males at 320 ppm, while relative kidney weight was increased in both sexes at 320 ppm. Furthermore, thyroid weight was elevated in males at 320 ppm beyond the range which can be considered normal for the strain of rats used in this study. The relative adrenals weight in females receiving 80 or 320 ppm showed a dose-dependent increase, however the values were still within the normal range of variation. An incidental finding was an increased weight of ovaries at 20 ppm. All organ weights appeared to be normal after 4 weeks except decreased liver weights in males at 20 ppm and females at 80 ppm.

Table 72: 3 months feeding study in rats with Fenoxaprop-ethyl
Statistically significant organ weight findings after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	20	80	320	0	20	80	320
Liver weight								
absolute (g)[1]	12.91	12.33	12.84	14.81	7.28	7.03	7.15	7.39
relative (% bw)	3.080	3.033	3.083	3.558*	3.190	3.221	3.151	3.257
Kidney weight								
absolute (g)[1]	2.42	2.37	2.45	2.65	1.49	1.46	1.55	1.57
relative (% bw)	0.579	0.583	0.589	0.641*	0.653	0.666	0.683	0.694*
Adrenals weight								
absolute (g)[1]	0.0552	0.0531	0.0573	0.0596	0.0629	0.0669	0.0722	0.0749
relative (% bw)	0.0133	0.0131	0.0138	0.0143	0.0277	0.0305	0.0319*	0.0331*
Thyroid weight								
absolute (g)[1]	0.0197	0.0211	0.0223	0.0238	0.0145	0.0153	0.0163	0.0160
relative (% bw)	0.0047	0.0052	0.0054	0.0057*	0.0064	0.0071	0.0072	0.0071

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: No substance-induced organ changes were seen.

Histopathological examination: Moderately enlarged hepatocytes in the centre of the hepatic lobules were seen on the first killing date in the male rats receiving 320 ppm. The cytoplasm of these cells was eosinophilic and finely granulated. These effects were reversible after a recovery period of 4 weeks. There were no histopathological findings noted in other organs.

Conclusion:

Body weight gain was normal throughout the study and all dose groups. A few changes were noted in haematology values at the top dose (haemoglobin, erythrocytes). In clinical chemistry, an influence of the test substance on lipid metabolism was obvious by decreased cholesterol and lipid levels at 80 and/or 320 ppm. Effects on the liver were also demonstrated by increased ALP levels, increased relative liver weight, and enlargement of hepatocytes in males at 320 ppm. Other relative organ weight changes were observed with no correlation at histopathology (kidney, thyroid, adrenals) at 80 ppm and/or 320 ppm.

The NOAEL is considered to be 20 ppm (equivalent to 1.57 mg/kg bw/d in males and 1.74 mg/kg bw/d in females).

The study is scientific valid and acceptable.

Toxicity test of Hoe 33171 0H AT203 in a 32-day study with SPF-mice

Reference: *Leist et al.*; 1980b; Doc. No. A26168 / Hoechst Report No. 336/80

Guideline: No guideline is mentioned in the study report. However, the study design is close to OECD Guideline 407.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

10 male and 10 female NMRI mice (strain: NMRKf, source: Hoechst) per dose group received a diet containing 0, 80, 315, 1250 or 5000 ppm Fenoxaprop-ethyl for 32 days (equivalent to 0, 14.6, 56.7, 215.0 or 556.7 mg/kg bw/d in males and 0, 14.9, 58.6, 222.7 or 463.6 mg/kg bw/d in females). At the beginning of the study the mice (age not reported) weighed 16 – 17 g (males) and 15 – 16 g (females). The purity of the test substance (Hoe 33171 0H AT203) was 97 % (according to certificate of analysis No. 00792). Diets were prepared at the beginning of the study and twice during the study at a 14-day interval.

Behaviour and general state of health (clinical signs) were assessed on 5 days per week. Food consumption and body weight were recorded twice weekly, while water consumption was controlled weekly. In hematology the following parameters were assessed: hemoglobin, erythrocytes, hematocrit, MCV, MCH, MCHC, leukocytes, differential blood count, reticulocytes, thrombocytes, and Heinz bodies. Clinical chemistry included bilirubin, glucose, urea nitrogen, total lipids, cholesterol, ASAT, ALAT, and ALP. At urinanalyis the following parameters were determined: appearance, colour, protein, glucose, haemoglobin, bilirubin, pH, and sediment. The urine of the watered but fasted animals was collected overnight in diuresis cages. All animals were necropsied and macroscopic changes were recorded. The following organ weights of all animals were determined: heart, lungs, liver, kidneys, spleen, testes, ovaries, adrenals, thyroid, and brain. Histopathological examinations were performed in all animals on heart, lungs, liver, kidneys, spleen, stomach, small intestine, large intestine, urinary bladder, testes, epididymes, prostate, seminal vesicles, ovaries, uterus, thyroid, pancreas, adrenals, thymus, pituitary, brain, eyes with optical nerve, and bone marrow. Statistical evaluation was performed on body weight development, some haematological parameters (leucocytes, thrombocytes, haemoglobin, erythrocytes, hematocrit and reticulocytes), all clinical chemistry data and relative organ weights.

Findings:

Mortality / Clinical Signs: All animals of the highest dose group (5000 ppm) were killed and examined prematurely on treatment day 8 or 9 because of poor general condition, refusal of food and marked decrease in body weight. The following clinical symptoms were observed: passiveness, crawling or crouching, retracted flanks, bristled hair and marked emaciation because of continous refusal of food. No signs of toxicity were seen in other treatment groups.

Food and water consumption: The relative food consumption, except for the 5000 ppm dose group was within the normal range of biological variation. The animals in the 5000 ppm dose group showed considerably reduced food consumption. No substance-induced changes of the relative water consumption were seen.

Body weight: A marked decrease in body weight was registered for all animals in the 5000 ppm dosage group which in connection with the refusal of food and the poor general state of health led to the premature sacrifice. For all other dose groups consistent or dose-dependent changes in body weight could not be observed.

Table 73: 32 day feeding study in mice with Fenoxaprop-ethyl
Food consumption and body weight

	Dose group level (ppm)									
	Males					Females				
	0	**80**	**315**	**1250**	**5000[1]**	**0**	**80**	**315**	**1250**	**5000[1]**
Food consumption[2] (g/100g), days 1 - 33	18.95	18.20	18.00	17.20	11.141	19.14	18.59	18.62	17.82	9.271
Body weight gain (g)	15	13	16	14	-1	7	8	7	7	-1
Terminal body weight (g)	35	33	36	34	17*1	27	26	26	26	16*1

* ($p < 0.05$); significantly different from controls
[1] animals were killed prematurely on treatment days 8 and 9 due to excessive toxicity
[2] statistical analysis have not been performed on this parameter

Hematology: Males and females of the 1250 ppm group showed a significant decrease in haemoglobin values. Other parameters were unaffected by the treatment.

Clinical chemistry: The only substance-related effects observed were increases in liver enzymes indicative of a marked liver toxicity ab 315 ppm and above. ALAT was increased in males and females at 1250 ppm while ALP was increased in males at 315 and 1250 ppm and in females at 1250 ppm.

Table 74: 32 day feeding study in mice with Fenoxaprop-ethyl
Relevant haematology and clinical chemistry findings after 32 days

	Dose group level (ppm)							
	Males				Females			
	0	**80**	**315**	**1250**	**0**	**80**	**315**	**1250**
Hematology								
Hemoglobin (g/L)	146	139	141	134*	159	163	156	152*
Clinical chemistry								
ALAT (U/L)	81	74	140	244*	76	95	92	317*
ALP (U/L)	198	193	471*	1560*	282	269	348	1370*

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

Urinalysis: No statistical analysis was performed on urinalysis results. However, results do not suggest any substance-induced effects in the treated animals.

Organ weight analysis: No statistical analysis was performed on absolute organ weights (g) but only on relative organ weights. A significant increase in relative liver weight was observed in males (315 ppm and above) and in females (80 ppm and above). Relative kidney weights were elevated in females receiving 315 or 1250 ppm.

Table 75: 32 day feeding study in mice with Fenoxaprop-ethyl
Relevant organ weight findings after 32 days

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Liver weight								
absolute (g)1	2.11	2.16	3.63	5.62	1.39	1.64	2.14	3.73
relative (% bw)	6.02	6.47	10.17*	16.43*	5.24	6.26*	8.39*	14.31*
Kidney weight								
absolute (g)1	0.54	0.50	0.54	0.55	0.33	0.36	0.36	0.37
relative (% bw)	1.55	1.50	1.52	1.62	1.26	1.36	1.40*	1.42*

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: The macroscopic examinations showed isolated markings of the hepatic lobules in a few control animals and with increasing concentrations also in the treated animals.

Histopathological examination: Changes in the livers were observed in all dose groups in both sexes and became more marked at higher dose groups. These changes included eosinophil, fine-granulated cytoplasm and enlargement of hepatocytes. Histopathological examination of animals of the 5000 ppm dose group which were killed prematurely showed the same findings with additional necroses of the hepatocytes and Kupffer´s cell proliferation. Effects on kidneys were observed in females only and started at a dose level of 315 ppm. Tubular cell necroses as well as tubular cells with large vesicular nuclei were found in 2/10 females receiving 315 ppm and in the majority of females receiving 1250 ppm.

Conclusion:

Fenoxaprop-ethyl demonstrated excessive toxicity at 5000 ppm so that animals had to be sacrificed prematurely on treatment days 8 and 9. Body weight gain was impaired only in the animals of the 5000 ppm dose group. Decreased haemoglobin values were noted at 1250 ppm. Clear signs of liver toxicity (increased ALAT and ALP levels) were noticed at 315 ppm and above. Furthermore, increases in relative liver weights were found in both sexes (males at 315 ppm and above, females at 80 ppm and above) together with histopathological findings of eosinophil, fine-granulated cytoplasm and enlargement of hepatocytes. Also kidneys of female mice were affected by treatment at doses of 315 ppm and above.

The NOAEL is considered to be smaller than 80 ppm.

Toxicity test of Hoe 33171 0H AT204 in a 30-day study with SPF-mice

Reference: *Leist et al.*; 1981; Doc. No. A26169 / Hoechst Report No. 356/81

Guideline: No guideline is mentioned in the study report. However, the study design is close to OECD Guideline 407.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

10 male and 10 female NMRI mice (strain: NMRKf, source: Hoechst) per dose group received a diet containing 0, 5, 10, 20 or 80 ppm Fenoxaprop-ethyl for 30 days (equivalent to 0, 0.87, 1.82, 3.52 or 14.35 mg/kg bw/d in males and 0, 0.96, 1.85, 3.52 or 15.35 mg/kg bw/d in females). At the beginning of the study the mice (age not reported) weighed 15 – 17 g (males) and 14 – 17 g (females). The purity of the test substance (Hoe 33171 0H AT204) was 96 % (according to certificate of analysis No. 01514). Diets were prepared at the beginning of the study and twice during the study at a 14-day interval.

Behaviour and general state of health (clinical signs) were assessed daily except on weekends. Food consumption and body weight were recorded twice weekly, while water consumption was controlled weekly during a 16-hour period. In hematology the following parameters were assessed: hemoglobin, erythrocytes, hematocrit, MCV, MCH, MCHC, leukocytes, differential blood count, reticulocytes and thrombocytes. Clinical chemistry included bilirubin, glucose, urea nitrogen, total lipids, cholesterol, ASAT, ALAT and ALP. At urinanalyis the following parameters were determined: appearance, colour, protein, glucose, haemoglobin, pH and sediment. The urine of the watered but fasted animals was collected overnight in diuresis cages. All animals were necropsied and macroscopic changes were recorded. The following organ weights of all animals were determined: heart, lungs, liver, kidneys, spleen, testes, ovaries, adrenals and brain. Histopathological examinations were performed in all animals on heart, lungs, liver, kidneys, spleen, stomach, small intestine, large intestine, urinary bladder, testes, epididymes, prostate, seminal vesicles, ovaries, uterus, thyroid, pancreas, adrenals, thymus, pituitary, brain, eyes with optical nerve and bone marrow. Statistical evaluation was performed on body weight development, some haematological parameters (leucocytes, thrombocytes, haemoglobin, erythrocytes, hematocrit and reticulocytes), all clinical chemistry data and relative organ weights.

Findings:

No clinical signs of toxicity or effects on food and water consumption or body weight gain were recorded in any of the treatment groups.

Hematology: No changes in haematological parameters were observed in the treated animals.

Clinical chemistry: Lipid metabolism was affected in both sexes. Cholesterol levels were increased in females at 80 ppm and total lipids were increased in males at 20 and 80 ppm.

Table 76: 30 day feeding study in mice with Fenoxaprop-ethyl
Relevant clinical chemistry findings after 30 days

	Dose group level (ppm)									
	Males					Females				
	0	5	10	20	80	0	5	10	20	80
Cholesterol (mmol/L)	2.51	2.67	2.87	2.89	2.91	1.95	1.92	1.99	2.17	3.14*
Total lipids (g/L)	6.92	7.28	7.34	7.86*	8.29*	5.37	5.16	4.84	5.68	5.57

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

Urinalysis: Protein was found in a few animals dosed 20 and 80 ppm. The content of protein in the urine in this study was reported to be indicative of a renal lesion. However, no statistical analysis was performed.

Organ weight analysis: No statistical analysis was performed on absolute organ weights (g) but only on relative organ weights. A significant increase in relative liver weight was observed in males (80 ppm) and in females (20 and 80 ppm). Increased brain weight (males, 5 ppm) and decreased ovaries weight (10 ppm) were considered not to be treatment-related.

Table 77: 30 day feeding study in mice with Fenoxaprop-ethyl
Relevant organ weight findings after 30 days

	Dose group level (ppm)									
	Males					Females				
	0	**5**	**10**	**20**	**80**	**0**	**5**	**10**	**20**	**80**
Liver weight										
absolute (g)[1]	1.79	1.59	1.83	1.70	2.23	1.39	1.40	1.41	1.60	1.65
relative (% bw)	5.338	5.323	5.457	5.178	6.507*	5.049	5.177	4.997	5.631*	5.911*

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: No organ lesions were found at necropsy.

Histopathological examination: Changes in the livers were observed at 20 ppm and above. 4 males and all females receiving 20 ppm showed slight enlargement of the epithelia with large nuclei and dense eosinophil cytoplasm in the centrolobular hepatic sections. At 80 ppm, all animals developed these changes which were more pronounced and also detectable in the intermediary lobular regions. The findings in the males were more intensive and extensive than in the females. One male receiving 80 ppm showed additionally sings of hypertrophy due to an increase in the mitotic rate.

Conclusion:

Effects on the liver were observed at doses of 20 ppm and above (changes in lipid metabolism, increased organ weight, histopathological findings of eosinophil cytoplasm and enlargement of epithelia).

The NOAEL is considered to be 10 ppm (equivalent to 1.82 mg/kg bw/d in males and 1.85 mg/kg bw/d in females).

Hoe 33171, substance technical. Subchronic oral toxicity (13-week range finding feeding study) in the NMRI mice

Reference: *Ehling G.*; 1993a; Doc. No. A50244 / Hoechst Report No. 93.0157

Guideline: EPA Guideline 82-1 (1984), MAFF Guidelines (1985), OECD Guideline 408 (adopted 1981)

Deviations: The objective of this study was to determine the maximally tolerable dose (MTD) of Hoe 33171 for an oncogenicity study. Therefore the dose levels were set rather high in this study and were not suitable for defining a NOAEL. Furthermore, additional investigations like electron microscopy and biochemical analysis were performed to investigate mechanistic action of Fenoxaprop-ethyl.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

20 NMRI mice per sex and dose group (strain: NMRKf, source: Hoechst) received a diet containing 0, 320, 640 or 1280 ppm Fenoxaprop-ethyl (equivalent to 0, 51.6, 100.7 or 211.9 mg/kg bw/d in males and 0, 54.4, 113.8 or 230.0 mg/kg bw/d in females) for a period of 3 months. The mice were approximately 4 weeks old and had a mean body weight of 24.28 g (males) and 21.65 g (females). The purity of the test substance (Hoe 033171 00 ZD96 0005) was 96.8 % according to the certificate of analysis No. 04663 (1991). Diets were prepared before and 3 times during the study period, with the stability of the test substance guaranteed for 30 days.

Clinical signs were observed twice daily, except on weekends and public holidays when animals were checked once daily.

Body weight, food consumption and water consumption were determined once weekly. Blood samples were taken from the non-fasted animals. In hematology the following parameters were assessed: erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, leukocytes, thrombocytes, differential blood count, reticulocytes, Heinz bodies and coagulation time. Clinical chemistry included ASAT, ALAT, ALP, albumin, cholesterol, triglycerides, total lipids, total protein, gamma-glutamyltransferase, total bilirubin, creatinine, glucose, urea-nitrogen, sodium, potassium, uric acid, calcium, chloride and inorganic phosphorus. All animals were necropsied and macroscopic changes were recorded. The following organ weights of all animals were determined: heart, lungs, liver kidneys, spleen, brain (medulla/pons, cerebellar and cerebral cortex), both testes, ovaries and adrenals. The following histopathology was performed: 1) all organs and tissues collected at scheduled sacrifice from all animals of the control and highest dose group (heart, lungs, liver kidneys, spleen, brain (medulla/pons, cerebellar and cerebral cortex), both testes, ovaries, adrenals, pituitary, thyroid/parathyroid, stomach, intestine, pancreas, urinary bladder, prostate, uterus, thymus, both eyes/optical nerves, bonemarrow (femur with knee-joint), aorta, parotid gland, submandibular gland, cervical/iliacal lymph nodes, esophagus and trachea, epididymides, diaphragm, skeletal muscle (femur), skin/mammary gland, seminal vesicle, Nervus ischiadicus, sternum and vagina); 2) target organs: liver, kidneys, heart and adrenals from all animals; 3) all gross lesions. Electron microscopy was performed from specified portions of the liver from 2 male mice of each group. Special biochemical investigations were conducted from samples of the livers of all animals: catalase, malic enzyme, lactate dehydrogenase, glycerophosphate dehydrogenase, glutathione content and pentylresorufin O-depentylase.

Findings:

Mortality / Clinical Signs: There was no mortality during the study. Several animals from all treatment groups showed non-specific clinical signs from study week 5 up to the end of treatment in the form of coat bristling, straddling hind limbs, swollen abdomen, drawn in flanks, squatting posture and stilted gait. In addition at 1280 ppm, a yellow discoloured bedding was observed in one cage of the males and in all 4 cages of the females.

Body weight: Body weight gains appeared to be raised in the two highest dose groups as a consequence of strongly increased liver weights and thus, were not significantly affected by the test substance. Only in the 1280 ppm dose group males there were marginally lower body weights without statistical significance, which had been masked by the liver weights.

Table 78: 3 months feeding study in mice with Fenoxaprop-ethyl
Body weights and body weights minus liver weights after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Terminal body weight (g)	35.9	37.2	39.7*	38.9*	28.7	29.0	30.7*	31.5*
Terminal body weight (g) minus liver weight	34.5	34.6	36.1	33.7	27.6	27.3	28.3	28.2

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

Food and water consumption: Food and water consumption were unaffected by the test substance in all of the treated groups.

Hematology: Some haematological findings were observed which did not follow a clear dose-relationship. A treatment related effect (impaired liver erythropoiesis) can not be excluded in view of the severe liver toxicity seen in this study. Reticulocytes and MCV were increased in males at 1280 ppm and females at 320 ppm and above. In females, erythrocytes (320 ppm and above) and thrombocytes (1280 ppm) were decreased, while leucocytes were increased (640 and 1280 ppm).

Clinical chemistry: At the end of the treatment period, statistical analysis revealed a large number of significant changes from which the following were considered as related to treatment: bilirubin (decreased in males at 320, 640 and 1280 ppm and in females at 320 and 1280 ppm), triglycerides and total protein (both increased in males at 640 and 1280 ppm, evaluation not possible in females), albumin (increased in males at 1280 ppm and in females at 320, 640 and 1280 ppm), ASAT (decreased in males at 320 ppm and increased in females at 1280 ppm), ALAT (increased in males at 640 ppm, 1280 ppm not evaluable, and increased in females at 1280 ppm) and ALP (increased in males at 640 and 1280 ppm and in females at 1280 ppm). All other significant changes (e.g. decreased creatinine in males at 320 and 640 ppm; decreased glucose at 640 ppm and above in females) were considered as incidental findings being within the normal biological variation. Due to small blood samples, the following clinical chemistry values could not be evaluated (males/females in brackets): sodium (m/f), potassium (m/f), calcium (m/f), chloride (m/f), inorganic phosphorus (m/f), uric acid (m/f), cholesterol (f), triglycerides (f) and total lipids (m/f).

Table 79: 3 months feeding study in mice with Fenoxaprop-ethyl
Relevant haematology and clinical chemistry findings after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Hematology								
Reticulocytes (U)	0.029	0.033	0.032	0.042*	0.023	0.030*	0.033*	0.032*
Erythrocytes (10^{12}/L)	9.68	9.67	9.81	9.53	9.79	9.37*	9.39*	9.40*
MCV (10^{-15}l)	48	49	49	50*	49	50*	51*	51*
Thrombocytes (10^{9}/L)	777	859	771	751	746	811	745	669*
Leucocytes (10^{9}/L)	6.6	8.0	8.8	6.6	6.0	6.3	8.6*	8.0*
Clinical chemistry								
Bilirubin (µmol/L)	21.6	9.9*	7.0*	8.6*	11.7	7.9*	9.9	7.8*
Triglycerides (mmol/L)	0.93	1.09	1.27*	1.28*	0.85	[1]	[1]	[1]

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Total protein (g/L)	49	50	54*	56*	[1]	[1]	[1]	[1]
Albumin (g/L)	25.3	24.4	28.2	30.2*	24.6	28.6*	28.4*	30.2*
ASAT (U/L)	276	115*	184	328	91	108	105	223*
ALAT (U/L)	70	45	307*	[1]	38	41	71	286*
ALP (U/L)	112	153	655*	833*	118	146	221	711*

* ($p < 0.05$); significantly different from controls
[1] evaluation not possible

Organ weight analysis: Absolute and relative organ weights were increased from the following organs and were considered as treatment related findings: liver (males and females at 320 ppm and above), kidneys (males at 640 ppm and above, females at 320 ppm and above), spleen (males at 1280 ppm) and adrenals (males at 320 ppm and above). Other statistical significant changes were considered to be incidental (increased absolute heart weight in females at 640 and 1280 ppm; decreased relative lung weight in males at 640 ppm; decreased relative testes weight at 1280 ppm; decreased relative brain weight in males and females at 640 and 1280 ppm; decreased relative ovaries weight at 1280 ppm).

Table 80: 3 months feeding study in mice with Fenoxaprop-ethyl statistically significant organ weight findings after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Liver weight								
absolute (g)	1.394	2.559*	3.636*	5.166*	1.143	1.727*	2.364*	3.332*
relative (% bw)	3.885	6.887*	9.158*	13.265*	3.985	5.958*	7.684*	10.604*
Kidneys weight								
absolute (g)	0.470	0.493	0.552*	0.537*	0.327	0.367*	0.393*	0.400*
relative (% bw)	1.308	1.325	1.389	1.381	1.138	1.268*	1.279*	1.272*
Spleen weight								
absolute (g)	0.133	0.146	0.147	0.163*	0.127	0.126	0.126	0.138
relative (% bw)	0.371	0.392	0.369	0.421*	0.443	0.435	0.409	0.438
Adrenals weight								
absolute (g)	0.0054	0.0077*	0.0083*	0.0095*	0.0128	0.0117	0.0121	0.0129
relative (% bw)	0.0150	0.0207*	0.0208*	0.0247*	0.0447	0.0405	0.0395	0.0409

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

Macroscopic examination: Macroscopic examination of the organs showed livers and kidneys to be enlarged in most of the treated-group animals.

Histopathological examination: The liver was the organ most affected after treatment with Fenoxaprop-ethyl with effects being more pronounced in males than in females. Centrilobular (320 ppm and above) and/or diffuse (640 ppm and above) hepatocellular hypertrophy was observed in males and females. Single cell necrosis was noted in males (320 ppm and above) and in females (640 ppm and above) and was much more severe in males. Furthermore, an increase in mitotic activity was seen in both sexes (640 ppm and above). Again, the average grade of mitotic activity was higher in males than in females. Substance-related alterations in the kidneys were only observed in female mice. Tubular atrophy combined with single cell necrosis was observed at doses of 640 ppm and higher. Additional single cell necrosis without tubular atrophy was noted at 1280 ppm. Minimal grade vacuolation of tubular cells was seen at 320 ppm and above. In the spleen of males only, a dose-related increase in extramedullary erythropoiesis was seen in all treatment groups.

Table 81: 3 months feeding study in mice with Fenoxaprop-ethyl
Relevant histopathological findings after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Liver								
- centrilobular	-	20/20	20/20	1/20	-	20/20	5/20	-
hypertrophy	-	-	-	19/20	-	-	15/20	20/20
- diffuse hypertrophy	3/20	16/20	20/20	20/20	4/20	6/20	18/20	20/20
- single cell necrosis	-	-	19/20	20/20	-	3/20	10/20	18/20
- mitoses increased								
Kidneys								
- tubular atrophy with single cell necrosis	-	-	-	-	-	-	3/20	6/20
- single cell necrosis without tubular atrophy	-	-	-	-	-	-	6/20	11/20
- vacuolation of tubular epithelial cells	-	-	-	-	-	2/20	2/20	6/20
Spleen								
- increased erythropoiesis	1/20	10/20	14/20	20/20	-	-	-	-

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

Electron microscopy: It was demonstrated that the hypertrophy of liver epithelia was caused by proliferation of peroxisomes. This was proven by counting peroxisomes in three representative pictures from each animal examined including the controls (males only). The number of peroxisomes in hepatocytes in treated animals was up to 7 or 11 times higher than in controls. The size of the peroxisomes varied, the simple membrane was always distinctly drawn out and, in the centre, an electron-dense crystalloid was frequently seen. Furthermore, a reduction of the lamellae of the rough endoplasmic reticulum was present.

Special biochemical investigations: Catalase and malic enzyme, both marker enzymes for peroxisome proliferation, were increased in males and females at 320 ppm and above. Liver necrosis was demonstrated by an increase in the activity of lactate dehydrogenase and glycerophosphate dehydrogenase in males (640 ppm and above) and females (320 ppm and above). Glutathione contents were elevated in all males and in the highest dose females. Pentylresorufin O-depentylase activities were not indicative of a biosynthesis of drug-metabolizing mixed-function oxidases.

Table 82: 3 months feeding study in mice with Fenoxaprop-ethyl
Special biochemical investigations from liver samples after 3 months

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Catalase (R/mg)	9.29	46.26*	40,60*	48.94*	8.06	30.73*	45.57*	42.52*
Malic enzyme (U/kg)	781	1023*	1153*	1160*	878	971	1267*	1483*
Lactate dehydrogenase (U/g)	119	119	137*	174*	106	132*	158*	175*
Glycerophosphate dehydrogenase (U/g)	10.9	10.6	13.7*	18.4*	9.2	13.2*	14.5*	22.1*
Glutathione (mg/g)	0.20	0.24*	0.28*	0.31*	0.24	0.17*	0.18*	0.29*
Pentylresorufin O-depentylase (U/kg)	55.2	38.9*	43.3*	72.3*	123.2	90.2*	66.0*	69.0*

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

Conclusion:

Severe organic toxicity was shown by hepatocellular hypertrophy and liver cell necrosis from 320 ppm onwards in both sexes and tubular atrophy and kidney cell necrosis in the females from 640 ppm onwards. Peroxisome proliferation could be confirmed by electron microscopy and special biochemistry. In addition, these findings were accompanied by some moderate haematological findings in all treated groups in the form of increased MCV, compensatory reticulocytosis in both sexes, erythrocytopenia, thrombocytopenia, leucocytosis in the females and extramedullary erythropoiesis in spleen of the males, which point to a slight macrocyteric anaemia due to impaired liver function.

The aim of the study was to find a maximum tolerable dose (MTD) for a chronic toxicity study. Based on the results of this study, the MTD was considered to be 320 ppm (equivalent to 51.6 mg/kg bw/d in males and 54.4 mg/kg bw/d in females). No NOAEL could be established.

Repeated-dose (30 days) oral toxicity study of Hoe 33171 0H AT203 in Beagle dogs (range-finding-test)

Reference: *Brunk et al.*; 1980; Doc. No. A25657 / Hoechst Report No. 165/80
Supplement to Document No. A25657, *Brunk*, 1986, Doc. No. A32691
Amendment to Report No. 165/80, *Harston S.J.*, 1987, Doc. No. A35547

Guideline: -

GLP: yes, deviation: the test substance was not analysed for concentration, stability and homogeneity in the diet

Only two animals per dose group were treated in this study. Therefore this study is considered of supplementary information only.

Material and Methods:

2 Beagle dogs per sex per dose group (strain: BEAK, source: Hoechst) were given Fenoxaprop-ethly in the diet for 30 days. The concentrations in the food were 0, 80, 400 or 2000 ppm (the actual test substance intake was not presented in the test report). The purity of the test substance (Hoe 33171 0H AT203) was 97.0 % (according to certificate of analysis No. 00792). The dogs had an average age of 14 months and weighed 12.9 – 15.2 kg (males) and 10.5 – 13.9 kg (females). As there were only a few animals in trial, no detailed calculations or statistical analyses were conducted.

Clinical signs, behaviour and food consumption were checked daily. Body weight gain was recorded weekly. The neurological status (several reflexes), ophthalmoscopic examinations and hearing tests were assessed prior to the first treatment and after termination of the study or prior to sacrifice. Blood samples were taken from fasted animals 18 – 20 hours after feeding and treatment. Hematological examinations consisted of haemoglobin, erythrocyte count, leucocyte count, hematocrit, reticulocytes, Heinz bodies, differential blood count, thrombocytes and coagulation time. At clinical chemistry the following parameters were assessed: sodium, potassium, inorganic phosphate, uric acid, bilirubin, creatinine, serum glucose, urea-nitrogen, calcium, chloride, serum iron, cholesterol, total glycerine (triglycerides), total lipids, total protein, electrophoresis, Met-hemoglobin, ASAT, ALAT and ALP. Urinalysis included appearance, colour, pH, protein, glucose, haemoglobin, bilirubin, ketone bodies, specific weight and urinary sediment. All animals were necropsied and

examined macroscopically. The weights of the following organs were determined: heart, lungs, liver, kidneys, spleen, brain, pituitary, pancreas, ovaries, testes, adrenals, thyroid and thymus. Histopathological examinations were made from the following tissues / organs: heart, lungs, liver, kidneys, spleen, adrenals, thyroid, pancreas, thymus, pituitary, cerebral cortex, brain stem, cerebellum (cortex and marrow), eyes with optic nerve, urinary bladder, testes, ovaries, epididymes, uterus, prostate, stomach (fundus and praepyloric region), jejunum, colon, gall bladder, lymph nodes (superficial, cerivical and iliac) and bone marrow (mid-sternal segment).

Findings:

Mortality / Clinical Signs: For reasons of animal protection the animals from the highest dose group were sacrificed prematurely on study day 3 (two males, one female) or on study day 5 (one female) because of very poor general state of health. The animals suffered from diarrhea, a wet pelage contaminated with excrements, and a markedly impaired general condition which deteriorated rapidly. All dogs from the remaining groups lived up to the scheduled end of the study and did not show any treatment-related clinical signs.

Food consumption: The food consumption was normal in all animals except in one female of the highest dose group which consumed only a reduced food ration.

Body weight: The weights of the dogs in control, 80 and 400 ppm groups did not change virtually as compared to the initial weights. Precise values for the dogs in the highest dose group cannot be given because they remained only a very short time in the study, but seemed to be slightly reduced.

Neurological status: The reflexes and attitudinal reactions of the animals killed prematurely (high dose group) were intact, because of general weakness these animals could, however, only raise their heads when their righting reaction was checked. The dogs of all remaining groups produced no findings deviating from the intitial status.

Ophthalmoscopic examination and hearing tests did not reveal any substance-related effects.

Hematology, clinical chemistry, urinalysis: No statistical analysis was performed due to low animal number (2 dogs/sex/treatment group). Since the animals from the high dose group had to be sacrificed on study day 3 or 5, laboratory examinations were conducted at sacrifice. Signs of hemoconcentration (increase in erythrocytes, haemoglobin concentration, hematocrit, total number of leucocytes) were probably due to reduced water intake in this dose group. Clinical chemistry showed slightly increased total lipid values. ASAT and ALP were also increased at 2000 ppm. Urine which could be only collected from the males showed an increased specific weight. At 80 and 400 ppm no treatment-related effects were obvious.

Organ weights: The absolute and relative weights of the adrenals at 400 ppm were slightly, those at 2000 ppm were distinctly above the adrenal weights in control and 80 ppm groups.

Macroscopic examination: All animals of the 2000 ppm dose group showed distinct lobular marking of the liver, in 3 cases the organ was clay-brownish discoloured and the wall of the gall bladder of 3 animals showed subserous hemorrhages. In addition the iliac lymph nodes in all dogs of this group and all visible lymph nodes of one female were enlarged.

Histopathological examination: The dogs at 2000 ppm showed irreversible morphological manifestations of an intoxication with the test substance in the form of fatty degeneration of the liver, atrophy of splenic corpuscles, acute lymphadenitis, hemorrhages of the adrenal cortex, thymus atrophy and changes of the cerebellum. It cannot be excluded that the changes observed in one male dog at 400 ppm were treatment-related (slight siderosis in the general

section of the lung, a disputable atrophy of the thymus and hyperplasia of lymph follicles in the thyroid, and a slight but bilateral focal atrophy of a few testicular canaliculi).

Conclusion:

Due to the low animal number (2 dogs/sex/dose group) the study is of supplementary information only. Excessive toxicity was observed at the highest dose level of 2000 ppm. No clear effects could be observed at lower dose levels.

Repeated-dose (3-month) oral toxicity study of Hoe 33171 0H AT204 in dogs

Reference: *Brunk et al.*; 1981a; Doc. No. A24131 / Hoechst Report No. 674/81

Guideline: No guideline is mentioned in the study report. However, the study design is similar to OECD Guideline 409.

Deviations: Food consumption data and test substance intake were not presented. The animals were older (11 months) than the recommended age of maximum 9 months at the beginning of study.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

6 male and female Beagle dogs per dose group (strain: BEAK, source: Hoechst) were fed diets containing 0, 16, 80 or 400 ppm Fenoxaprop-ethyl for 3 months (test substance intake was not reported). From these animals 2 dogs/sex/dose group were used to test the reversibility of effects after a recovery period of 4 weeks after the end of dosing. At the beginning of the study the dogs were 11 months old and had an average body weight of 12.9 kg (males, range 10.9 – 14.9 kg) and 11.7 kg (females, range 10.0 – 15.2 kg). The purity of the test substance (Hoe 33171 0H AT204) was 96 % (according to certificate of analysis No. 01514).

Viability, clinical signs and food consumption were checked daily. Body weights were recorded weekly. The following additional investigations were performed before first dosing, after about 6 weeks, before end of dosing, and before end of recovery: neurological condition, ophthalmoscopic examinations, hearing test, teeth and visible mucous membranes examinations. Blood samples were taken from fasted animals before study, after about 4 and 8 weeks, before end of dosing and about 4 weeks after end of dosing in the recovery animals. The haematological examinations covered haemoglobin, erythrocytes, leukocytes, hematocrit, reticulocytes, Heinz bodies, differential blood count, thrombocytes and coagulation time. Clinical chemistry included sodium, potassium, inorganic phosphorus, uric acid, total bilirubin, direct bilirubin, creatinine, serum glucose, urea nitrogen, calcium, chloride, serum iron, cholesterol, triglycerides, total lipids, total protein, electrophoresis, methemoglobin (only final values), ASAT, ALAT, ALP and LDH. Urine was collected from each animal at the same times when blood samples were taken. The following parameters were determined at urinalysis: appearance, color, pH, protein, glucose, haemoglobin, bilirubin, ketone bodies, specific weight, sediment and urobilinogen. A liver function test (BSP, sulfobromophthalein sodium test) and a renal function test (PSP, phenolsulfonphthalein test) were performed before the start of the study, at the end of dosing and at the end of recovery. One day after the last dosing four males and four females of each group were sacrificed while recovery animals

were observed for about 4 weeks and then sacrificed 30 – 32 days after end of dosing. Dissection and macroscopic examination were performed directly after sacrifice. The weights of the following organs were recorded: heart, lungs, liver, kidneys, spleen, brain, pituitary, pancreas, ovaries, testes, adrenals, thyroid, thymus and prostate. Histopathological examinations were performed on the following organs: heart, lungs, liver, kidneys, spleen, adrenals, thyroid, pancreas, thymus, pituitary, cerebral cortex, brain stem, cerebellar cortex and medulla, medulla oblongata, eyes with optic nerves, urinary bladder, testes, ovaries, epididymides, uterus, prostate, midsternal bone marrow, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, gall bladder, tonsils, salivary glands (parotid and submandibular), lymph nodes (cervical and iliac), esophagus, trachea, aorta (thoracic), diaphragm, skeletal muscle (psoas) and skin with mammary gland. Statistical evaluation was performed on hematological and clinical chemistry values and the relative organ weights, except the following: differential blood count, Heinz bodies, methemoglobin, iron, electrophoresis, total protein, total lipids, triglycerides, LDH, cholesterol, liver function test, renal function test and gonad weights. The treated groups were compared with the control group, males and females separately except for organ weights.

Findings:

Mortality / Clinical Signs: All dogs survived up to the scheduled end of the study. There was no treatment-related impairment of the general condition.

Food consumption: The dogs always consumed their feed rations completely. No further information was presented in the study report.

Body weight: There was no perceptible effect on body weights. However, no statistical analysis was performed on the body weight data.

No substance-related changes were noted regarding neurological condition, ophthalmoscopy, hearing, teeth and visible mucous membranes.

Hematology, clinical chemistry and urinalysis: Changes attributable to the compound were not found. The significant differences from controls detected by statistical analysis were transient and still within the physiological range and considered not to be related to treatment.

Liver and renal function tests: No pathological retention values were measured in the liver function tests and no reduction in tubular excretion was seen in renal function tests.

Organ weight analysis: No statistical analysis was performed on absolute organ weights but only on relative organ weights. The only change observed was an increase in relative pituitary weight in males receiving 400 ppm. The relevance of this finding is not clear.

Table 83: 3 months feeding study in dogs with Fenoxaprop-ethyl
Organ weights after 13 weeks

	Dose group level (ppm)							
	Males				**Females**			
	0	**16**	**80**	**400**	**0**	**16**	**80**	**400**
Pituitary weight absolute (g)[1] relative (% bw)	60 0.0004	92 0.0007	82 0.0006	105 0.0007*	81 0.0007	83 0.0007	79 0.0006	87 0.0007

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: No treatment-related changes were observed.

Histopathological examination: Dogs receiving 16 ppm remained free of morphologically detectable organ changes whereas higher doses (80 and 400 ppm) obviously induced chronic interstitial pyelonephritis or at least promoted its development. This finding was noted at 80 ppm in 2/4 males from the main group and in 1/2 males after recovery, and at 400 ppm in 3/4 males and 3/4 females from the main group.

Conclusion:

No substance-related effects were noted in the dogs except an increased pituitary weight in males at 400 ppm and histopathological findings of interstitial pyelonephritis at 80 and 400 ppm in both sexes.

The NOAEL is considered to be 16 ppm (values in mg/kg bw/d are not presented in the study report).

Toxicological testing of Hoe 33171 – active ingredient technical by repeated oral administration to beagle dogs for one year

Reference: *Brunk et al*.; 1984; Doc. No. A29692 / Hoechst Report No. 84.0437
Amendment to report 84.0437, *Brunk et al*., 1987; Doc.No. A35727

Guideline: No guideline is mentioned in the study report. However, the study design is similar to OECD Guideline 452 (adopted 1981)

Deviations: Animals were 14 months of age. Urine volume, and some clinical chemistry values (gamma glutamyl transpeptidase, ornithine decarboxylase, albumin concentration) were not performed. At histopathology, spinal cord (cervical, thoracic, lumbar) and parathyroids were not assessed.

GLP: yes

No NOAEL could be defined in this study as no treatment-related effects were observed at any dose level. With this limitation the study is scientific valid and acceptable.

Material and Methods:

6 male and 6 female Beagle dogs per dose group (strain: BEAK, source: Hoechst) received diets containing 0, 3, 15 or 75 ppm Fenoxaprop-ethyl for 1 year (test substance intake was not reported). At the start of the study the dogs had a mean age of 14 months and a mean weight of 14.1 kg (males) or 12.5 kg (females). The test substance (Hoe 33171 0H ZC94 0001) had a purity of 94 % (according to certificate of analysis dated 27 April 1982). Homogeneity and stability of the mixture of test substance in the food were checked regularly. Premixes of the test substance in cornmeal were stirred daily into the diet.

Viability, clinical signs, behaviour and food consumption were checked daily. Body weights were recorded weekly. Additional investigations were performed before first dosing, then once every 3 months and before study termination: neurological status, ophthalmoscopic examinations, hearing test, dental and visible mucous membranes inspections. Blood samples were collected from fasted animals before the study, after approximately 6 weeks, at 3 monthly intervals, and before the termination of the study. The haematological examinations covered haemoglobin, erythrocytes, leukocytes, hematocrit, reticulocytes, Heinz bodies, differential blood count, thrombocytes, prothrombin time and methemoglobin. Clinical chemistry included sodium, potassium, inorganic phosphorus, uric acid, total bilirubin, direct bilirubin, creatinine, serum glucose, urea nitrogen, calcium, chloride, iron, cholesterol,

triglycerides, total lipids, total protein, electrophoresis, ASAT, ALAT, ALP and LDH. The 24-hour urine was collected from each animal at the same times when blood samples were taken. The following parameters were determined at urinalysis: appearance, color, pH, protein, glucose, haemoglobin, bilirubin, ketone bodies, specific gravity, urinary sediment and urobilinogen. A liver function test (BSP, bromsulphthalein sodium test) and a renal function test (PSP, phenolsulfonphthalein test) were performed before the start of the study, at three-monthly intervals and before the termination of the study. All animals were sacrificed on the day after the final application. Dissection and macroscopic examination were performed directly after sacrifice. The weights of the following organs were recorded: heart, lungs, liver, kidneys, spleen, brain, pituitary, pancreas, ovaries, testes, adrenals, thyroids, thymus, prostate and uterus. Histopathological examinations were performed on the following organs: heart, lungs, liver, kidneys, spleen, adrenals, thyroid, pancreas, thymus, pituitary, cerebral cortex, brain stem, cerebellum (cortex and marrow), medulla oblongata, eyes with optic nerve, urinary bladder, testes, ovaries, epididymides, uterus, prostate, stomach (fundus and prepyloric region), duodenum, jejunum, ileum, cecum, colon, rectum, gall bladder, tonsils, salivary glands (parotid and submandibular), lymph nodes (cervical and iliac), esophagus, trachea, aorta (thoracic), diaphragm, skeletal muscle (psoas), skin and mammary glands, and bone marrow (middle sternal segment). Statistical evaluation was performed on certain parameters of haematology (combined analysis for both sexes: erythrocytes, haemoglobin, hematocrit, reticulocytes, prothrombin time, leukocytes, thrombocytes) and clinical chemistry (analysis for each sex separately: calcium, total bilirubin, urea nitrogen, ASAT, ALAT, ALP, electrophoresis; combined analysis for both sexes: sodium, potassium, chloride, inorganic phosphorus, glucose, uric acid, creatinine, protein, cholesterin, triglycerides, iron, total lipids, LDH). Liver and renal function tests values were evaluated pooled for both sexes. For urinalysis parameters, specific weight and ph-value were evaluated statistically. Regarding organ weights, absolute and relative values were checked for statistical significance. In the amendment report of this study, body weights were evaluated statistically.

Findings:

Mortality / Clinical Signs: On study day 107 (after 106 applications) one male dog from the 15 ppm dose group had to be killed intercurrently because of very poor general condition (cachexia). This condition was not due to the treatment but caused by intestinal stenosis following fatty tissue necrosis, as was shown by autopsy and histological examination. All other dogs survived up to the scheduled end of the study.

The dogs in all groups (with the exception of the male receiving 15 ppm which had to be killed prematurely) remained in good health. Diarrhoea was observed on very few occasions in some animals from all groups including controls and was not substance-related.

Food consumption: With the exception of the male dog receiving 15 ppm which had to be killed prematurely, there was no noticeable inhibition of food intake.

Body weight: During the study there were occasionally statistically significant increased body weights observed in males at 15 ppm and 75 ppm. However, initial mean body weight of the animals of these dose groups was higher than those of controls at the beginning of the study therefore no relation to treatment is suggested.

No substance-related changes were noted regarding behaviour, neurological status, ophthalmoscopy, hearing, teeth and visible mucous membranes.

Hematology, clinical chemistry and urinalysis: At the beginning and throughout the study various statistical significancies were observed between control and treatment groups. These statistical differences were in general transient, not dose-related and described to be within the

physiological range of biological variation and therefore considered not to be related to treatment.

Liver and renal function tests: None of the measured parameters indicated impairment of hepatic or renal function.

Organ weight analysis: No statistically significant changes were recorded at organ weight analysis.

Macroscopic examination: No substance-related changes were observed at the scheduled dissection. The male which was sacrificed intercurrently due to very poor general health showed numerous adhesions of the intestinal loops and in particular a localized luminal constriction caused by an egg-sized thickening of the wall of the small intestine. One female from the 3 ppm dose group showed extensive adhesions throughout the whole abdominal organ region.

Histopathological examination: No organic changes attributable to treatment with the test substance were found.

Conclusion:

No substance-related effects were noted at any concentration of Fenoxaprop-ethyl in the food.

The NOAEL is considered to be larger than 75 ppm (values in mg/kg bw/d are not presented in the study report).

4.7.1.2 Repeated dose toxicity: inhalation

Table 84: Repeated dose toxicity: inhalation with Fenoxaprop-P-ethyl

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Wistar rat 28 day inhalation *Hofmann T. et al., 1989*	0, 0.015, 0.07 and 0.3 mg/L air	0.015 mg/L	**- haematology and clinical chemistry findings** **- increased liver weight** - ≥ 0.015 mg/L: ↑ liver weights with no corresponding histopathology - ≥ 0.07 mg/L: ↓ thromboplastin time (M), ↓ Ca (M) - 0.3 mg/L: ↓ body weight gains, ↓ hemoglobin and hematocrit values, ↑ activated partial thromboplastin time (F), changes in lipid status, ↓ urea nitrogen, ↑ kidney weights with no corresponding histopathology

Hoe 046360 – substance technical. Testing for subchronic inhalation toxicity (28 applications within 40 days) in male and female Wistar rats

Reference: *Hofmann T. et al*.; 1989; Doc. No. A40799 / Hoechst Report No. 89.0584

Guideline: OECD Guideline 412 (1981), EPA Guideline 82-4 (revised 1984), EC Guideline B.8 (1984)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

15 male and 15 female Wistar rats per dose group (strain: WISKf(SPF71), source: Hoechst) were exposed to 0, 0.015, 0.07 or 0.3 mg/L (analytical) dust of Fenoxaprop-P-ethyl by nose-only inhalation. The duration of exposure was 6 hours/day and 5 days/week, with a total number of 28 exposures within 40 days. 10 rats/sex/dose group were necropsied 1 day after final exposure while 5 rats/sex/dose group were sacrificed the day after the recovery period of 28 days. At the beginning of the study the rats were about 5 – 6 weeks old and weighed 121 – 132 g (males) and 118 – 132 g (females). The test substance (Hoe 046360 0H ZC96 0002) showed a purity of 95.6 % (according to certificate of analysis No. 02912). The inhalation chambers operated under dynamic conditions. 98 % of the particles had an aerodynamic diameter less than 7 µm in all treatment groups, and 22 – 49 % were less than 1 µm.

Behaviour and clinical signs were observed at least once daily in all groups. Body weights and food consumption were recorded twice weekly, and water consumption once weekly. Ophthalmoscopic examinations were performed at the start and at the termination of the study. Blood samples were taken at study termination and after recovery period without fasting of the animals. Urine was collected from 10 rats/sex/dose group a few days before study termination by using metabolism cages. Food and water were withdrawn during this period. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, leukocyte count, thrombocyte count, differential leucocyte count, red cell morphology, reticulocyte count, Heinz bodies, coagulation time, thromboplastin time, methemoglobin and activated partial thromboplastin time. In clinical chemistry the following parameters were assessed: sodium, potassium, anorganic phosphorus, bilirubin total and direct, creatinine, serum-glucose, urea nitrogen, calcium, chloride, ASAT, ALAT, ALP, GGT, cholesterol, triglycerides, total lipids, total protein and electrophoresis (albumin, globulin). Urinalysis included appearance, colour, pH-value, haemoglobin, protein, glucose, ketone bodies, bilirubin, urobilinogen, nitrite, ascorbic acid, specific weight and sediment. All animals were checked for macroscopic changes. The following organ weights were recorded: heart, lung, liver, kidneys, spleen, testes (without epididymides), ovaries, adrenals, pituitary, thyroid gland and brain. Histopathological examinations were performed on all animals of the main and recovery groups and included the following organs: heart, lung, liver, kidneys, spleen, stomach, jejunum, colon, oesophagus, duodenum, rectum, nasal cavity, urinary bladder, testes, epididymides, prostate gland, seminal vesicles, ovaries, uterus, thyroid gland, aorta, ileum, diaphragm, nasopharynx, pancreas, adrenal gland, thymus, pituitary gland, brain, eye with optic nerve, bone marrow (femur), trachea, salivary glands, caecum, skeletal muscle and turbinates.

Findings:

Mortality / Clinical Signs: No deaths and no clinical signs of toxicity were observed during the study. Irregular breathing occurred during exposure in all groups including the control group and is therefore not considered to be substance-related.

Food and water consumption: Food consumption remained unaffected by the treatment. A slight increase in water consumption was observed in females exposed to 0.3 mg/L.

Body weight: Body weight gain was impaired in females exposed to 0.3 mg/L, which was statistically different from controls only on study days 8, 12 and 22. In males exposed to 0.3 mg/L, body weight gain was also slightly lower than those of controls, but without any statistical significance.

Table 85: Subchronic inhalation toxicity study in rats with Fenoxaprop-P-ethyl Food and water consumption (complete study) and body weights (terminal, recovery)

	Dose group level (mg/L air)							
	Males				**Females**			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**
Food consumption (g/day)	20.1	20.9	21.0	20.1	16.6	16.7	16.8	16.3
Water consumption (g/day)	29.2	29.7	30.6	29.1	23.7	25.5	24.4	25.9
Body weight gain study days 1 – 41 (g)	98	107	109	87	51	54	53	46
Terminal body weight on study day 41 (g)	255	272	258	241	206	212	206	196
Terminal body weight recovery (g)	341	349	378*	351	234	231	239	229

* (p = 0.05); significantly different from controls

Ophthalmological examinations: No abnormalities were noted at examinations.

Hematology: Hemoglobin and hematocrit concentrations were decreased in males of the high dose group (0.3 mg/L) after treatment and recovery period. Thromboplastin time was decreased in males exposed to 0.07 and 0.3 mg/L, which was reversible for the 0.07 mg/L dose group. In females, activated partial thromboplastin time was increased in the high dose group (0.3 mg/L). The effects on coagulation parameters were only slight but a relation to treatment cannot be ruled out. In other cases of statistical significance no dose-dependency was observed and no treatment-relation is considered.

Table 86: Subchronic inhalation toxicity study in rats with Fenoxaprop-P-ethyl Relevant haematology findings on study day 41 and after recovery

	Dose group level (mg/L air)							
	Males				**Females**			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**
Haemoglobin (g/L)								
study day 41	154	152	150	139*	135	142	142	138
after recovery	157	146*	149	147*	140	146	142	144
Hematocrit (unity)								
study day 41	0.46	0.45	0.45	0.41*	0.41	0.43	0.42	0.41
after recovery	0.48	0.45	0.44	0.43*	0.43	0.44	0.43	0.43
Thromboplastin time (s)								
study day 41	11.8	9.9	9.7*	9.7*	9.4	9.3	9.7	9.3
after recovery	11.3	10.5	10.2	9.8*	9.6	9.5	9.8	9.4
Activated partial thromboplastin time (s)								
study day 41								
after recovery	14.0	13.8	14.2	14.2	12.6	13.1	15.2	14.4*
	12.5	11.9	13.6	12.7	16.5	16.2	15.0	14.6

* (p = 0.05); significantly different from controls

Clinical chemistry: At the highest exposure level (0.3 mg/L) the following effects have been observed: increased urea nitrogen (males, females), decreased cholesterol (males, females), increased triglycerides (males), decreased total lipids (males, females) and decreased alpha-2 globulin levels (males). The toxicological relevance of further statistical signficancies remains unclear: decreased sodium level (females, 0.3 mg/L), decreased calcium levels (males, 0.07 and 0.3 mg/L) and decreased chloride level (males, 0.3 mg/L). All these changes were reversible after the recovery period of 28 days. Other statistical significances were within the normal range or showed no dose-dependency. A compound-related effect is thus not appearant.

Table 87: Subchronic inhalation toxicity study in rats with Fenoxaprop-P-ethyl Relevant clinical chemistry findings on study day 41 and after recovery

	Dose group level (mg/L air)							
	Males				**Females**			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**
Sodium (mmol/L)								
study day 41	145	143	144	145	146	145	143	141*
after recovery	145	146	150*	148	142	150*	143	146
Calcium (mmol/L)								
study day 41	2.63	2.68	2.49*	2.47*	2.68	2.62	2.60	2.65
after recovery	2.63	2.62	2.76*	2.67	2.48	2.64*	2.62	2.64*
Chloride (mmol/L)								
study day 41	104	103	102	101*	102	103	103	101
after recovery	101	102	101	103	102	106*	105	107*
Urea nitrogen (mmol/L)								
study day 41	7.3	8.3	7.2	9.1*	7.3	8.8	7.9	10.0*
after recovery	8.7	9.2	8.3	7.9	11.0	8.9	9.5	9.9
Cholesterol (mmol/L)								
study day 41	1.34	1.35	1.19	1.02*	1.25	1.15	1.23	0.91*
after recovery	1.46	1.51	1.50	1.33	1.35	1.38	1.50	1.58
Triglycerides (mmol/L)								
study day 41	1.65	1.67	1.89	2.10*	1.46	1.12	1.11	1.41
after recovery	1.24	1.45	1.51	1.31	1.42	1.18	1.43	1.29
Total lipids (g/L)								
study day 41	3.45	3.22	3.33	3.03*	4.25	3.71	4.33	3.71*
after recovery	3.86	4.06	4.04	4.83	4.10	3.82	4.00	4.27
Alpha-2 globulin								
study day 41	0.057	0.059	0.049	0.040*	0.045	0.046	0.042	0.050
after recovery	0.055	0.061	0.069	0.064	0.040	0.049	0.051	0.048

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

Urinalysis: No treatment-related effects were observed.

Organ weight analysis: After treatment period, males showed an increase in absolute liver weights (0.015 mg/L and above) and relative liver weights (0.07 mg/L and above). In females, absolute and relative liver weights were increased only at the highest dose group (0.3 mg/L). In kidneys, an increase in absolute weight was observed in the highest dose group (0.3 mg/L) in males, while relative kidney weight was increased in both males and females (0.3 mg/L). The effects on liver and kidney weight were largely reversible after a recovery period of 28 days. The relevance of the slightly decreased absolute testes weight in the highest dose group remains unclear and could not be confirmed at recovery.

Table 88: Subchronic inhalation toxicity study in rats with Fenoxaprop-P-ethyl Relevant organ weight findings on study day 41 and after recovery

	Dose group level (mg/L air)							
	Males				**Females**			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**
Liver weight Day 41								
absolute (g)	8.15	9.20*	9.96*	11.50*	7.75	8.20	8.16	8.70*
relative (% bw)	3.202	3.386	3.848*	4.779*	3.769	3.873	3.966	4.443*
Liver weight Recovery								
absolute (g)	10.76	12.12	12.55	12.15	8.29	7.80	8.14	8.14
relative (% bw)	3.154	3.470*	3.317	3.451*	3.555	3.377	3.409	3.545
Kidney weight Day 41								
absolute (g)	1.59	1.69	1.72	1.78*	1.42	1.49	1.49	1.47
relative (% bw)	0.627	0.620	0.667	0.740*	0.692	0.702	0.727	0.749*
Kidney weight Recovery								
absolute (g)	2.11	1.92	2.22	2.07	1.49	1.41	1.47	1.45
relative (% bw)	0.616	0.551	0.588	0.590	0.641	0.611	0.615	0.629
Testes weight Day 41								
absolute (g)	2.97	2.88	2.94	2.56*	-	-	-	-
relative (% bw)	1.167	1.054	1.131	1.061				
Testes weight Recovery								
absolute (g)	3.03	2.89	3.29	3.16	-	-	-	-
relative (% bw)	0.892	0.822	0.872	0.903				

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

Macroscopic examination / Histopathological examination: No compound-related macroscopically visible changes were found at necropsy. The histopathological examinations also revealed no treatment-related findings.

Conclusion:

The main target organ of Fenoxaprop-P-ethyl was the liver (organ weight changes, effects in lipid metabolism), with effects being more pronounced in males than in females. Increased absolute (all dose groups) and relative (0.07 mg/L and above) liver weights were recorded. Effects on lipid metabolism were evident at 0.3 mg/L. Furthermore, slight changes were noted in haematology at 0.07 mg/L and above. Another target organ of Fenoxaprop-P-ethyl was the kidney, with increases of absolute and/or relative organ weights being observed in both sexes at 0.3 mg/L.

In conclusion, the NOAEL is considered to be 0.015 mg/L.

4.7.1.3 Repeated dose toxicity: dermal

Table 89:: Repeated dose toxicity: dermal with Fenoxaprop-P-ethyl

Study; Reference	Dose levels	NOAEL	Relevant effects (in bold for setting the NOAEL)
Wistar rat 21 day dermal application *Ebert E. et al., 1988*	0, 10, 20, 100 and 500 mg/kg bw/d	20 mg/kg bw/d	**- increased kidney weight** - ≥ 20 mg/kg: ↑ relative kidney weights (both sexes at 100 and 500 mg/kg, females only at 20 mg/kg) - ≥ 100 mg/kg: ↓ erythrocytes, haemoglobin, hematocrit, thromboplastin time, activated partial thromboplastin time, cholesterol and total lipid levels, ↑ relative liver weights - 500 mg/kg only: ↓ body weights, ↓ activated partial thromboplastin time (M), ↑ heart and spleen weights

Hoe 046360 – active ingredient technical. Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rat

Reference: *Ebert E. et al.*; 1988; Doc. No. A40800 / Hoechst Report No. 88.1774

Guideline: OECD Guideline 410 (adopted 1981), EPA Guideline 82-2 (1982)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

6 Wistar rats/sex/dose group (strain: WISKf(SPF71), source: Hoechst) received dermal applications of 0, 10, 20, 100 or 500 mg/kg bw/d Fenoxaprop-P-ethyl. Additional 6 rats/sex were assigned to recovery groups at dose levels of 0, 100 and 500 mg/kg bw/d. At the beginning of the study the rats were about 6 weeks old and weighed 198 – 230 g (males) and 186 – 214 g (females). The test substance (Hoe 046360 0H ZC96 0002) had a purity of 95.6 % (according to certificate of analysis No. 02912). At the start of the study period and subsequently at least once weekly, the hair on the dorsal treatment sites (10% of total body surface) was removed with an electric clipper. The test substance (vehicle: sesame oil) was applied to the intact dorsal skin once daily from Mondays to Fridays. During the 30-day study period, 21 work-day dermal treatments were performed. The concentrations of the test substance which were prepared daily were 1, 2, 10 or 25 % in sesame oil, with a constant application volume of 1 or 2 ml/kg bw/d. Exposure took place for a period of 6 hours under an occlusive bandage. After removal of the bandage the treated skin areas were washed with warm water. The animals in the main groups were killed one day after the final treatment, those in the recovery groups 15 days after the end of treatment.

Behaviour and clinical signs were observed at least once daily in all groups. The animals were examined weekly for neurological disturbances, opacity of the refractory media of the eyes, damage to the oral mucosa and impairment of dental growth. The macroscopically visible

changes and irritant effects on the treated skin were examined before each application according to Draize. Body weights and food consumption were recorded twice weekly and water consumption once weekly. Blood samples were taken at study termination and after recovery period without fasting of the animals. Urinalysis was carried out on day 24 of the study for the males and females of the main groups. The urine of the fasted animals was collected during the night (about 16 hours) from each animal. Hematology consisted of erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, leukocytes, thrombocytes, differential blood count, reticulocytes, Heinz bodies, coagulation time, thromboplastin time and activated partial thromboplastin time. In clinical chemistry the following parameters were assessed: sodium, potassium, inorganic phosphorus, uric acid, total bilirubin, creatinine, serum glucose, urea nitrogen, calcium, chloride, ASAT, ALAT, ALP, LDH, GGT, cholesterol, triglycerides, total lipids, total protein and electrophoresis. Urinalysis included appearance, colour, pH-value, haemoglobin, protein, glucose, ketone bodies, bilirubin, urobilinogen, ascorbic acid, nitrite, sediment and volume of urine. All animals were checked for macroscopic changes. The following organ weights were recorded: heart, lungs, liver, kidneys, spleen, brain, testes (without epididymides), ovaries, adrenals, pituitary, thyroid gland (both lobes) and thymus. Histopathological examinations were performed on all animals of the main and recovery groups and included the following organs: heart, lung, liver, kidneys, spleen, brain, testes, ovaries, adrenals, pituitary, thyroid (both lobes), seminal vesicles, stomach, small intestine, large intestine, urinary bladder, prostate, uterus, epididymides (both), thymus, both eyes with optic nerve, bone marrow, pancreas, any macroscopic abnormalities and approximately 2 x 2 cm pieces of treated and untreated skin.

Findings:

Mortality / Clinical Signs: There was no mortality during the treatment or recovery period. Behaviour and general health condition showed no treatment-related effects. No signs of neurological disturbance, opacity of the refracting media of the eyes, damage to the oral mucosa or impairment of dental growth were observed in any group.

Findings on treated skin: Neither erythema nor edema were observed on the treated skin area of the animals. However, dry and chapped skin, and fine or coarse scales were noted during treatment and recovery period in some of the animals. In males, these changes on the surface of the skin were seen from study day 4 – 10 in all treatment groups including controls, and from study day 22 - 30 in the 100 and 500 mg/kg dose group. During recovery, these changes were visible from study day 30 – 37 only in the highest dose group (500 mg/kg). In females, the treated areas of some of the animals of control and treatment groups showed dry and chapped skin with fine scales from study day 4 – 9 and 14 – 17. From study day 21 – 30 and during recovery study day 31 – 32, such findings were observed only in the 100 and 500 mg/kg dose groups.

Food and water consumption: The food and water consumption remained unaffected by the test substance in all dose groups.

Body weight: The body weight gains in the highest dose group (500 mg/kg) appeared to be slightly retarded in both males and females.

Table 90: Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl Food consumption (complete study) and body weights (main study, recovery)

	Dose group level (mg/kg bw/d)									
	Males					**Females**				
	0	**10**	**20**	**100**	**500**	**0**	**10**	**20**	**100**	**500**

	Dose group level (mg/kg bw/d)									
	Males					**Females**				
	0	**10**	**20**	**100**	**500**	**0**	**10**	**20**	**100**	**500**
Food consumption (mg/kg bw/d)	9.8	10.3	10.1	9.5	10.0	9.9	10.0	10.2	10.1	10.0
Body weight on day 1 (g)	227	230	228	231	222	214	213	213	212	214
Terminal body weight after main study (g)	327	330	319	330	319	240	238	230	228	230
Terminal body weight after recovery (g)	362	-	-	369	356	252	-	-	251	244

Hematology: Erythrocyte count, haemoglobin, and hematocrit values were significantly decreased in males receiving 100 and 500 mg/kg. Thromboplastin time and activated partial thromboplastin time were reduced in males at 500 mg/kg. In females, thromboplastin time was only reduced at 100 mg/kg, while the number of reticulocytes was decreased at 500 mg/kg. All of these effects were reversible during recovery period.

Table 91: Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl Relevant haematology findings after treatment and recovery

	Dose group level (mg/kg bw/d)									
	Males					**Females**				
	0	**10**	**20**	**100**	**500**	**0**	**10**	**20**	**100**	**500**
Erythrocyte count (10^{12}/L)										
after treatment	8.06	7.89	7.59	7.55*	7.56*	7.80	8.04	7.92	8.15	7.65
after recovery	8.26	-	-	8.07	7.65	7.53	-	-	7.38	7.38
Haemoglobin (g/L)										
after treatment	153	149	146	145*	143*	146	151	149	151	142
after recovery	153	-	-	146	143	140	-	-	141	138
Hematocrit (unity)										
after treatment	0.48	0.47	0.45	0.44*	0.43*	0.46	0.46	0.46	0.47	0.44
after recovery	0.47	-	-	0.45	0.43	0.43	-	-	0.43	0.43
Reticulocytes (unity)										
after treatment	0.033	0.035	0.023	0.028	0.021	0.045	0.042	0.036	0.045	0.026
after recovery	0.067	-	-	0.046	0.025 *	0.013	-	-	0.023	* 0.010
Thromboplastin time (s)										
after treatment	13.2	13.2	12.1	11.2	11.1*	11.7	12.2	10.1	9.4*	9.7
after recovery	11.3	-	-	11.5	11.5	11.1	-	-	10.4	11.2
Activated partial thromboplastin time (s)										
after treatment	21.2	20.8	18.8	18.6	18.2*	17.7	20.7	19.9	19.7	20.0
after recovery	19.3	-	-	19.8	20.0	19.2	-	-	18.4	-[1]

* (p = 0.05); significantly different from controls
[1] not readable in study report

Clinical chemistry: Clear treatment-related effects were observed in the two highest dose groups (100 and 500 mg/kg): cholesterol was decreased in males receiving 100 and 500 mg/kg and in females receiving 500 mg/kg. Total lipids were decreased in males (100 and 500 mg/kg) only. These effects on lipid metabolism were partially reversible during recovery. Slightly changed sodium and chloride levels were observed in both males and females in the

highest dose group. Other statistical significancies were not dose-related and within biological variation and therefore not considered as toxicologically relevant.

Table 92: Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl Relevant clinical chemistry findings after treatment and recovery

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Sodium (mmol/L)										
after treatment	142	142	143	143	146*	144	143	143	142	141*
after recovery	143	-	-	141	145	143	-	-	142	140*
Chloride										
after treatment	104	102	103	102	102*	106	104	105	102	104*
after recovery	105	-	-	103	104	105	-	-	106	105
Cholesterol (mmol/L)										
after treatment	1.60	1.54	1.40	1.19*	1.10*	1.48	1.54	1.45	1.15	1.05*
after recovery	1.92	-	-	1.66	1.58*	1.77	-	-	1.73	1.56
Total lipids (g/L)										
after treatment	3.58	3.37	3.33	3.13*	3.25*	3.34	3.38	3.34	3.41	3.43
after recovery	4.66	-	-	4.64	4.15*	4.18	-	-	4.35	4.09

* (p = 0.05); significantly different from controls

Urinalysis: No treatment-related effects were observed.

Organ weight analysis: Absolute liver weight was increased in males receiving 500 mg/kg, while relative liver weight was increased in both males (100 and 500 mg/kg) and females (500 mg/kg). Males receiving 500 mg/kg showed an increased absolute kidney weight, while relative kidney weight was increased in both males (100 and 500 mg/kg) and females (20, 100 and 500 mg/kg). The relevance of the decrease in absolute and relative spleen and heart weights in males receiving 500 mg/kg is not clear. The effects on liver, kidney and spleen were reversible after the recovery period, while heart weights still remained decreased after recovery.

Table 93: Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl Statistically significant organ weight findings after treatment and recovery

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Liver absolute										
after treatment	12.65	13.32	12.85	14.70	17.31*	9.02	9.41	8.95	9.50	10.39
after recovery	13.65	-	-	13.79	13.75	9.07	-	-	9.53	9.44
Liver relative										
after treatment	3.866	4.033	4.030	4.449*	5.414*	3.761	3.960	3.890	4.151	4.526*
after recovery	3.766	-	-	3.741	3.867	3.597	-	-	3.798	3.863
Kidney absolute										
after treatment	2.12	2.23	2.19	2.34	2.40*	1.55	1.67	1.70	1.69	1.72
after recovery	2.27	-	-	2.22	2.23	1.59	-	-	1.54	1.60
Kidney relative										
after treatment	0.650	0.674	0.688	0.710*	0.750*	0.646	0.701	0.739*	0.739*	0.749*
after recovery	0.627	-	-	0.604	0.628	0.630	-	-	0.614	0.654
Spleen absolute										
after treatment	0.61	0.63	0.56	0.55	0.46*	0.49	0.45	0.49	0.45	0.44
after recovery	0.59	-	-	0.58	0.62	0.48	-	-	0.51	0.44

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Spleen relative										
after treatment	0.187	0.191	0.177	0.165	0.144*	0.206	0.189	0.215	0.197	0.193
after recovery	0.163	-	-	0.156	0.175	0.189	-	-	0.202	0.181
Heart absolute										
after treatment	1.26	1.26	1.15	1.11	1.04*	0.93	0.87	0.94	0.90	0.94
after recovery	1.44	-	-	1.28	1.19*	0.93	-	-	0.98	0.94
Heart relative										
after treatment	0.387	0.381	0.363	0.336	0.325*	0.385	0.366	0.407	0.394	0.408
after recovery	0.398	-	-	0.349	0.334*	0.369	-	-	0.391	0.382

* (p = 0.05); significantly different from controls

Macroscopic examination / Histopathological examination: The macroscopic and microscopic examinations gave no indications of substance-related changes in the internal organs. In particular, no pathomorphological changes were found in the liver or the kidneys. Due to the application technique, hyperkeratosis and epidermal thickening were present on the treated skin areas, ranging in degree from slight to moderate. These effects were observed in all groups including controls, but seemed to be more frequent in the highest dose group.

Table 94: Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl Histopathological findings on treated skin area after treatment and recovery

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Hyperkeratosis										
after treatment	0/6	0/6	2/6	0/6	5/6	0/6	0/6	0/6	0/6	5/6
after recovery	2/6	0/6	0/6	3/6	3/6	1/6	0/6	0/6	0/6	0/6
Epidermal thickening										
after treatment	0/6	3/6	4/6	1/6	4/6	2/6	2/6	1/6	3/6	6/6
after recovery	0/6	0/6	0/6	3/6	4/6	1/6	0/6	0/6	0/6	0/6

Conclusion:

A slight but statistically non-significant decrease in body weight appeared at the highest dose level of 500 mg/kg bw/d. Clear effects on liver and kidney (lipid metabolism, increased organ weights) were observed in this study at 100 mg/kg bw/d and above. Furthermore, slight effects on haematology were observed in males at 100 and 500 mg/kg.

In conclusion, the NOAEL is considered to be 20 mg/kg bw/d.

4.7.1.4 Repeated dose toxicity: other routes

No data

4.7.1.5 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.7.1.6 Other relevant information

See 4.12.1.3 Specific investigations: other studies

4.7.1.7 Summary and discussion of repeated dose toxicity

Oral Rats: Fenoxaprop-P-ethyl induced comparable effects in the 28 day dose finding study and the 13 week feeding studies in Wistar rats.

28 days: Reductions of body weight gain and food consumption were found at doses of 320 ppm and above, while terminal bodyweight was reduced at 1280 ppm and were more distinct in males than in females. Severe toxicity was observed in all animals receiving 5210 ppm leading to an interim kill in extremis. No further examination (e.g. histopathology) was made for this group. Thromboplastin time and partial thromboplastin time were increased in males at 1280 ppm, while thromboplastin time was decreased in females at 80 ppm and above. In clinical chemistry, the most striking effects were observed on lipid metabolism and liver enzymes partly beginning at a concentration of 80 ppm. Total cholesterol, HDL-cholesterol and HDL-phospholipid levels were decreased in males, while triglyceride levels were increased in both sexes. Regarding liver enzymes, ALP and LAP levels were increased (significant at 1280 ppm). Slight effects on plasma electrolytes were noted, with decreased calcium levels at 320 ppm and above. Albumin levels were increased in males at 320 ppm and above and in females at 1280 ppm. Changes in lipid metabolism were also reflected in urinalysis, where increased ketone bodies were noted at 80 ppm and above. Also, bilirubin and urobilinogen scores were increased at the same dose level and above, however showing no clear dose pattern in females. Organ weight analysis demonstrated effects on liver and kidney with increases in relative and/or absolute organ weights at dose levels of 320 ppm and above.

13-weeks: Reductions of body weights were found at doses of 640 ppm and above and were more distinct in males than in females. The effects on haematology at 640 ppm comprised decreases in haemoglobin, hematocrit and MCV as well as increased MCHC. Thromboplastin time and partial thromboplastin time were increased in males at 640 ppm, while thromboplastin time was decreased in females. In clinical chemistry, the most striking effects were observed on lipid metabolism and liver enzymes partly beginning at a concentration of 80 ppm in both sexes. Total cholesterol, HDL-cholesterol and HDL-phospholipid levels were decreased (more pronounced in males) while triglyceride levels were increased. Regarding liver enzymes, ALP levels were increased. Slight effects on plasma electrolytes were noted in both sexes, with decreased calcium and increased sodium levels at 80 ppm and above. Total protein was decreased. Changes in lipid metabolism were also reflected in urinalysis where increased ketone bodies were noted in males at 80 ppm and above. Also, bilirubin and urobilinogen scores were increased at the same dose level and above. Organ weight analysis demonstrated effects on liver and kidney with increases in relative and/or absolute organ weights at dose levels of 80 ppm and above. Effects on the target organs were obvious also at macroscopic examination where enlargements of liver (both sexes, 640 ppm) and kidneys (females, 80 and 640 ppm) were noticed. Furthermore, histopathology revealed centrilobular hypertrophy in the 640 ppm dose group.

Oral Mice:

28 days: An increase in body weight was observed in the 28 day study at the highest dose level of 1280 ppm in females, which was discussed to be caused by the markedly increased liver weight in these animals. Haematology was not performed in the 28 day study. Clinical chemistry evaluations revealed marked effects on lipid metabolism and liver enzymes at concentrations of 320 ppm and above. Phospholipids and total cholesterol were decreased in males. Liver enzymes (ASAT, ALAT and ALP) and total protein and albumin levels were increased in males and females at 1280 ppm. Absolute and/or relative liver weights were increased in males and females starting at a dose level of 320 ppm. For kidney weights, effects were evident at 1280 ppm. Effects on liver and kidney were also confirmed at histopathological evaluation. In the liver, hepatocellular hypertrophy, single cell necrosis and increased mitotic activity were observed at 320 ppm and above and were more pronounced in males than in females. In kidneys, tubular injury was more marked in females than in males and was noted starting at doses of 320 ppm.

13 weeks: Marginal effects in haematology were noticed in the highest dose group (640 ppm) (increased MCV, reticulocytes and platelets). Clinical chemistry evaluations revealed effects on lipid metabolism and liver enzymes at concentrations of 640 ppm. Phospholipids and total cholesterol were decreased in males while total cholesterol was increased in females. Liver enzymes (ASAT, ALAT and ALP) and total protein and albumin levels were increased (significantly in males). An increase of urea in females at 640 ppm suggested changes in kidney function. Absolute and/or relative liver weights were increased in males and females starting at a dose level of 80 ppm. For kidney weights, clear effects were evident at 640 ppm. Macroscopic examination showed enlarged livers (males, females) and irregular kidney surface (females) at 640 ppm. Effects on liver and kidney were also confirmed at histopathological evaluation. In the liver, hepatocellular hypertrophy, single cell necrosis and increased mitotic activity were observed at 640 ppm. In kidneys, tubular injury was more marked in females than in males and was noted starting at doses of 80 ppm (1/10 females).

Oral Dogs:

28 days: The 28 day feeding study served as a dose finding study and employed only 1 animal per sex per dose group that is why no statistical analysis could be performed. No obvious treatment-related effects could be found in this study.

13 weeks: The 13 week feeding study which was performed according to EPA Guideline is valid and acceptable and showed the following results: a decrease in body weight gain was only observed at the highest dose of 2000 ppm in males. Some liver toxicity was demonstrated by increased ASAT and LDH levels in males and a decrease in ALAT in both sexes at 2000 ppm. Also, total protein levels were increased in this dose group. No statistically significant changes were noted at organ weight analysis. No treatment-related effects were seen at macroscopical and microscopical examination.

Inhalation Rat: Body weight gains were decreased transiently but significantly during the study in the highest concentration of 0.3 mg/L. Hemoglobin and hematocrit values were decreased in males at 0.3 mg/L. Thromboplastin time was shortened in males at 0.07 and 0.3 mg/L, while activated partial thromboplastin time was prolonged in females exposed to 0.3 mg/L. Changes in lipid status (higher triglyceride levels, lower cholesterol and total lipid levels) were observed in both sexes at 0.3 mg/L. Furthermore, urea nitrogen was increased at this concentration. Marginal decreases of sodium (females), and calcium and chloride (males) were also noted. Liver weight was more affected in males with absolute organ weights being

increased already at 0.015 mg/L and above, while relative liver weights were elevated at 0.07 mg/L and above. In females, absolute and relative liver weights were increased only at the highest dose of 0.3 mg/L. Regarding kidney weights, increases in absolute and/or relative organ weights were observed in both sexes exposed to 0.3 mg/L. No treatment-related effects were seen at macroscopical and microscopical examination.

Dermal Rat: Hematology revealed findings in males at 100 and/or 500 mg/kg (decreased erythrocytes, haemoglobin, hematocrit and activated partial thromboplastin time). Thromboplastin time was decreased in both sexes. In clinical chemistry, effects on lipid metabolism were more distinct in males and included decreased cholesterol and total lipid levels at doses of 100 and 500 mg/kg. Marginal effects on sodium and chloride were observed in males and females receiving 500 mg/kg. Relative liver weights were increased in males at 100 and 500 mg/kg and in females at 500 mg/kg. On the other hand, relative kidney weights were increased in males at 100 and 500 mg/kg while females were affected at 20 mg/kg and above, however without a clear dose-relation. Absolute and relative heart and spleen weights were elevated in males at 500 mg/kg only.

Supportive information fenoxaprop-ethyl

Oral Rats:

32 days: Excessive toxicity was found at a dose level of 5000 ppm leading to a premature sacrifice of these animals. A reduction in body weight gain was observed at a dose level of 1250 ppm. Changes in lipid status were observed at doses of 80 ppm and above (decreased cholesterol and total lipids). Signs of hepatotoxicity were demonstrated by increased ALP levels at 1250 ppm. Elevated relative liver weights were observed at doses of 315 ppm and higher. This finding was accompanied with an enlargement of hepatocytes, with effects being more marked in males than in females. Also, relative kidney weights were increased at doses of 80 ppm and above.

90 days: Hematological effects were observed at 320 ppm (decreased haemoglobin and erythrocyte levels, more pronounced in males). Changes in lipid status were observed at doses of 20 ppm and above (decreased cholesterol and total lipids). Signs of hepatotoxicity were demonstrated by increased ALP levels at 320 ppm. Increased relative liver and kidney weights were observed at doses of 320 ppm. This finding was accompanied with an enlargement of hepatocytes, with effects being more marked in males than in females. Relative adrenal weights were increased in females at doses of 80 ppm and above. Relative thyroid weight was significantly increased in males at 320 ppm.

Oral Mice:

30 days: Clinical chemistry revealed effects on the lipid status (increased total lipids and cholesterol at 20 and/or 80 ppm. An increase of relative liver weight was already observed at a dose level of 20 ppm. Histopathological examination of the livers revealed enlargement of hepatocytes starting at a dose level of 20 ppm. One male receiving 80 ppm showed additionally signs of hypertrophy.

32 days: 5000 ppm Fenoxaprop-ethyl led to excessive toxicity and subsequently to an interim sacrifice of animals in the 32-day feeding study. Histopathological examination of this group

showed additionally to eosinophil, fine-granulated cytoplasm and enlargement of hepatocytes, necrosis of hepatocytes and Kupffer`s cell proliferation. Decrease in haemoglobin could be found at 1250 ppm. Elevated levels of liver enzymes (315 ppm and above) were indicative of hepatotoxicity. An increase of relative liver weight was already observed at a dose level of 80 ppm. Histopathological examination of the livers revealed enlargement of hepatocytes starting at a dose level of 80 ppm. Kidneys weights were increased in females at 315 ppm and above which was accompanied by focal tubular necrosis (2/10 females).

90 days: An increased body weight was observed at 640 ppm and higher, which was discussed to be a result of markedly increased liver weight in these dose groups. Hematological effects were observed at doses of 320 ppm and/or above including a decrease in erythrocytes and thrombocytes, and an increase in MCV, reticulocytes and leucocytes. Clinical chemistry revealed effects on the lipid status (increased triglycerides at 640 ppm and above), and on bilirubin (increased at 320 ppm and above), total protein (increased at 640 ppm and above) and albumin (increased at 320 ppm and above). Elevated levels of liver enzymes (320 ppm and above) were indicative of hepatotoxicity. An increase of relative liver weight was observed at a dose level of 320 ppm and increased markedly with dose. Histopathological examination of the livers revealed hepatocellular hypertrophy and single cell necrosis. Liver peroxisome proliferation was confirmed by electron microscopy and special biochemical investigations. Kidneys weights were increased at 320 ppm and above which was accompanied by vacuolation of tubular epithelial cells (2/10 females). Tubular atrophy combined with single cell necrosis was observed in female mice at doses of 640 ppm and higher. Furthermore, increased erythropoiesis was noted at histopathological investigations of the spleen (320 ppm and higher) with an increased spleen weight at 1280 ppm in males only. Also in males only, adrenals weight was increased at 320 ppm and above without correlating histopathological findings.

Oral Dog:

30 days: The dogs of the highest dose group (2000 ppm) had to be sacrificed prematurely due to excessive toxicity. These dogs showed signs of intoxication at macroscopic (liver: lobular marking, clay-brownish discoloration; lymph nodes: enlargement) and microscopic examination (fatty degeneration of the liver, atrophy of splenic corpuscles, acute lymphadenitis, hemorrhages of the adrenal cortex, thymus atrophy and changes of the cerebellum). Except in those prematurely killed animals which seemed to have a slightly reduced body weight, no effect on body weight gain was noted. No substance related changes were observed in haematological, clinical chemistry and urinalysis parameters and at liver and renal function tests. Adrenals weights seemed to be increased slightly at 400 ppm and distinctly at 2000 ppm.

90 days: Relative pituitary weights were increased in males at 400 ppm. Chronic interstitial pyelonephritis was detected at histopathological investigation of males and females of the 80 and 400 ppm dose groups.

1 year: No treatment-related effects could be identified at any of the investigated doses (3, 15 or 75 ppm).

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

The effects, below the cut-off value for R48/22, observed in subchronic and chronic studies in rats, mice and dogs are summarised in table below:

Table 95: Summary of effects observed in rats, mice and dogs in comparison to cut off vales

Species-Route (Reference)	Study duration	Cut off value R 48/22 (67/548/EC) [mg/kg bw/d]	Effects below cut off value	Significance of toxicological effect (67/548/EC) below cut off value
Fenoxaprop-p-ethyl				
Rat- oral (Suter P. et al, 1987a)	28 days	150	- ≥ 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, kidney and liver weights - 95 mg/kg bw/d: ↑ leucine aminopeptidase and alkaline phosphatase – indicative of hepatotoxicity, prolonged thromboplastin and partial thromboplastin times (M) - 126 (M) – 144 (F) mg/kg bw/d: group terminated on treatment day 9 due to severe impairment of food consumption, resulting in stagnation of growth (no further examination)	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 urinanalysis Changes in liver weight with no evidence of organ dysfunction
Rat- oral (Tennekes H. et al., 1987)	90 days	50	- ≥ 5.8 (M)-6.3 (F) mg/kg bw/d: changes in lipid metabolism, ↑ in liver and kidney weights, ketonuria, urobili- and bilirubinuria - 49 (m) – 51.8 (F) mg/kg bw/d only: ↓ in body weight and food consumption. ↓ haemoglobin, haematocrit, MCV, ↑ MCHC, alkaline phosphatase, prolonged thromboplastin and partial thromboplastin times (M), shorter thromboplastin time (F), centrilobular hepatocellular hypertrophy	Changes in bw, food consumption and small changes in clinical biochemistry, haematology and urinanalysis Changes in liver weight with no evidence of organ dysfunction
Mouse- oral (Suter P. et al., 1987b)	28 days	150	- ≥ 56 (M)- 61 (F) mg/kg bw/d: changes in lipid metabolism, ↑ liver weight associated with hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes, tubular injury in the kidney	Small changes in clinical biochemistry Only minimal tubular injury at 56-61 mg/kg bw/d Changes in liver weight with no evidence of organ dysfunction
Mouse- oral (Suter P. and Luetkemeier	90 days	50	- ≥ 11.9 (M)- 16.5 (F) mg/kg bw/d: ↑ liver weight, tubular injury in the kidney	Changes in liver weight with no evidence of organ

Species-Route (Reference)	**Study duration**	**Cut off value R 48/22 (67/548/EC) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (67/548/EC) below cut off value**
H., 1987a)				dysfunction Only minimal renal unilateral tubular injury in 1 female
Dog- oral (Sachsse K. et al., 1987a)	28 days	? *	none	-
Dog- oral (Sachsse K. et al., 1987b)	90 days	? *	- 77.7 (M)- 83.4 (F) mg/kg bw/d: ↓ body weight gain, ↑ aspartate aminotransferase, lactate dehydrogenase and total protein (M), ↓ alkaline aminotransferase (M + F)	Changes in bw gain and small changes in clinical biochemistry
Rat- inhalative (Hofmann T. et al. 1989)	28 applications (6 hs/d) within 40 days	0.5 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 thrombiplastin time (F), ↓ cholesterol, total lipids, ↑ 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
Rat- dermal (Ebert E. et al. 1988)	21 applications (6 hs/d) within 30 days	300	- ≥ 20 mg/kg bw/d: ↑ kidney weight (F) - ≥ 100 mg/kg bw/d: ↓ haemoglobin, hematocrit and erythrocytes (M), ↓ thromboplastin time (F), ↓ cholesterol, total lipids (M), ↑ liver and kidney weight (M)	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Supportive information: combined toxicity fenoxaprop-P-ethyl with mefenpyr-diethyl				
Rat- oral (Schmid H. et al. 1996)	90 days	50	- ≥ 0.74 (M)- 0.81 (F) mg/kg bw/d: ↓ bilirubin (F) - ≥ 5.79 (M)- 6.39 (F) mg/kg bw/d: ↓ bilirubin (both sexes), ketonuria (M), hepatocellular hypertrophy (M) - 48.2 (M)- 50.89 (F) mg/kg bw/d: ↓ bodyweight, food consumption, ↓ haemoglobin, hematocrit and platelets, ↑ high reticulocyte fluorescence ratio (M), ↑ thromboplastin time (M), ↓ thromboplastin time (F), ↓ cholesterol, HDL phospholipid, total protein, glucose and creatinine (M), ↑ ASAT, LDH, uric acid (M), ↑ ALP, phosphorus, sodium, slight changes in in some plasma protein fractions, bilirubinuria (M), urobilinogenuria (M), ↑ liver and kidney weight, dark brown discoloration of the	Changes in bw and small changes in clinical biochemistry, haematology and urinanalysis Changes in organ weights with no evidence of organ dysfunction

Species-Route (Reference)	**Study duration**	**Cut off value R 48/22 (67/548/EC) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (67/548/EC) below cut off value**
			liver, hepatocellular hypertrophy	
Supportive information: Fenoxaprop-ethyl				
Rat- oral (Leist et al., 1980a)	32 days	150	- ≥ 6.91 (F)- 7.22 (M) mg/kg bw/d: hypolipidaemia, ↑ kidney weight - ≥ 27.22 (F)- 27.94 (M) mg/kg bw/d: ↑ liver weight correlated with histopathology changes including enlarged hepatocytes, ↓ phosphorus (males only) - 94.63 (f)- 103.3 (M) mg /kg bw/d: clinical signs including reduced activity and shallow breathing, ↓ body weight gain and food consumption, ↑ alkaline phosphatase, ↓ phosphorus (both species)	Clinical observations, changes in bw gain, food consumtpion and small changes in clinical biochemistry Changes in organ weights with no evidence of organ dysfunction
Rat- oral (Donaubauer et al., 1981)	90 days	50	- ≥ 1.57 (M)- 1.74 (F) mg/kg bw/d: hypolipidaemia - ≥ 6.29 (M)- 6.93 (F) mg/kg bw/d: ↑ adrenal weights - 25.27 (M)- 27.53 (F) mg/kg bw/d only: ↓ water consumption, slight anaemia, liver toxicity consisting of ↑ alkaline phosphatase and liver weight with hepatocyte enlargement, ↑ kidney and thyroid weight	Changes in water consumption and small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Mouse- oral (Leist et al., 1981)	30 days	150	- ≥ 3.52 mg/kg bw/d: ↑ total lipids, ↑ liver weight correlated with enlarged hepatic epithelia, large nuclei and dense eosinophilic cytoplasm - 14.35 (M)- 15.35 (F) mg/kg bw/d only: ↑ cholesterol	Small changes in clinical biochemistry Changes in liver weight with no evidence of organ dysfunction
Mouse- oral (Leist et al., 1980b)	32 days	150	- ≥ 14.6 (M)- 14.9 (F) mg/kg bw/d: ↑ liver weight correlated with hepatocyte enlargement - ≥ 56.7 (M)- 58.6 (F) mg/kg bw/d: ↑ kidney weight correlated with tubular lesions (2/10 females), ↑ alkaline phosphatase	Small changes in clinical biochemistry and haematology Changes in liver weight with no evidence of organ dysfunction Changes in kidney weight with no evidence of organ dysfunction
Mouse- oral (Ehling G., 1993a)	90 days	50	- ≥ 51.6 (M)- 54.4 (F) mg/kg bw/d: ↓ erythrocytes, ↑ reticulocytes (F) liver – impaired liver erythropoiesis, ↑ bilirubin, albumin, ↑ liver weight, hepatocellular hypertrophy due to peroxisome proliferation and single cell	Small changes in haematology Changes in organ weights with no evidence of organ dysfunction

Species-Route (Reference)	**Study duration**	**Cut off value R 48/22 (67/548/EC) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (67/548/EC) below cut off value**
			necrosis. Kidney - ↑ kidney weight and tubular vacuolation (F) Spleen - extramedullary erythropoiesis (M) Adrenals - ↑ adrenal weight (M) electron microscopy and special biochemistry findings (peroxisome proliferation)	
Dog- oral (Brunk et al., 1980)	30 days	? *	- 400 ppm: ↑ adrenal weights with no corresponding histopathology - 2000 ppm: excessive toxicity leading to premature sacrifice by treatment day 3 (2M, 1F) or 5 (1F)	Changes in organ weights with no evidence of organ dysfunction 2000 ppm: histopathological changes, only 2 animals/sex/ dose group
Dog- oral (Brunk et al., 1981a)	90 days	? *	- ≥ 80 ppm: chronic interstitial pyelonephritis - 400 ppm only: ↑ relative pituitary weight with no corresponding histopathology	Pyelonephritis: not seen in the 30 day study with higher doses Changes in pituitary weight with no evidence of organ dysfunction
Dog- oral (Brunk et al., 1984)	1 year	? *	none	-
Rat	24 months	25 **	After 6 months: - ≥ 0.3 (M)- 0.4 (F) mg/kg bw/d: ↓ transient total lipids - ≥ 2 (M)- 2.5 (F) mg/kg bw/d: ↓ cholesterol - 11.9 (M)- 14.6 (F) mg/kg bw/d: ↑ kidney, spleen and thymus weight (F), kidneys hyperplasia and calcification of the renal pelvis After 12 months: - ≥ 0.3 (M)- 0.4 (F) mg/kg bw/d: ↓ transient total lipids - ≥ 1.7 (M)- 2.1 (F) mg/kg bw/d: ↓ cholesterol (F), ↑ adrenals weight (M), adrenals slight to moderate sinus dilatation (M) - 10.2 (M)- 13.3 (F) mg/kg bw/d: ↓ cholesterol (M), total lipids, adrenals slight (M+F) to moderate (M+F) to severe sinus dilatation (F), ↑ LDH After 24 months: - 9.4 (M)- 11.9 (F) mg/kg bw/d: ↓ cholesterol, total lipids (M), ↓ liver weight (M) After 28 months: - ≥ 1.5 (M)- 2 (F) mg/kg bw/d: ↓ liver	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction

Species-Route (Reference)	**Study duration**	**Cut off value R 48/22 (67/548/EC) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (67/548/EC) below cut off value**
			weight (M)	
Mouse	18 months	25 **	After 12 months: - 5.54 (M)- 6.59 (F) mg/kg bw/d: ↑ kidney weight (F), After 24 months: - ≥ 1.38 (M)- 1.61 (F) mg/kg bw/d: ↓ liver weight (F) - 5.48 (M)- 6.54 (F) mg/kg bw/d: ↓ γ-glutamyl transferase (F), ↑ haemoglobin (F), ↓ LDH (M)	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Mouse	18 months	25 **	- ≥ 5.7 (M)- 6.8 (F) mg/kg bw/d: - ≥ 16.6 (M)- 19.4 (F) mg/kg bw/d: swollen abdomen, ↑ liver weight (M), hepatocellular hypertrophy (M), liver (M): single cell necrosis, pigment in macrophages, lipofuscin deposits, adenoma and carcinoma due to peroxisome proliferation - 44.6 (M)- 53.7 (F) mg/kg bw/d: ↑ kidney weight, liver (F): hepatocellular hypertrophy, pigment in macrophages, lipofuscin deposits, carcinoma due to peroxisome proliferation, adrenals: subcapsular adenoma typ B (M) within historical control range	See 4.10 Changes in organ weights with no evidence of organ dysfunction
Dog	24 months	? *	- ≥ 1.1 mg/kg bw/d (M): ↓ bodyweight - 4.6 mg/kg bw/d (F): ↓ bodyweight (F)	Changes in bw

* For cut off values in dog studies, the only available document is ECBI/64/06 "Dose limits for classification with R48 based on dogs studies", 2006. In this document it is proposed that the cut off values for dog studies should be below the limit dose for the rat.

** For extrapolation from subchronic to chronic studies in rodents regarding cut off values for effects observed, different approaches were found: whereas in the ECBI/64/06 "Dose limits for classification with R48 based on dogs studies", 2006, the cut off value for chronic studies in rodents of 6.25 mg/kg bw/d is found, in the REACH guidance on information requirements and chemical safety assessment, chapter R8 is stated that factor of 2 should be applied resulting in the cut off value of 25 mg/kg bw/d in chronic studies in rodents.

The oral short term toxicity of fenoxaprop-P-ethyl has been investigated in 28 days and 13 weeks dietary studies in rats, mice and dogs. The target organs were the liver and the kidneys. The rat was the most sensitive species with a NOAEL of 0.7 mg/kg bw/day based on the 13-week study.

In repeat-dose studies by inhalation or dermal administration, effects were also observed in the liver, in the kidney and –to a small extent- in the haematological parameters with NOAEL values of 0.015 mg/L/day and 20 mg/kg bw/day.

Oral studies performed with fenoxaprop-ethyl gave similar results in rats. In mice, additional target organs were shown (spleen- increased erythropoiesis with an increased spleen weight and adrenals- increased weight) but the effects levels were generally comparable with

fenoxaprop-P-ethyl. The results of the dog studies with fenoxaprop-P-ethyl and fenoxaprop-ethyl showed no consistent pattern of effects.

Regarding fenoxaprop-P-ethyl the effects seen below the cut off values included changes in bodyweight, bodyweight gain and food consumption, small changes in clinical biochemistry, haematology and urinanalysis, as well as changes in organ weights with no evidence of organ dysfunction.

These effects did not result in clear functional disturbance or morphological change which has toxicological significance.

In the 28 day study in rats animals treated with 126 (M)- 144 (F) mg/kg bw/d were terminated on day 9. 126 (M) – 144 (F) mg/kg bw/d is due to the low food intake and stagnation of growth equivalent to 5000 ppm. For all other doses the factor of increase between ppm and mg/kg bw/d was more similar. According to the Directive on Dangerous Substances changes in body weight gain as well as food consumption and water intake are not indicating classification and labeling with R48. It is considered likely that preliminar termination of this group might be related to starvation whereby palatability effects can not be excluded. As conclusions regarding earlier termination of this dose group are only speculative, this dose group should not be used for application of R48.

Table 96: ppm and dose comparison for the 28 day study in rats

ppm	factor of increase (ppm)	mg/kg bw/d (males)	factor of increase (males)	mg/kg bw/d (females)	factor of increase (females)
20		2		2	
80	4	6	3	6	3
320	4	26	4.3	28	4.7
1280	4	95	3.7	94	3.6
5120	4	126	1.3	144	1.5

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

In the available sub-acute and sub-chronic studies in the rat, mice and dog no clear serious adverse effects were observed below the harmful (Xn) cut-off values for classification.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No classification is proposed for repeated dose toxicity findings according to Directive 67/548.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

The effects, below the guidance cut-off value for STOT-RE, observed in subchronic and chronic studies in rats, mice and dogs are summarised in table below:

Table 97: Summary of effects observed in rats, mice and dogs in comparison to cut off values

Species-Route (Reference)	Study duration	Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]	Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]	Effects below cut off value	Significance of toxicological effect (1272/2008) 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, kidney and liver weights - 95 mg/kg bw/d: ↑ leucine aminopeptidase and alkaline phosphatase – indicative of hepatotoxicity, prolonged thromboplastin and partial thromboplastin times (M) - 126 (M) – 144 (F) mg/kg bw/d: group terminated on treatment day 9 due to severe impairment of food consumption, resulting in stagnation of growth (no further examination)	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 urinanalysis Changes in liver weight with no evidence of organ dysfunction
Rat- oral (Tennekes H. et al., 1987)	90 days	10	100	- ≥ 5.8 (M)-6.3 (F) mg/kg bw/d: changes in lipid metabolism, ↑ in liver and kidney weights, ketonuria, urobili- and bilirubinuria - 49 (m) – 51.8 (F) mg/kg bw/d only: ↓ in body weight and food consumption. ↓ haemoglobin, haematocrit, MCV, ↑ MCHC, alkaline phosphatase, prolonged thromboplastin and partial thromboplastin times (M), shorter thromboplastin time (F),	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

Species-Route (Reference)	**Study duration**	**Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]**	**Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (1272/2008) below cut off value**
				centrilobular hepatocellular hypertrophy	
Mouse- oral (Suter P. et al., 1987b)	28 days	30	300	- ≥ 56 (M)- 61 (F) mg/kg bw/d: changes in lipid metabolism, ↑ liver weight associated with hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes, tubular injury in the kidney - 260 (M)- 280 (F) mg/kg bw/d only: ↑ aspartate and alkaline aminotransferase, alkaline phosphatase, albumin and protein levels,↑ kidney weights	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 male 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 response to enzyme induction
Mouse- oral (Suter P. and Luetkemeier 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, ↑ 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
Dog- oral (Sachsse K. et al., 1987a)	28 days	? *	? *	none	-
Dog- oral (Sachsse K. et al., 1987b)	90 days	? *	? *	- 77.7 (M)- 83.4 mg/kg bw/d: ↓ body weight gain, ↑ aspartate aminotransferase, lactate dehydrogenase and total protein (M), ↓ alkaline aminotransferase (M + F)	Changes in bw gain and small changes in clinical biochemistry

Species-Route (Reference)	**Study duration**	**Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]**	**Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (1272/2008) below cut off value**
Rat-inhalative (Hofmann T. et al. 1989)	28 applications (6 hs/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 thrombiplastin time (F), ↓ cholesterol, total lipids, ↑ 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
Rat- dermal (Ebert E. et al. 1988)	21 applications (6 hs/d) within 30 days	60	600	- ≥ 20 mg/kg bw/d: ↑ kidney weight (F) - ≥ 100 mg/kg bw/d: ↓ haemoglobin, hematocrit and erythrocytes (M), ↓ thromboplastin time (F), ↓ cholesterol, total lipids (M), ↑ liver and kidney weight (M), - 500 mg/kg bw/d: ↓ thromboplastin time (M), ↓ cholesterol (F), ↑ liver weight (F), heart and spleen weight (M)	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Supportive information: combined toxicity fenoxaprop-P-ethyl with mefenpyr-diethyl					
Rat- oral (Schmid H. et al. 1996)	90 days	10	100	- ≥ 0.74 (M)- 0.81 (F) mg/kg bw/d: ↓ bilirubin (F) - ≥ 5.79 (M)- 6.39 (F) mg/kg bw/d: ↓ bilirubin (both sexes), ketonuria (M), hepatocellular hypertrophy (M) - 48.2 (M)- 50.89 (F) mg/kg bw/d: ↓ bodyweight, food consumption, ↓ haemoglobin, hematocrit and platelets, ↑ high reticulocyte fluorescence ratio (M), ↑ thromboplastin time (M), ↓ thromboplastin time (F), ↓ cholesterol, HDL phospholipid, total protein, glucose and creatinine (M), ↑ ASAT, LDH, uric acid (M), ↑ ALP, phosphorus, sodium, slight changes in in some plasma protein fractions, bilirubinuria (M), urobilinogenuria (M), ↑ liver and kidney weight, dark brown discoloration of the liver,	Changes in bw and small changes in clinical biochemistry, haematology and urinanalysis Changes in organ weights with no evidence of organ dysfunction

Species-Route (Reference)	Study duration	Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]	Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]	Effects below cut off value	Significance of toxicological effect (1272/2008) below cut off value
				hepatocellular hypertrophy	
Supportive information: Fenoxaprop-ethyl					
Rat- oral (Leist et al., 1980a)	32 days	30	300	- ≥ 6.91 (F)- 7.22 (M) mg/kg bw/d: hypolipidaemia, ↑ kidney weight - ≥ 27.22 (F)- 27.94 (M) mg/kg bw/d: ↑ liver weight correlated with histopathology changes including enlarged hepatocytes, ↓ phosphorus (males only) - 94.63 (f)- 103.3 (M) mg /kg bw/d: clinical signs including reduced activity and shallow breathing, ↓ body weight gain and food consumption, ↑ alkaline phosphatase, ↓ phosphorus (both species) - 162 (F). 180.5 (M) mg/kg bw/d: terminated after 1 week of treatment as this dose level clearly exceeded the MTD (no further examination)	162-180.5 mg/kg bw/d: severe impairment of food consumption and growth, no further examination was done for the 162-180.5 mg/kg bw/d group which was terminated earlier Clinical observations, changes in bw gain, food consumtpion and small changes in clinical biochemistry Changes in organ weights with no evidence of organ dysfunction
Rat- oral (Donaubauer et al., 1981)	90 days	10	100	- ≥ 1.57 (M)- 1.74 (F) mg/kg bw/d: hypolipidaemia - ≥ 6.29 (M)- 6.93 (F) mg/kg bw/d: ↑ adrenal weights - 25.27 (M)- 27.53 (F) mg/kg bw/d only: ↓ water consumption, slight anaemia, liver toxicity consisting of ↑ alkaline phosphatase and liver weight with hepatocyte enlargement, ↑ kidney and thyroid weight	Changes in water consumption and small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Mouse- oral (Leist et al., 1981)	30 days	30	300	- ≥ 3.52 mg/kg bw/d: ↑ total lipids, ↑ liver weight correlated with enlarged hepatic epithelia, large nuclei and dense eosinophilic cytoplasm - 14.35 (M)- 15.35 (F) mg/kg bw/d only: ↑ cholesterol	Small changes in clinical biochemistry Changes in liver weight with no evidence of organ dysfunction
Mouse- oral (Leist et al., 1980b)	32 days	30	300	- ≥ 14.6 (M)- 14.9 (F) mg/kg bw/d: ↑ liver weight correlated with hepatocyte enlargement - ≥ 56.7 (M)- 58.6 (F) mg/kg	Small changes in clinical biochemistry and haematology Changes in liver weight with

Species-Route (Reference)	**Study duration**	**Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]**	**Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (1272/2008) below cut off value**
				bw/d: ↑ kidney weight correlated with tubular lesions, ↑ alkaline phosphatase - 215 (M)- 222.7 (F) mg/kg bw/d: ↓ haemoglobin, ↑ alanine aminotransferase	no evidence of organ dysfunction tubular injury: → 56.7-58.6 mg/kg bw/d: isolated focal tubular atrophies (5/10 males, 4/10 females), single cell necrosis (2/10 females) → 215-222.7 mg/kg bw/d group: isolated focal tubular atrophies (2/10 males, 1/10 females), necroses of tubular cells and mitotic cells (7/10 females)
Mouse- oral (Ehling G., 1993a)	90 days	10	100	- ≥ 51.6 (M)- 54.4 (F) mg/kg bw/d: ↓ erythrocytes, ↑ reticulocytes (F) liver – impaired liver erythropoiesis, ↑ bilirubin, albumin, ↑ liver weight, hepatocellular hypertrophy due to peroxisome proliferation and single cell necrosis. Kidney - ↑ kidney weight and tubular vacuolation (F) Spleen - extramedullary erythropoiesis (M) Adrenals - ↑ adrenal weight (M) electron microscopy and special biochemistry findings (peroxisome proliferation) - ≥ 100.7 (M)- 113.8 (F) mg/kg bw/d: ↑ leucocytes (F), ↑ total protein, trigylcerides, ↑ enzymic activity in the liver Kidney – tubular atrophy and cell necrosis (F)	Small changes in haematology Changes in liver and adrenal weights with no evidence of organ dysfunction Extramedullary erythropoiesis without alteration of other tissues tubular injury: → 51.6-54.4 mg/kg bw/d: tubular atrophy with single cell necrois (0/20 males, 3/20 females), additionally single cell necrosis (0/20 males, 6/20 females) → 100.7-113.8 mg/kg bw/d group: tubular atrophy with single cell necrois (0/20 males, 6/20 females), additionally single cell necrosis (0/20 males, 11/20 females)
Dog- oral (Brunk et al., 1980)	30 days	? *	? *	- 400 ppm: ↑ adrenal weights with no corresponding histopathology - 2000 ppm: excessive toxicity leading to premature sacrifice by treatment day 3 (2M, 1F) or 5 (1F)	Changes in organ weights with no evidence of organ dysfunction 2000 ppm: histopathological changes, only 2 animals/sex/ dose group
Dog- oral (Brunk et al., 1981a)	90 days	? *	? *	-≥ 80 ppm: chronic interstitial pyelonephritis - 400 ppm only: ↑ relative pituitary weight with no	Pyelonephritis: not seen in the 30 day study with higher doses Changes in pituitary weight with no evidence of organ

Species-Route (Reference)	**Study duration**	**Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]**	**Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (1272/2008) below cut off value**
				corresponding histopathology	dysfunction
Dog- oral (Brunk et al., 1984)	1 year	? *	? *	none	-
Rat	24 months	< 5	< 50	After 6 months: - ≥ 0.3 (M)- 0.4 (F) mg/kg bw/d: ↓ transient total lipids - ≥ 2 (M)- 2.5 (F) mg/kg bw/d: ↓ cholesterol - 11.9 (M)- 14.6 (F) mg/kg bw/d: ↑ kidney, spleen and thymus weight (F), kidneys hyperplasia and calcification of the renal pelvis After 12 months: - ≥ 0.3 (M)- 0.4 (F) mg/kg bw/d: ↓ transient total lipids - ≥ 1.7 (M)- 2.1 (F) mg/kg bw/d: ↓ cholesterol (F), ↑ adrenals weight (M), adrenals slight to moderate sinus dilatation (M) - 10.2 (M)- 13.3 (F) mg/kg bw/d: ↓ cholesterol (M), total lipids, adrenals slight (M+F) to moderate (M+F) to severe sinus dilatation (F), ↑ LDH After 24 months: - 9.4 (M)- 11.9 (F) mg/kg bw/d: ↓ cholesterol, total lipids (M), ↓ liver weight (M) After 28 months: - ≥ 1.5 (M)- 2 (F) mg/kg bw/d: ↓ liver weight (M)	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction Histopathological changes in kidneys and adrenals
Mouse	18 months	< 5	< 50	After 12 months: - 5.54 (M)- 6.59 (F) mg/kg bw/d: ↑ kidney weight (F), After 24 months: - ≥ 1.38 (M)- 1.61 (F) mg/kg bw/d: ↓ liver weight (F) - 5.48 (M)- 6.54 (F) mg/kg bw/d: ↓ γ-glutamyl transferase (F), ↑ haemoglobin (F), ↓ LDH (M)	Small changes in clinical biochemistry and haematology Changes in organ weights with no evidence of organ dysfunction
Mouse	18 months	< 5	< 50	- ≥ 5.7 (M)- 6.8 (F) mg/kg bw/d: - ≥ 16.6 (M)- 19.4 (F) mg/kg bw/d: swollen abdomen, ↑ liver weight (M), hepatocellular	See 4.10 Changes in organ weights with no evidence of organ dysfunction

Species-Route (Reference)	**Study duration**	**Cut off value Cat 1 STOT RE (1272/2008) [mg/kg bw/d]**	**Cut off value Cat 2 STOT RE (1272/2008) [mg/kg bw/d]**	**Effects below cut off value**	**Significance of toxicological effect (1272/2008) below cut off value**
				hypertrophy (M), liver (M): single cell necrosis, pigment in macrophages, lipofuscin deposits, adenoma and carcinoma due to peroxisome proliferation - 44.6 (M)- 53.7 (F) mg/kg bw/d: ↑ kidney weight, liver (F): hepatocellular hypertrophy, pigment in macrophages, lipofuscin deposits, carcinoma due to peroxisome proliferation, adrenals: subcapsular adenoma typ B (M) within historical control range	
Dog	24 months	? *	? *	- ≥ 1.1 mg/kg bw/d (M): ↓ bodyweight - 4.6 mg/kg bw/d (F): ↓ bodyweight (F)	Changes in bw

* For cut off values in dog studies, the only available document is ECBI/64/06 "Dose limits for classification with R48 based on dogs studies", 2006. In this document it is proposed that the cut off values for dog studies should be below the limit dose for the rat.

Further summary on repeated dose toxicity studies can befound in section 4.7.1.8. Especially regarding fenoxaprop-P-ethyl, in the 28 day study in rats animals treated with 126 (M)- 144 (F) mg/kg bw/d were terminated on day 9- the reader is referred to section 4.7.1.8.

According to the Guidance on the Application of the CLP criteria significant organ damage should be considered in the classification process.

Sex-specific nephrotoxicity could bge found in the mouse studies. In the 28 day mouse study moderate to marked tubular injury in females was found slightly below the cut-off value of the CLP guidance of 300 mg/kg bw/d. Furthermore moderate to marked tubular injury in females in the 90 day mouse study occurs just above the guidance value of 100 mg/kg bw/d for oral STOT-RE. At the next lower dose (11.9 (M)-16.5 (F) mg/kg bw/d) minimal tubular injury in 1 female was observed. In the ADME studies females showed higher urinary excretion than males which might be the reason for the sex sensitivity of females.

Nephrotoxicity should be considered for classification as STOT-RE, H373.

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

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

In the available sub-acute and sub-chronic studies in mice nephrotoxicity was observed below the guidance cut off values of the CLP-regulation for classification as STOT-RE.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Classification with H373 is proposed for repeated dose toxicity findings as STOT RE, Cat. 2 according to Regulation (EC) No 1272/2008.

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 hepatotoxicity, prolonged thromboplastin and partial thromboplastin times (M), urinalysis: ↓ creatinine and creatinine clearance, ↑ GGT and LDH 126 (M) – 144 (F) mg/kg bw/d: 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))	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

↓ = 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)

Rat - oral (Tennekes H. *et al*., 1987)	90 days	10	100	≥ 5.8 (M)-6.3 (F) mg/kg bw/d: changes in lipid metabolism, ↑ in liver and kidney weights, ketonuria, urobilinogenuria and bilirubinuria 49 (M) – 51.8 (F) mg/kg bw/d only: ↓ in body weight (non-reversible in M). and food consumption (n.s.), ↓ haemoglobin, haematocrit, MCV, ↑ MCHC, alkaline phosphatase, prolonged thromboplastin and partial thromboplastin times (M), shorter thromboplastin time (F), centrilobular hepatocellular hypertrophy	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

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)

Mouse - oral (Suter P. *et al*., 1987b)	28 days	30	300	≥ 56 (M) - 61 (F) mg/kg bw/d: changes in lipid metabolism, ↑ liver weight associated with hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes, tubular injury in the kidney 260 (M) - 280 (F) mg/kg bw/d only: ↑ terminal BW (F), food consumption + 25% (M), ↑ aspartate and alkaline aminotransferase, alkaline phosphatase, albumin and protein levels,↑ kidney weights	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 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)

Mouse - oral (Suter P. and Luetke-	90 days	10	100	≥ 11.9 (M) - 16.5 (F) mg/kg bw/d: ↑ liver weight, tubular injury in the kidney	Changes in liver weight with no evidence of organ dysfunction →

meier H., 1987a)				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	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)

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)

Dog - oral (Sachsse K. *et al*.,	90 days	? *	? *	77.7 (M) - 83.4 mg/kg bw/d: ↓ food consumption (F), ↓ body weight gain (M),	Changes in bw gain and small changes in clinical biochemistry

1987b)				↑ aspartate aminotransferase, lactate dehydrogenase, and total protein (M), ↓ alkaline aminotransferase (M + F)	

* 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)

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)

Rat -	21	60	600	≥ 10 mg/kg bw/d:	Small changes in

dermal (Ebert E. *et al*. 1988)	applications (6 h/d) within 30 days, Recovery OECD 410 (1981)			hyperkeratosis and epidermal thickening <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)	clinical biochemistry and haematology 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.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 98: Summary table of relevant *in vitro* and *in vivo* mutagenicity studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Reverse mutation assay (*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP2uvrA) (OECD 471 and 472)	Negative	+/- S9-mix	*Müller W., 1994*
Forward mutation assay in *Schizosaccharomyces pombe* P1	Negative	+/- S9-mix	*Edwards C.N., 1986a*
Gene mutation assay in Chinese hamster V79 cells (OECD 476)	Negative	+/- S9-mix	*Seeberg A.H., 1986*
Chromosome aberration test in human lymphocytes (OECD 473)	Negative	+/- S9-mix	*Mosesso P., 1987*
Mitotic gene conversion in *Saccharomyces cerevisiae* D4	Negative	+/- S9-mix	*Edwards C.N., 1986b*
In vitro UDS test in primary rat hepatocytes (OECD 473)	Negative		*Cifone M.A., 1986*
In vitro UDS test in mammalian cells (A 549) (OECD 482)	Negative	+/- S9-mix	*Müller W., 1995*
Oral micronucleus test in NMRI mice	Negative	*in vivo*	*Jung, Weigand, 1986*
Fenoxaprop-ethyl (supportive information)			
Oral micronucleus test in NMRI mice (OECD 474)	Negative	*in vivo*	*Banduhn N., 1986*

4.9.1 Non-human information

4.9.1.1 In vitro data

Table 99: *in vitro* mutagenicity studies with Fenoxaprop-P-ethyl

Type of study / guideline	Dose range	Results	Remarks	Reference
Reverse mutation assay (*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP2uvrA) OECD 471 (1983) and 472 (1983)	0, 4, 20, 100, 500, 2500 and 5000 µg/plate for experiment 1 and 2 (dissolved in DMSO)	Negative (+/- S9-mix)	Precipitation and cytotoxicity observed at ≥ 2500 µg/plate	*Müller W., 1994*

Type of study / guideline	Dose range	Results	Remarks	Reference
Forward mutation assay in *Schizosaccharomyces pombe* P1 No specific guidelines available	0, 2.5, 5, 10, 20 and 40 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)	Precipitation was observed at 40 µg/ml, no cytotoxicity observed	*Edwards C.N., 1986a*
Gene mutation assay in Chinese hamster V79 cells Directive 79/831/EEC Part B OECD 476	0, 6.25, 12.5, 25, 50 and 100 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)	Precipitation but no signs of cytotoxicity observed at 100 µg/ml	*Seeberg A.H., 1986*
Chromosome aberration test in human lymphocytes Directive 79/831/EEC Part B OECD 473	0, 50, 79 and 125 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)	Precipitation was observed at ≥ 125 µg/ml. At dose levels ranging from 5.0 – 125 µg/ml, dose-related decrease in mitotic indeces observed for –S9 mix, reduced mitotic indeces observed at high dose only for +S9 mix	*Mosesso P., 1987*
Mitotic gene conversion in *Saccharomyces cerevisiae* D4 Directive 79/831/EEC Part B	0, 1.25, 2.5, 5, 10 and 20 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)	In the prelim assay at doses ranging from 0.200 – 20.0 µg/ml, precipitation was observed at 20.0 µg/ml, no toxicity was observed at any dose level with either –S9 mix or +S9 mix	*Edwards C.N., 1986b*
In vitro UDS test in primary rat hepatocytes Similar to OECD 473	0, 2.51, 5.02, 10, 25.1, 50.2, 100, 201 and 301 µg/ml (dissolved in DMSO)	Negative	Dose levels of 502 and 1000 µg/ml were excessively toxic, whilst dose levels of 100 to 300 µg/ml caused low to moderate toxicity	*Cifone M.A., 1986*
In vitro UDS test in mammalian cells (A 549) EEC Directive 88/302 (1988) OECD 482 (1986)	0, 0.1, 0.3, 1, 3, 10, 30 and 100 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)	In the prelim. assay 100 µg/ml was the highest dose level which did not cause precipitation, no cytotoxicity was observed at any dose level tested	*Müller W., 1995*

Supportive information:

Table 100: *in vitro* mutagenicity studies with Fenoxaprop-ethyl

Type of study / guideline	Dose range	Results	Remarks	Reference
Reverse mutation assay (*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *E. coli* WP2uvrA) Similar to OECD 471 (1983) OECD 472 (1983)	0, 4, 20, 100, 500, 2500 and 5000 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix) Supplementary information only	Precipitation was observed at ≥ 500 µg/plate, slight cytotoxicity was observed at ≥ 2500 µg/plate	*Jung et al., 1982*
Forward mutation assay in *Schizosaccharomyces pombe* No specific guidelines available	0, 125, 250, 500 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix) Limited validity	Some cytotoxicity was observed at 1000 µg/ml, both +/- S9-mix	*Mellano D., Mondino A., 1982a*
Chromosome aberration test in human lymphocytes Similar to OECD 473	0, 1, 10, 100 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix) Limited validity	Cytotoxicity observed at and 1000 µg/ml with S9-mix	*Mellano D., Mondino A., 1982b*
Mitotic gene conversion in *Saccharomyces cerevisiae* D4 Similar to EEC Directive 79/831 Annex V, Part B	0, 125, 250, 500 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix) Limited validity	No information on solubility or cytotoxicity is present in the study report	*Mellano D., Mondino A., 1982c*
In vitro UDS test in mammalian cells (HeLa) Similar to OECD 473	0, 5, 50 and 500 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix) Limited validity	Cytotoxicity observed at 500 µg/ml - S9-mix	*Mellano D., Mondino A., 1982d*

4.9.1.2 In vivo data

Table 101: *in vivo* mutagenicity study with Fenoxaprop-P-ethyl

Type of study / guideline	Dose range	Sampling times	Results	Remarks	Reference
Oral micronucleus test in NMRI mice (5M + 5F/dose group) EEC Directive 84/449 Method B.12 OECD 474 (1983)	0, 1000, 2000 and 4000 mg/kg bw (dissolved in sesame oil)	24, 48, 72 hours	Negative	In the prelim. assay 4000 mg/kg bw found to be MTD (lethality in a prelim assay ≥ 4500 mg/kg bw)	*Jung, Weigand, 1986*

Supportive information:

Table 102: *in vivo* mutagenicity study with Fenoxaprop-ethyl

Type of study / guideline	Dose range	Sampling times	Results	Remarks	Reference
Oral micronucleus test in NMRI mice (6M + 6F/dose group) EEC Directive 84/449 Method B.12 OECD 474 (1983)	0, 750, 1500 and 3000 mg/kg bw (dissolved in sesame oil)	24, 48, 72 hours	Negative	Based on acute oral LD_{50} value, 3000 mg/kg bw considered to be MTD	*Banduhn N., 1986*

4.9.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.9.3 Other relevant information

No data

4.9.4 Summary and discussion of mutagenicity

Fenoxaprop-P-ethyl was tested in a battery of *in vitro* and *in vivo* genotoxicity testings. All experiments were performed according to GLP and, if available, to OECD, EPA or EEC study 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 testings 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 study guidelines. However, all of the *in vitro* studies lack a second, independent repeat experiment which confirms the results obtained in the genotoxicity testing. For this reason, all the *in vitro* studies are of limited validity. On the other hand, the *in vivo* micronucleus assay with NMRI mice was conducted according to OECD, EPA or EEC guidelines and can be considered scientific valid and acceptable. All the *in vitro* and *in vivo* genotoxicity testings performed with Fenoxaprop-ethyl did not show any genotoxic potential of Fenoxaprop-ethyl. Taken together, it can be assumed that Fenoxaprop-ethyl is not genotoxic *in vitro* or *in vivo*.

4.9.5 Comparison with criteria

Fenoxaprop-P-ethyl was tested in a battery of *in vitro* genotoxicity tests and also in oral micronucleus tests in mice. The *in vitro* tests included gene mutation in several bacterial strains (Ames test), forward mutation assay in *S. pombe*, gene mutation in V79 cells, chromosome aberration tests in human lymphocytes, mitotic gene conversion in *S. cerevisiae*, and *in vitro* UDS tests in primary rat hepatocytes as well as mammalian cells (A549). None of

the genotoxicity tests with Fenoxaprop-P-ethyl showed any indication of genotoxcity. In conclusion, Fenoxaprop-P-ethyl is considered to be non-genotoxic.

4.9.6 Conclusions on classification and labelling

No classification for mutagenicity is proposed.

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.

4.10 Carcinogenicity

Table 103: Summary table of relevant carcinogenicity studies

Method	Results	Remarks	Reference
Fenoxaprop-ethyl (read across)			
Chronic toxicity and carcinogenicity study in Wistar rats (OECD 453)	Changes in lipid status (decreased cholesterol, total lipids) - Organ weight changes and histopathological findings at different times of investigation 6 months: increased kidney weight; increased calcification and hyperplasia of the pelvic region of the kidneys 12 months: increased adrenals weight; distension of the sinuses of the zona reticularis and medulla of adrenals 24 and 28 months: decreased liver weight - no carcinogenicity observed	Dose levels: 0, 5, 30 and 180 ppm NOAEL: 30 ppm (males: 1.6 mg/kg bw/d; females: 2.0 mg/kg bw/d)	Donaubauer et al., 1985a
Carcinogenicity study in NMRI mice (OECD 451)	-	Dose levels: 0, 2.5, 10 and 40 ppm NOAEL: 40 ppm (males: 5.48 mg/kg bw/d; females: 6.54 mg/kg bw/d)	*Donaubauer et al., 1985c*
Carcinogenicity study in NMRI mice (OECD 451)	- Swollen abdomen - increased liver and kidney weights - liver and adrenals enlargement - hepatocellular hypertrophy, single cell necrosis, pigment in macrophages, lipofuscin deposits - liver foci - liver adenomas and carcinomas due to peroxisome proliferation	Dose levels: 0, 40, 115 and 320 ppm NOAEL: 40 ppm (males: 5.67 mg/kg bw/d; females: 6.83 mg/kg bw/d)	*Troschau et al., 1996*
2 year chronic toxicity study in Beagle dogs (OECD 452)	- reduced body weight	Dose levels: 0, 3, 15 and 75 ppm NOAEL: 15 ppm (males: 1.1 mg/kg bw/d; females: 0.9 mg/kg bw/d)	*Brunk et al., 1985*

4.10.1 Non-human information

No long term toxicity or carcinogenicity study has been performed with Fenoxaprop-P-ethyl. Therefore information on long term toxicity and carcinogenicity was bridged from studies with Fenoxaprop-ethyl.

4.10.1.1 Carcinogenicity: oral

The long term toxicity and carcinogenicity of Fenoxaprop-ethyl was tested in GLP studies in rats, mice and dogs. The studies were conducted according to international study guidelines or were at least close to these guidelines and therefore considered acceptable and scientifically valid.

Rats:

A long term toxicity / carcinogenicity study has been performed with the racemate Fenoxaprop-ethyl (Hoe 33171). This combined study included a 28-month period of dietary administration for carcinogenicity assessment and also several interim sacrifices (after 6, 12 and 24 months) to assess chronic toxicity. Determination of specific hepatic enzymes was also performed for the 12-month interim sacrifice group and evaluation of liver and kidney functions (BSP/PSP function test) were performed after 24 months of treatment. In addition, content of Fenoxaprop-ethyl residues in main tissues was evaluated at different time-points (6, 12, 18 and 24 months). For each of these sacrifice times or specific investigations, a specific report was issued.

The first report presented in this section is a summary of the whole study and includes material and methods and all the relevant findings. Further reports address different sacrifice times and specific investigations. In order to avoid repetition, the study design will only be presented once at the beginning but no more for individual reports.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Combined chronic toxicity and carcinogenicity study in rats (24 and 48 months feeding study)

Reference: *Donaubauer et al*, 1985a; Doc. No. A31880 / Hoechst Report No. 85.0688

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

116 male and 116 female Wistar rats (strain: Hoe:WISKf(SPF71), source: Hoechst) per dose group were treated with 0, 5, 30 or 180 ppm Fenoxaprop-ethyl for different periods of time. The animals were about 4 weeks old and had a mean body weight of 133 g (males) or 118 g (females) after a one-week adaptation period.

Table 104: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats: Study design and number of animals

	Number of animals/group	Reference	Report No.
Chronic toxicity			
6-month interim sacrifice	10 males / 10 females	Donaubauer et al., 1983a	24/83
12-month interim sacrifice Determination of hepatic enzyme levels	10 males / 10 females	Donaubauer et al., 1983b Schütz et al., 1984	83.0613 84.0639
24 months treatment period BSP/PSP function tests	26 males / 26 females	Donaubauer et al., 1984	84.0632
Residue examination	10 males / 10 females	Schütz et al., 1985	85.0205
Carcinogenicity			
28 months treatment period	60 males / 60 females	Donaubauer et al., 1985b	85.0682

The actual intake of Fenoxaprop-ethyl was calculated separately for each period of treatment time.

Table 105: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats: Test substance intake in mg/kg bw/d

	Test substance intake in mg/kg bw/d							
	Males				Females			
Dietary level	6 mo	12 mo	24 mo	28 mo	6 mo	12 mo	24 mo	28 mo
5 ppm	0.3	0.3	0.3	0.3	0.4	0.4	0.3	0.3
30 ppm	2.0	1.7	1.6	1.5	2.5	2.1	2.0	2.0
180 ppm	11.9	10.2	9.4	9.1	14.6	13.3	11.9	11.7

Two batches were used in this study: Hoe 33171 0H AT206 for the first month of the study (purity 95.8 % according to certificate of analysis No. 01805), and Hoe 33171 0H AS201 for the rest/major part of the study (purity 94.0% according to certificate of analysis No. 01888). The standard pulverized diet Altromin 1321 and the test substance were premixed at 14-day intervals. The final diet for the study was prepared weekly and was checked for content and homogeneity weekly.

Chronic toxicity

The following examinations were performed during the study: bodyweight (weekly), food consumption (weekly), water consumption (at 6, 12 and 24 months), behaviour and general health conditions (eyes, visible mucosae, teeth, neurological status, survival checks).

Hematology (at 6, 12 and 24 months), non-starved animals: erythrocytes, haemoglobin, hematocrit, Heinz bodies, reticulocytes, thrombocytes, coagulation time, leucocytes, differential blood count, Howell-Jolly bodies, MCV, MCH, MCHC

Clinical chemistry (at 6, 12 and 24 months), non-starved animals: sodium, potassium, calcium, chloride, inorganic phosphorus, bilirubin (total and direct), glucose, uric acid, creatinine, urea nitrogen, ALAT, ASAT, ALP, LDH, protein, cholesterol, total lipids, serum electrophoresis

Function tests (24-month interim sacrifice): BSP (liver), PSP (kidneys)

Determination of hepatic enzyme levels (12-month interim sacrifice): aminopyrine N-demethylase, anisic acid ester O-demethylase, etho-oxycoumarin O-deethylase, cytochrome c-reductase, glucuronyltransferase I and glucuronyltransferase II. To test for peroxisomal proliferation, the activities of catalase and carnitine acetyltransferase were measured. Further enzymes analyzed were ALP, LDH, glycerophosphate dehydrogenase and malate enzyme together with microsomal lipidperoxidation.

Urinalysis (at 6, 12 and 24 months), overnight in diuresis cages with deprivation of food and water: appearance, colour, pH, specific weight, glucose, ketone bodies, protein, bilirubin, urobilinogen, haemoglobin, ascorbic acid, sediment

Organ weights (at 6, 12 and 24 months): heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, prostate, adrenals, pituitary, thymus, thyroid

Histopathology (at 6, 12 and 24 months): heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, prostate, adrenals, pituitary, thymus, thyroid, salivary glands (parotid, mandibular), trachea, esophagus, aorta, stomach, intestinal segments, urinary bladder, seminal vesicles, epididymides, uterus, eyes with optic nerve, skeletal muscle, bone marrow, lymph nodes, skin with mammary gland, nasal septum, pancreas, sciatic nerve, spinal cord, tongue, sternum, and any other organs or tissues with macroscopic findings

Residue examinations (at 6, 12 and 24 months): blood, intestine, brain, heart, liver, fatty tissue, spleen, muscle, kidneys, carcass

Carcinogenicity:

The following examinations were conducted after a treatment period of 28 months:
bodyweight, food consumption, behaviour and general health conditions (eyes, visible mucosae, teeth, neurological status, palpation and survival checks).

Organ weights and histopathology were conducted as for chronic toxicity.

Findings (more details are presented later when each specific study report is discussed):

General observation / clinical signs: Behaviour and general health condition were not impaired by chronic feeding.

Mortality rate: Survival was not influenced by the test substance.

Body weight: Body weight gains were unimpaired by administration of the test substance. Statistically significant deviations in the first 2 weeks of the study were attributable to slight differences in the initial bodyweights of the test animals. Differences in the bodyweights of the rats receiving 180 ppm as compared with the control animals (slight increases or inhibitions of body weight gains) in the collectives treated for 6 or 12 months were considered to be random occurrences and not due to feeding of Hoe 33171 (but rather to the small number of animals in these collectives).

Food and water consumption: Both parameters were not affected by treatment.

Hematology: The results of the haematological examinations were within the normal range. After 6 months of treatment, a slight increase in the leucocyte count was observed, but this was confined to the female rats receiving 180 ppm and did not recur subsequently during the study.

Clinical chemistry: Changes in the lipid status occurred especially at the highest concentration of 180 ppm (lowering cholesterol and total lipids in serum). A fairly large number of

statistically significant deviations in various serum parameters were observed in the treated groups as compared to the controls, but these were considered as random occurrences. The values were within the range of normal physiological variation for the strain of rat used for the study.

Hepatic enzyme levels: There was no evidence for induction of foreign body metabolism or peroxisomal proliferation.

BSP/PSP function tests: No detectable disturbances of the hepatic or renal functions were found.

Urinalysis: There was no evidence for a harmful effect of the test substance.

Residue investigations: The examinations after 6, 12, 18 and 24 months revealed dose-dependent amounts of residues in the organs and tissues of the rats. However, there was not time-related accumulation of substance residues. There was no observable difference between the male and female rats.

Organ weights: After 6 months of treatment, a significant increase in relative kidney weight was observed in females receiving 180 ppm, but not at any of the other scheduled sacrifices. There was also a slight increase in the absolute but not the relative liver weight of the males receiving 180 ppm, but again only at the sacrifice after 6 months. After 12 months, but at no other time, the absolute and relative adrenal weights of the male rats showed a dose-related increase from 30 ppm onwards. Also, a light decrease in liver weights was observed with statistical significance at 30 ppm in the males. After 24 months, there was a significant decrease in the absolute and relative liver weights of the males at 180 ppm. After 28 months, there was a significant decrease in the liver weights (absolute and relative) in the male rats of the 30 and 180 ppm groups. However, the liver weights remained within the normal range for the strain of rat used and no clear dose-dependency was observed.

Histopathology: Following treatment with 180 ppm, increased calcification and hyperplasia were observed in the pelvic region of the kidneys after 6 months treatment predominantly in males. Histological examination of the liver revealed no morphologically detectable organ changes. After 12 months, the sinuses of the zona reticularis and medulla of the adrenals were more frequently, and in some cases more markedly, distended in the 180 ppm groups than in the other groups. The most strongly marked sinus dilatations were found in the females. After 24 and 28 months, no changes which might have been attributed to the test substance were found. The tumour incidences recorded after 24 or 28 months were comparable in all groups and were therefore interpreted as age-related and of spontaneous origin. The most frequent types of tumour, typical for this strain of rats, were pituitary adenomas, mammary adenomas, mammary carcinomas, uterine polyps, adrenal adenomas, phaeochromocytomas and pancreatic islet cell adenomas.

Conclusion:

Chronic feeding of the test substance led to a lowering of cholesterol and total lipids in the serum at the highest dose of 180 ppm, and occasionally also at lower dose levels but without clear dose-dependency. The males were more sensitive in this respect. However, determination of the hepatic enzyme levels gave no clear indication of peroxisomal proliferation. After 6 months of treatment, an increase of relative organ weights (kidney) was observed in females only at 180 ppm. Increased calcification and hyperplasia were observed in the pelvic region of the kidneys in males receiving 180 ppm. After 12 months, increased relative adrenals weights (males, 30 and 180 ppm) and decreased relative liver weights (males, 30 ppm) were noted. Histopathologic correlates of these findings were only noted for

adrenals at 180 ppm (more marked in females), when sinus dilatation was observed. However, the effects observed on kidneys at 6 months and on adrenals at 12 months could not be detected at subsequent sacrifices. At the end of the treatment of the chronic toxicity study (after 24 months), the absolute and relative liver weights of the male rats receiving 180 ppm were lowered by about 10 % as compared with the controls. This effect was significant, although no pathological findings were revealed by the hepatic function test, hepatic enzyme level or the histological examination of the organ. After 28 months of treatment (carcinogenicity study), relative and/or absolute liver weights were decreased in males at 30 ppm and above, but with no clear dose-dependency. The renal function test, urinalysis and clinical chemistry provided no evidence for any impairment of the urinary production and excretion system. No carcinogenic potential of Fenoxaprop-ethyl was found in this study.

The overall NOAEL of the chronic toxicity study (24 months) in Wistar rats is considered to be 30 ppm (equivalent to 1.6 mg/kg bw/d for males and 2.0 mg/kg bw/d for females), as consistent and repeatable effects were only noted at the dose level of 180 ppm. No carcinogenic effects were induced by Fenoxaprop-ethyl.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Chronic feeding study in rats (interim killing after 6 months)

Reference: *Donaubauer et al, 1983a*; Doc. No. A30803 / Hoechst Report No. 24/83

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al*., 1985a, in this section

Findings (the findings are generally related to an animal number of 10 / sex / dose group):

General observation / clinical signs: Throughout the study the rats remained unaffected by the test substance.

Mortality: One male rat receiving 5 ppm died during week 3 of the study from the effects of a hemorrhage of the urinary bladder. The cause of the hemorrhage could not be identified but was not considered to be related to treatment.

Body weight: Feeding of 30 or 180 ppm resulted in an increase in body weight gains in the males as compared with the controls, which was statistically significant from week 10 onwards in the 180 ppm group only. A slight but statistically non-significant inhibition of body weight gains was observed in the females of the 30 and 180 ppm groups.

Table 106: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice: Body weight data

	Dose group level (ppm)

	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Initial body weight (g)	133	134	130	134	121	120	114	115
Terminal body weight (g)	433	430	455	475*	258	254	243	245

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

Food consumption: There was no effect observed.

Hematology: No changes were noted in haematology except a slight but statistically significant increase in total leucocyte count which was found in females of the highest dose group (180 ppm) only.

Clinical chemistry: A lipid-lowering action of the test substance was observed in males and females. Cholesterol levels were decreased (males: 30 and 180 ppm, females: 30 ppm) and also total lipid levels (males and females: 5 ppm). Various other parameters were statistically significantly changed but remained without effect on the clinical picture of the animals and were not reflected in the histopathological findings. These changes were therefore considered to be spontaneous and not substance related.

Table 107: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice: Relevant haematology and clinical chemistry findings

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Hematology								
Leucocyte count (10^9/L)	5.3	5.2	6.7	6.8	4.1	4.3	4.5	5.5*
Clinical chemistry								
Cholesterol (mmol/L)	2.14	1.86	1.66*	1.46*	2.10	1.79	1.59*	1.78
Total lipids (g/L)	3.47	2.49*	2.81	3.07	3.18	2.59*	3.04	3.55

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

Urinalysis: There was no evidence for a harmful effect of the test substance on the urinary production or excretion system.

Macroscopic examination: Dilatation of the renal pelvis, in some cases with gravely contents, was observed in 1 male from the control group and the 5 ppm group, respectively, 2 males and 2 females from the 30 ppm group, and 2 males and 1 female from the 180 ppm group. A swelling of the liver was noted in 2 males and 1 female receiving 180 ppm.

Organ weights: Only the relative organ weights were subjected to statistical examination, not the absolute weights. Relative kidney weights were increased in females at the highest dose group, which was considered to be related to treatment. The relevance of other significant relative organ weight changes (decreased pituitary weight in males at 5 ppm; increased spleen and thymus weight in females at 180 ppm; increased adrenals weight in females at 30 ppm) remained unclear as no histopathological findings were detected in these organs. Absolute liver weights were slightly higher in the 180 ppm group (males only) than in the controls.

Table 108: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice: Absolute[1] and relative organ weights

	Dose group level (ppm)

	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Kidneys weight								
absolute (g)[1]	2.47	2.35	2.64	2.93	1.53	1.63	1.55	1.72
relative (% bw)	0.571	0.551	0.585	0.612	0.594	0.639	0.636	0.707*
Liver weight								
absolute (g)[1]	12.42	12.35	12.55	13.89	8.09	7.55	7.72	8.10
relative (% bw)	2.863	2.863	2.760	2.932	3.141	2.972	3.173	3.290
Spleen weight								
absolute (g)[1]	0.68	0.65	0.71	0.72	0.46	0.50	0.49	0.53
relative (% bw)	0.158	0.152	0.156	0.151	0.179	0.198	0.202	0.216*
Adrenals weight								
absolute (g)[1]	0.0469	0.0483	0.0530	0.0549	0.0724	0.0726	0.0802	0.0732
relative (% bw)	0.0108	0.0113	0.0117	0.0116	0.0282	0.0287	0.0330*	0.0299
Thymus weight								
absolute (g)[1]	0.334	0.498	0.442	0.529	0.273	0.337	0.337	0.361
relative (% bw)	0.077	0.115	0.097	0.110	0.106	0.132	0.137	0.146*
Pituitary weight								
absolute (g)[1]	0.0103	0.0082	0.0104	0.0122	0.0153	0.0148	0.0140	0.0134
relative (% bw)	0.0024	0.0019*	0.0023	0.0026	0.0060	0.0059	0.0058	0.0054

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Histopathology: 6 animals from the control group, 3 animals each from the 5 and 30 ppm concentration groups, and 10 animals from the 180 ppm group showed partially hyperplastic epithelia of the renal pelvis, together with calcareous precipitates below the epithelium and even in the lumen of the renal pelvis.

Table 109: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice: Histopathology findings

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Kidneys hyperplasia and calcification of the renal pelvis	4/10	2/9	1/10	7/10	2/10	1/10	1/10	3/10

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

Conclusion:

Please see overall conclusion at the beginning of this section, Ref.: *Donaubauer et al.*, 1985a, Doc. No. A31880, Hoechst Report No. 85.0688

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Chronic feeding study in rats (interim killing after 12 months)

Reference: *Donaubauer et al, 1983b*; Doc. No. A29693 / Hoechst Report No. 83.0613

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al., 1985a,* in this section

Findings (the findings are generally related to an animal number of 10 / sex / dose group):

General observation / clinical signs: No clinical signs were observed during the study.

Mortality: No mortality occurred.

Body weight: In males, slight increases in body weight were noted but these were neither dose-related nor statistically significant.

Table 110: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice: Body weight data

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Initial body weight (g)	134	132	131	139	120	116	115	109
Terminal body weight (g)	496	522	511	530	282	297	296	280

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

Food consumption: Food consumption was similar in controls and treatment groups.

Hematology: Statistical significance was only reached in females of the 30 ppm group which showed increases in haemoglobin and hematocrit values. These changes were considered to be of random occurrence and of no toxicological relevance.

Clinical chemistry: A substance-related change of the lipid status was noted in males and females. Cholesterol was lowered in males at 180 ppm and in females at 30 and 180 ppm, while total lipids were lowered in males at 5 and 180 ppm and in females at 180 ppm. Various serum electrolyte values were significantly raised or lowered as compared with controls (sodium: lowered in males at 30 and 180 ppm; potassium: raised in males at 180 ppm; chloride: lowered in males at 30 and 180 ppm; calcium: lowered in females at 30 and 180 ppm; inorganic phosphorus: raised in males at 30 ppm and females at 30 and 80 ppm). Furthermore, uric acid was lowered in males at 180 ppm. In females, total bilirubin was raised in all treatment groups, creatinine was raised at 30 and 80 ppm, and glucose was raised at 30 ppm. Serum electrophoresis showed in both males and females slight alterations in the distribution of individual globulin fractions (alpha-1-globulin: lowered in males at 180 ppm and raised in females at 30 ppm; alpha-3-globulin: raised in males at 5 and 30 ppm; gamma-1-globulin: raised in females at 180 ppm). The total protein content remained constant.

The deviations in clinical chemistry had no discernible effect on the general appearance or health conditions in the animals, and there were no histopathological correlates. Therefore, these findings were considered to be of no toxicological relevance.

Table 111: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice: Relevant clinical chemistry findings

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Cholesterol (mmol/L)	3.00	2.81	2.67	2.36*	2.86	2.58	2.10*	1.87*
Total lipids (g/L)	4.71	4.02*	4.28	3.60*	4.05	3.53	3.94	3.19*

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

Urinalysis: There was no evidence for a harmful effect of the test substance on the urinary production or excretion system.

Organ weights: Only the relative organ weights were subjected to statistical examination, not the absolute weights. Relative adrenals weight was increased in males at 30 and 180 ppm. Decreases of the relative organ weights were noted in the liver (males, 30 ppm), heart (females, 30 ppm), thyroid (females, 5 and 30 ppm) and pituitary (females, 30 ppm).

Table 112: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice: Absolute[1] and relative organ weights

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Adrenals weight								
absolute (g)[1]	0.0443	0.0473	0.0538	0.0574	0.0722	0.0706	0.0662	0.0711
relative (% bw)	0.0090	0.0091	0.0106*	0.0108*	0.0258	0.0238	0.0227	0.0254
Liver weight								
absolute (g)[1]	14.16	14.21	13.35	14.53	8.78	8.49	8.22	8.00
relative (% bw)	2.864	2.722	2.599*	2.742	3.120	2.868	2.791	2.862
Heart weight								
absolute (g)[1]	1.36	1.20	1.41	1.49	0.97	0.97	0.90	0.91
relative (% bw)	0.275	0.232	0.281	0.283	0.345	0.328	0.308*	0.326
Thyroid weight								
absolute (g)[1]	0.0240	0.0266	0.0248	0.0294	0.0296	0.0197	0.0197	0.0195
relative (% bw)	0.0048	0.0051	0.0049	0.0056	0.0105	0.0067*	0.0067*	0.0070
Pituitary weight								
absolute (g)[1]	0.0113	0.0130	0.0110	0.0117	0.0171	0.0166	0.0140	0.0136
relative (% bw)	0.0023	0.0025	0.0022	0.0022	0.0061	0.0056	0.0048*	0.0049

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Macroscopic examination: Autopsy revealed a slightly more frequent occurrence of lobular markings of the liver at 180 ppm as compared with the controls. However, this finding had no correlate in histopathology and was considered to be an outcome of exsanguination which by chance occurred more frequently in the medium and high dose group.

Histopathology: The sinuses of the zona reticularis and medulla of the adrenals were more frequently, and in some cases more markedly, distended in the 180 ppm groups than in the other groups. The most strongly marked sinus dilatations were found in the females.

Table 113: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice: Pathology findings

	Dose group level (ppm)

	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Macroscopic examination								
Liver								
Lobular markings	4/10	3/10	4/10	9/10		1/10	3/10	1/10
Histopathology								
Adrenals								
Sinus dilatation								
-slight	3/10	4/10	3/10	2/10	5/10	3/10	4/10	2/10
-moderate			2/10	3/10	3/10	2/10		2/10
-severe								6/10

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

Conclusion:

Please see overall conclusion at the beginning of this section, Ref.: Donaubauer et al., 1985a, Doc. No. A31880, Hoechst Report No. 85.0688

Supplement to Report No. 83.0613. Hoe 33171 – active ingredient technical. Chronic feeding study in rats (interim killing after 12 months). Determination of hepatic enzyme levels

Reference: *Schütz et al*, 1984; Doc. No. A29694 / Hoechst Report No. 84.0639

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al*., 1985a, in this section

To test for induction of foreign substance metabolism, the activities of the following hepatic enzymes were determined: aminopyrine N-demethylase, anisic acid ester O-demethylase, ethoxycoumarin O-deethylase, cytochrome c-reductase, glucuronyltransferase I and glucuronyltransferase II. To test for peroxisomal proliferation, the activities of catalase and carnitine acetyltransferase were measured. Further enzymes which were analyzed were ALP, LDH, glycerophosphate dehydrogenase and malate enzyme together with microsomal lipidperoxidation.

Findings (the findings are generally related to an animal number of 10 / sex / dose group):

Determination of the two glucuronyltransferases was successful in the females, but not in the males. Of the foreign substance metabolism enzymes examined, only aminopyrine N-demethylase proved to be definitely increased in the females of the high concentration group (180 ppm). In all other cases there were only marginal or statistically insignificant increases, or even decreases of enzyme activity at the highest concentration. With regard to peroxisomal proliferation, there were no signs of increased catalase activity. However, carnitine acteyltransferase activity was increased in both sexes at 180 ppm. Carnitine acteyltransferase

occurs not only in peroxisomes but also in the mitochondria. The author suggests that the increase of this enzyme resulted from an increase of the mitochondrial enzyme, but this was not investigated in this study. Of the enzymes of intermediate metabolism examined in this study, only LDH at the highest concentration was increased. No increase of malate enzyme activity was observed which was discussed by the author as an indication that no peroxisomal proliferation had taken place, since this enzyme has been shown to be greatly increased by administration of peroxisome proliferators. Since there was no increase of microsomal lipid peroxidation, it is very unlikely that the microsomal membranes were damaged by the treatment.

Table 114: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice: Special biochemical investigations of hepatic enzyme levels

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Aminopyrine N-demethylase (U/g liver)	0.503	0.539	0.533	0.597*	0.0395	0.0642	0,0586	0,0883*
Anisic acid ester O-demethylase (U/g liver)	0.156	0.175*	0.184*	0.195*	0.0609	0.0341	0.0423	0.0658
Ethoxycoumarin O-deethylase (U/g liver)	0.0306	0.0297	0.0235*	0.0260*	0.0448	0.0533*	0.0587*	0.0524
Cytochrome c-reductase (U/g liver)	9.98	8.06*	6.50*	6.06*	6.95	5.23*	4.46*	6.02
Lipoperoxidation (E/g liver)	0.917	0.976	0.895	0.911	0.0349	0.0236*	0.0198*	0.0232*
Glucuronyltransferase I (U/g liver)	nd	nd	nd	nd	0.0956	0.0608	0.0737	0.0691
Glucuronyltransferase II (U/g liver)	nd	nd	nd	nd	0.614	0.673	0.663	0.881*
ALP (U/g liver)	0.471	0.447	0.398	0.394	0.459	0.418	0.393	0.360
Catalase (R/g liver)	12510	13260	9878	5459	3735	2562	1992	1911
Carnitine acetyl transferase (E/g liver)	0.00351	0.00465	0.00606	0.01888*	0.00821	0.00848	0.01146	0.03309*
LDH (U/g liver)	277	313	333	400*	147	160	157	205*
Glycerophosphate dehydrogenase (U/g liver)	21.8	15.3*	15.2*	13.4*	6.75	8.79	7.13	10.15*
Malate enzyme (U/g liver)	1.008	0.755*	0.388*	0.404*	0.585	0.461*	0.444*	0.320*

* ($p < 0.05$); significantly different from controls
nd = not determined

Conclusion:

There was an increase of aminopyrine N-demethylase activity observed at 180 ppm, as well as an increase of carnitine acteyltransferase and LDH. The study author concludes from the results of the biochemical investigations that the test substance did not lead to an induction of foreign substance metabolism or peroxisomal proliferation. However, it was not investigated if the increased activity of carnitine acteyltransferase at 180 ppm derived from peroxisomes or from mitochondrions.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Chronic feeding study (24 months) in rats

Reference: *Donaubauer et al,* 1984a; Doc. No. A30807 / Hoechst Report No. 84.0632

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al.*, 1985a, in this section

Number of animals: 20/sex/group for chronic toxicity; 6 /sex/group for BSP/PSP function tests

Duration of study: 24 months; or 26 months for BSP/PSP function tests

Laboratory examinations: Hematology and clinical chemistry were evaluated before the start of the study (initial value), in weeks 26, 54 and 79 of the study (intermediate values), and in week 106 (terminal value). Urinalysis was performed before the start of the study (initial value), in weeks 25, 53 and 78 (intermediate values), and in week 105 (terminal value).

Findings:

General observation / clinical signs: The behaviour of the rats remained unaffected throughout the study. No neurological disturbances, impairments of dental growth or changes in the oral mucosa occurred which might have been attributed to treatment.

Mortality: Mortality was not influenced by the administration of test substance. The number of animals which died intercurrently or were killed before the termination of the study are presented in the following table.

Table 115: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 24 month sacrifice, final investigations: Mortality rates

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Chronic toxicity testing (20/sex/group)	1	7	2	3	7	7	7	6
BSP/PSP function tests (6/sex/group)	0	0	1	2	1	2	3	1
Residue examinations (10/sex/group)	0	0	0	0	2	0	0	0

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

Body weight: In males of the lowest dose group (5 ppm), body weight gains were slightly more pronounced as compared with the other treatment groups and the controls. The deviation was statistically significant at various intervals, but not at the end of the study.

Table 116: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 24 month sacrifice, final investigations: Body weight data

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Initial body weight (g)	130	128	128	122	118	114	113	112
Terminal body weight (g)	529	542	513	526	344	352	319	324

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

Food and water consumption: No significant differences were noted among the control and treatment groups.

Hematology: No changes were found at haematology examinations which were attributed to the treatment. In males receiving 180 ppm, the only statistically significant deviation was a shortening of the coagulation time after 26 weeks. In the females of the 5 ppm group the erythrocyte count was increased after 26 and 54 weeks. Both findings are considered as random occurrence.

Clinical chemistry: A number of clinical chemistry parameters showed statistically significant differences between treated and untreated animals at the various scheduled examinations, and in particular also before the start of the study. A lipid-lowering effect of the test substance was observed in males receiving 180 ppm. Other changes in parameters were discussed not to be indicative of a substance-related effect. The values were well within the normal range of physiological variation of the strain of rat used, and general appearance, health condition and histopathological findings offer no evidence of a toxic effect of the test substance.

Table 117: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 24 month sacrifice: Relevant clinical chemistry findings

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Cholesterol (mmol/L)								
Initial	2.15	2.36	3.09*	2.65*	2.25	2.57	2.49	2.59
Week 26	2.41	2.71	2.52	1.96*	2.67	2.65	2.64	2.38
Week 54	3.43	3.74	3.58	2.69*	3.53	3.03	2.90	2.89
Week 79	3.46	4.38	4.03	3.14	2.88	2.54	2.97	2.76
Terminal (Week 106)	4.92	4.84	4.36	3.85*	3.58	3.08	3.35	3.33
Total lipids (g/L)								
Initial, Week 26, Week 54, Week 79	n.d.	n.d	n.d	n.d	n.d.	n.d	n.d	n.d
Terminal (Week 106)	6.66	6.03	6.67	4.98*	5.25	5.55	4.75	4.76

* ($p < 0.05$); significantly different from controls
n.d. = not determined

BSP/PSP function tests: The results showed no statistical significant differences between control and treated animals and gave no indication of functional disturbances of the liver and kidneys.

Urinalysis: The results offer no evicence of a harmful effect of the test substance on the urinary production or secretion system.

Organ weights: The decrease in absolute and relative liver weights among the males at the highest dose group, although slight, was nevertheless statistically significant as compared with the controls. Since the histopathological examination gave no indication of hepatic

lesions, no toxicological significance was attached to these lower values. All other organ weights showed no differences between treatment and control groups.

Table 118: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 24 month sacrifice: Relevant absolute and relative organ weights

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Liver weight								
absolute (g)	16.78	16.51	15.47	14.89*	11.25	11.83	10.01	10.32
relative (% bw)	3.168	3.039	3.023	2.844*	3.251	3.320	3.129	3.196

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

Macroscopic examination: Most of the control and treatment animals showed macroscopically visible organ changes and in many cases also neoplasms. No differences between the various groups were observed.

Histopathology: Findings consisted exclusively of typical age-related changes in a great variety of organ systems, but more particular in the liver, the kidneys and the myocardium. There was nothing to indicate that these ageing processes were affected by the test substance. Furthermore, there was no evidence that the incidence of tumours was affected by the test substance.

Conclusion:

Please see overall conclusion at the beginning of this section, Ref.: *Donaubauer et al.*, 1985a, Doc. No. A31880, Hoechst Report No. 85.0688

Supplement to Report No. 84.0632 of 29 September 1984. Hoe 33171 – active ingredient technical. Chronic feeding study (24 months) in rats. Determination of residues in organs and tissues

Reference: *Schütz et al*., 1985; Doc. No. A30804 / Hoechst Report No. 85.0205

Guideline: -

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al.*, 1985a, in this section

Special investigation on residues of the test substance: Groups of 10 male and 10 female rats each were fed the test substance in concentrations of 5, 30 or 180 ppm. Interim sacrifices and determination of residues in organs and tissues were performed after 6 months (week 26), 12 months (week 54) and 18 months (week 79), in each case on 2 males and 2 females from each group. The remaining 4 males and 4 females (control group: 4 males and 2 females) were killed after 24 months (week 104).

The following organs and tissues were taken from animals of both sexes: blood, intestine, fatty tissue, brain, heart, carcass, liver, spleen, muscle and kidneys. The organs and tissues of

the males and the females of each dose group were combined to form a mixed sample for analysis. The detection limits varied from 0.02 to 0.1 mg/kg in the different tissues.

Findings:

The organs of animals from the control groups showed no residues of the test substance. The amounts of residues found in the treatment groups were dose-related. There was no time-related accumulation of residues observed. Within the individual dose groups there was no significant difference between males and females with regard to residue levels in organs and tissues.

Table 119: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, Residue levels in various organs and tissues after 6, 12, 18 and 24 months

	Dose group level (mg/kg)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Blood								
6 months	n.d.	0.2	2.1	22	n.d.	0.2	1.0	9.9
12 months	n.d.	0.3	2.7	8.3	n.d.	0.3	0.5	13
18 months	n.d.	0.3	2.1	17	n.d.	0.3	1.4	11
24 months	n.d.	0.4	1.2	4.4	n.d.	0.3	1.9	7.6
Intestine								
6 months	n.d.	0.1	0.7	4.2	n.d.	0.07	0.7	4.4
12 months	n.d.	0.04	0.3	2.8	n.d.	0.1	1.0	3.6
18 months	n.d.	0.05	0.5	2.6	n.d.	0.08	0.7	3.4
24 months	n.d.	0.09	0.9	3.4	n.d.	0.08	0.7	4.9
Fatty tissue								
6 months	n.d.	0.07	1.3	8.6	n.d.	0.2	1.5	9.0
12 months	n.d.	0.1	0.5	4.2	n.d.	0.3	2.0	5.9
18 months	n.d.	0.05	0.6	4.3	n.d.	0.1	0.7	4.8
24 months	n.d.	0.08	0.8	3.7	n.d.	0.1	0.4	2.7
Brain								
6 months	n.d.	0.01	0.07	0.7	n.d.	n.d.	0.06	0.2
12 months	n.d.	0.01	0.08	0.4	n.d.	n.d.	0.05	0.6
18 months	n.d.	n.d.	0.06	0.8	n.d.	n.d.	0.04	0.4
24 months	n.d.	0.02	0.07	0.6	n.d.	n.d.	0.06	0.6
Heart								
6 months	n.d.	n.d.	0.5	3.7	n.d.	0.1	1.1	2.2
12 months	n.d.	0.1	0.6	4.4	n.d.	0.1	1.1	2.2
18 months	n.d.	n.d.	0.6	3.8	n.d.	0.1	0.5	3.7
24 months	n.d.	0.2	0.8	5.4	n.d.	0.1	0.6	3.9
Carcass								
6 months	n.d.	0.04	0.3	1.8	n.d.	0.05	0.4	2.2
12 months	n.d.	0.05	0.3	2.1	n.d.	0.07	0.5	2.5
18 months	n.d.	0.04	0.03	2.2	n.d.	0.06	0.4	2.5
24 months	n.d.	0.06	0.4	2.6	n.d.	0.08	0.4	2.4
Liver								
6 months	n.d.	0.2	1.3	7.3	n.d.	0.1	1.4	10
12 months	n.d.	0.2	1.4	7.2	n.d.	0.4	0.6	8.4
18 months	n.d.	0.1	1.3	5.4	n.d.	0.1	1.5	8.8
24 months	n.d.	0.3	1.4	5.9	n.d.	0.09	1.6	8.7
Spleen								
6 months	n.d.	n.d.	0.3	3.2	n.d.	n.d.	0.4	2.3
12 months	n.d.	0.1	0.3	2.2	n.d.	0.1	0.6	2.4
18 months	n.d.	n.d.	0.2	3.0	n.d.	n.d.	0.3	1.8
24 months	n.d.	0.07	0.6	3.1	n.d.	0.06	no data	1.8

	Dose group level (mg/kg)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Muscle								
6 months	n.d.	n.d.	0.2	1.9	n.d.	n.d.	0.4	1.4
12 months	n.d.	n.d.	0.2	1.8	n.d.	n.d.	0.2	1.3
18 months	n.d.	n.d.	0.3	1.8	n.d.	n.d.	0.3	0.7
24 months	n.d.	n.d.	0.3	1.7	n.d.	n.d.	0.3	1.3
Kidney								
6 months	n.d.	0.6	3.9	27	n.d.	0.6	3.7	19
12 months	n.d.	0.6	3.6	23	n.d.	1.2	4.7	25
18 months	n.d.	0.4	2.9	23	n.d.	1.0	5.2	21
24 months	n.d.	0.9	5.8	27	n.d.	1.2	5.2	21

n.d. = not detectable (below detection limit)
Detection limit = 0.1 mg/kg for heart, muscle; 0.06 mg/kg for spleen; 0.05 mg/kg for blood, intestine, fatty tissue, kidney; 0.04 mg/kg for liver; 0.03 mg/kg for carcass; 0.02 mg/kg for brain

Conclusion:

The highest residue levels for Fenoxaprop-ethyl were found in the kidneys, blood and liver. There was no sex difference observed and no accumulation over the entire course of the study.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Combined chronic toxicity and carcinogenicity study in rats. Part II: Carcinogenicity study (28-month feeding study)

Reference: *Donaubauer et al*, 1985b; Doc. No. A31878 / Hoechst Report No. 85.0682
Amendment to Report No. 85.0682, *Krieg*, 1987, Doc. No. A36064

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al*., 1985a, in this section

Findings:

General observation / clinical signs: The behaviour of the rats remained unaffected throughout the study. No neurological disturbances, impairments of dental growth or changes in the oral mucosa occurred which might have been attributed to treatment.

Mortality: No statistical significant differences were observed between the control and treatment animals. There was, however, a slight increase in mortality in the female rats of the 30 and 180 ppm during the last 4 months of the study, which was not attributed to the feeding of the test substance.

Table 120: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations: Mortality rates

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Treatment periods								
Week 1 – 26	0	1	0	0	1	1	0	1
Week 27 – 52	0	0	3	1	0	0	0	1
Week 53 – 78	5	0	0	0	4	5	1	3
Week 79 – 104	5	7	7	4	9	7	9	9
Week 105 – sacrifice	9	13	7	11	7	7	15	13
Total mortality	19	21	17	16	21	20	25	27
Total mortality (%)	31.7	35.0	28.3	26.7	35.0	33.3	41.7	45.0

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

Body weight: The body weight gains of both male and female rats was normal and remained unaffected by the test substance.

Food consumption: There was no effect of test substance intake observed.

Organ weights: There was a statistically significant lowering of the absolute liver weight in males receiving 30 ppm, and of absolute brain weights in females receiving 30 ppm. Evaluation of the relative organ weights revealed a statistically significant lowering of liver weights as compared with the controls in the males at 30 and 180 ppm. The findings showed no dose-dependency and were within the normal range for the strain of rat used for this study.

Table 121: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations: Absolute and relative organ weights

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Liver weight								
absolute (g)	16.40	15.84	15.13*	15.38	11.40	10.93	10.86	10.66
relative (% bw)	3.306	3.194	2.903*	2.960*	3.411	3.362	3.395	3.231
Brain weight								
absolute (g)	2.26	2.24	2.27	2.26	2.08	2.03	2.00*	2.06
relative (% bw)	0.459	0.457	0.438	0.439	0.629	0.636	0.634	0.639

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

Macroscopic examination: The macroscopic findings for the rats sacrificed or found dead during the course of the study, as well as for those sacrificed at study termination, showed no connection with the feeding of the test substance.

Histopathology: Feeding of the test substance caused no morphologically detectable organ lesions. Statistical evaluation of the tumour incidence yielded no significant differences between the treatment and control animals. There was no evidence of a carcinogenic effect in rats.

Table 122: Combined chronic toxicity and carcinogenicity study of Fenoxaprop-ethyl in Wistar rats, 28 month sacrifice: Pathology findings

	Dose group level (ppm)	
	Males	**Females**

	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Number of animals examined microscopically	60	60	60	60	59	60	60	59
Number of animals with tumours	36	39	35	37	49	45	52	47
Animals with malignant tumours	13	14	6	9	16[1]	12[2]	18[2]	8
Animals with a single tumour	23	26	25	28	23	24	28	29
Animals with two tumours	11	12	10	9	20	18	16	11
Animals with three or more tumours	2	1	-	-	6	3	8	7

* ($p < 0.05$); significantly different from controls
[1] including 1 animal with 2 different malignant tumours
[2] including 4 animals with 2 different malignant tumours

Detailed information on tumour incidences can be found in the tables below.

Table 123:: Histopathology – benign neoplastic findings in rats at the study termination

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Benign neoplasms								
Skin - Fibroma - Fibrolipoma - Fibromyxoma	 - - 2 (60)	 2 (60) 1 (60) -	 - - -	 - - -	 - - -	 - - -	 - -* 1 (60)	 1 (59) -
Pituitary gland - adenoma - Invasive tumour of anterior lobe	 12 (60) -	 10 (60) 4 (60)	 15 (60) -	 7 (60) -	 31 (59) 1 (59)	 23 (60) 2 (60)	 33 (60) -	 33 (59) -
Thyroid gland - Follicular cell adenoma - Parafollicular cell adenoma	 2 (60) 4 (60)	 3 (60) 2 (60)	 3 (60) 2 (60)	 2 (60) 4 (60)	 1 (59) 1 (59)	 - 1 (60)	 1 (60) 1 (60)	 2 (59) 2 (59)
Parathyroid - Adenoma	 2 (60)	 -	 -	 -	 -	 -	 -	 -
Adrenals - Adenoma - Phaeochromocytoma - Immature ganglioneuroma	 3 (60) 3 (60) 1 (60)	 4 (60) 1 (60) -	 2 (60) 2 (60) -	 4 (60) 6 (60) 1 (60)	 5 (59) - -	 2 (60) 1 (60) -	 1 (60) 1 (60) -	 2 (59) 1 (59) -
Pancreas - Islet-cell adenoma - Adenoma (exocrine)	 5 (60) 1 (60)	 6 (60) 1 (60)	 8 (60) -	 3 (60) 1 (60)	 5 (59) -	 4 (60) -	 4 (60) -	 1 (59) -
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)
Mammary gland area - Adenoma/Fibroadenoma	 -	 -	 -	 1 (60)	 4 (59)	 9 (60)	 4 (60)	 4 (59)
Uterus - Fibro-adenomatous polyp					 10 (59)	 6 (60)	 11 (60)	 10 (59)
Thymus - Lympho-epithelial thymoma	 -	 1 (60)	 -	 1 (60)	 1 (59)	 2 (60)	 4 (60)	 1 (59)
Salivary glands - Carcinoma	 -	 -	 -	 1 (60)	 -	 -	 1 (60)-	 -
Liver - Hyperplastic hepatocellular nodule	 1 (60)	 1 (60)	 -	 -	 1 (59)	 1 (60)	 1 (60)	 -
Kidneys - pelvic pappiloma	 -	 -	 -	 -	 1 (59)	 -	 -	 -
Urinary bladder - Pappiloma - Papillomatosis	 - -	 - 1 (60)	 - -	 - 1 (60)	 1 (59) -	 - -	 - -	 1 (59) -
Abdominal cavity - Lipoma	 -	 -	 -	 -	 1 (59)	 -	 -	 -
Lymph nodes - Haemangioma	 -	 2 (60)	 3 (60)	 1 (60)	 1 (59)	 1 (60)	 -	 1 (59)
Brain - granular cell tumor	 3 (60)	 1 (60)	 2 (60)	 1 (60)	 3 (59)	 -	 -	 -

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Benign neoplasms								
- Ependymoma	-	1 (60)-	-	-	-	-	-	-

Table 124: Histopathology – malign neoplastic findings in rats at the study termination

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Malign neoplasms								
Skin - Sarcoma - Carcinoma	2 (60) -	2 (60) 1 (60)	3 (60) -	1 (60) 1 (60)	1 (59) 1 (60)	- -	- -	- 1 (60)
Thyroid gland - Follicular cell carcinoma - Parafollicular cell carcinoma	1 (60) -	- 1 (60)	1 (60) -	- -	- -	- 1 (60)	1 (60) -	- -
Adrenals - Immature ganglioneuroma	1 (60)	-	-	1 (60)	-	-	-	-
Seminal vesicles/ Prostate - Carcinoma	-	1 (60)	-	-				
Mamma - Carcinoma	-	-	-	-	7 (59)	6 (60)	12 (60)	3 (59)
Uterus - Sarcoma - Carcinoma					1 (59) 4 (59)	1 (60) 1 (60)	1 (60) 3 (60)	2 (59) -
Thymus - Lymphosarcoma	1 (60)	-	-	-	-	-	2 (60)	-
Salivary glands - Fibrosarcoma	1 (60)	-	-	-	-	-	-	-
Lungs - Alveolar carcinoma	2 (60)	1 (60)	-	1 (60)	-	1 (60)	-	1 (59)
Kidneys - cortical carcinoma	-	-	-	-	1 (59)	-	-	-
Intestine - Sarcoma - Carcinoma	- -	1 (60) -	- 1 (60)	- -	- -	1 (60)- -	- -	- -
Abdominal cavity - Mesothelioma - Reticularsarcoma - Fibrosarcoma	- - -	- - -	- - -	- 1(60) -	- - -	- - -	1 (60) - -	- - 1 (59)
Lymph nodes - Lymphoma	2 (60)	-	1 (60)	1 (60)	1 (59)	2 (60)	-	-
Brain - Meningeal sarcoma - Astroblastoma - Oligodendroglioma	1 (60 1 (60) -	- 1 (60) -	- - -	- - -	- - -	- - -	- - 1 (60)	- - -
Spinal cord - Immature ganglioneuroma	-	-	-	-	-	1 (60)	-	-
Bone - Haemangioma - Osteosarcoma	- 1 (60)	1 (60) -	- -	- 2 (60)	- -	- -	- -	- -

According to the study author the absence of Leydig cells tumours in the male control animals as well as theca granulosa cell tumours in female controls it is a remarkable fact and must have been random. In another 28-month carcinogenicity study conducted at much the same time in animals of the same strain, 8 Leydig cell tumours were observed in 100 male control animals and 2 theca granulosa cell tumours in 99 female control animals.

Conclusion:

Statistical evaluation of the tumour incidences yielded no significant differences between the treated and the control animals. In conclusion, Fenoxaprop-ethyl had no carcinogenic effect in rats after a treatment period of 28 months.

Mice:

Two long term toxicity / carcinogenicity studies have been performed with the racemate Fenoxaprop-ethyl (Hoe 33171). As the maximum tolerated dose (MTD) was not reached in the first study, a second study using higher dose levels was conducted.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0H AS201). Carcinogenicity study in mice (24-month feeding study)

Reference: *Donaubauer et al*, 1985c; Doc. No. A30816 / Hoechst Report No. 85.0046

Guideline: OECD guideline 451 (adopted 1981); EPA guideline 83-2 (1982)

Deviations: Histopathology was not performed on sternum and femur.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

60 male and 60 female NMRI mice (strain: NMRKf(SPF71), source: Hoechst) per dose group were treated with 0, 2.5, 10 or 40 ppm of Fenoxaprop-ethyl. Of these mice, 10 sex/group were sacrificed intercurrently after 12 months. The results of this interim sacrifice are reported in a separate report later in this section. 50 mice/sex/group were sacrificed after 24 months of treatment. The actual intake of Fenoxaprop-ethyl was calculated separately for each period of treatment time.

Table 125: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice: Test substance intake in mg/kg bw/d

	Test substance intake in mg/kg bw/d			
	Males		**Females**	
Dietary level	**12 mo**	**24 mo**	**12 mo**	**24 mo**
2.5 ppm	0.35	0.34	0.43	0.40
10 ppm	1.30	1.38	1.63	1.61
40 ppm	5.54	5.48	6.59	6.54

At the beginning of the study the mice were about 3 – 4 weeks old and had a mean body weight of 22 g (males) and 19.5 g (females) after a one-week adaptation period. The standard pulverized diet Altromin and the test substance were premixed at 14-day intervals. The diet

was prepared fresh once weekly. Analytical trials were carried out weekly to check the content and homogeneity of the test substance. The test substance used in this study (Hoe 33171 0H AS 201) had a purity of 94 % according to certificate of analysis No. 01888.

Behaviour and general health conditions (neurological disturbances, eyes, dental growth, oral mucosa) were observed twice daily. Body weights and food consumption were determined once weekly. Hematology (weeks 52 and 105) was performed on non-starved animals and included haemoglobin, erythrocytes, hematocrit, thrombocytes, leucocytes, differential blood count, MCV, MCH and MCHC. At clinical chemistry (weeks 52 and 105), the following parameters were examined from the blood of non-starved animals: ALAT, ASAT, ALP and gamma-glutamyl transferase. Determination of hepatic enzyme levels was only performed at the 12-month interim sacrifice. To test for induction of foreign substance metabolism, the enzymatic activity of the following enzymes was determined: aminopyrine N-demethylase, anisic acid ester O-demethylase, ethoxycoumarin O-demethylase, cytochrome c reductase, glucuronyltransferase I and II. Further enzymes like catalase, alkaline phosphatase, lactate dehydrogenase, glycerophosphate dehydrogenase and malate enzyme together with microsomal lipid peroxidation were also determined to provide additional information on possible effects on metabolic processes in the liver. Macroscopic examination was performed on all animals. The weights of the following organs were determined in all animals: heart, lungs, liver, kidneys, spleen, brain, testes and ovaries. Histopathology included heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, salivary glands (parotid and mandibular), trachea and esophagus, stomach (fundus and prepyloric region), intestine (duodenum, jejunum, ileum, caecum, colon, rectum), urinary bladder, epididymides, seminal vesicles, uterus, both eyes with optic nerves, skeletal muscle, prostate, adrenals, pituitary, thymus, bone marrow, lymph nodes (mesenteric, iliac and submandibular), skin with mammary gland, nasal septum, pancreas, sciatic nerve, spinal marrow, tumours (where detected marcoscopically) and any other organs with macroscopic findings. Statistical evaluation was performed for the following parameters: body weight, haemoglobin, erythrocytes, hematocrit, leucocytes, thrombocytes, ALAT, ASAT, ALP, gamma-glutamyl transferase, hepatic enzymes and all relative organ weights.

Findings of the 24 month sacrifice (the results of the interim sacrifice at 12 months are reported in a special report later in this section):

Behaviour and general health conditions: Throughout the study the behaviour remained unaffected and clinical signs could not be observed.

Mortality: No changes which could be attributed to treatment were found between control and treated animals. Some differences in mortality began to arise during the last six months of the study (i.e. towards the end of the natural lifespan of this strain of mouse) and were not dose-related.

Table 126: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, mortality rates

	Dose group level (ppm)							
	Males				Females			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Treatment periods								
Week 1 – 26	1	1	1	0	0	1	0	0
Week 27 – 52	4	5	2	6	2	1	1	2
Week 53 – 78	3	4	3	4	6	6	3	4
Week 79 – termination	6	11	15	9	13	22	22	14
Total mortality	14	21	21	19	21	30	26	20

	Dose group level (ppm)							
	Males				Females			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Total mortality (%)	28	42	42	38	42	60	52	40

Body weight: In spite of occasional statistically significant deviations as compared with the control groups, the body weight gains of the mice in all test groups were on the whole normal and gave no indication of an effect induced by feeding of the test substance.

Table 127: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, body weight data

	Dose group level (ppm)							
	Males				Females			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Initial body weight (g)	21	22	22	22	19	19	19	19
Terminal body weight (g)	36	36	37	37	34	34	34	34

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

Food consumption: Food consumption, both absolute and relative, at all concentration levels corresponded to that of the controls.

Hematology: In females of the highest dose group, haemoglobin values were increased as compared to controls. In females receiving 2.5 ppm, leucocyte levels were decreased. However, leucocyte values were very variable within each group and were seen as age-related spontaneous changes.

Clinical chemistry: Gamma-glutamyl transferase was decreased in females at 10 and 40 ppm with no clear dose-dependency, which was considered to be of no biological relevance.

Table 128: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, relevant haematology and clinical chemistry findings

	Dose group level (ppm)							
	Males				Females			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Hematology								
Haemoglobin (g/L)	143	147	144	145	132	138	142	146*
Leucocytes (10^9/L)	19.9	10.0	17.1	5.9	10.8	4.4*	25.1	39.8
Clinical chemistry								
γ-glutamyl transferase	4.4	3.4	2.3	3.8	7.4	2.5	3.9*	1.3*

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

Hepatic enzyme levels: After 12 month of the study, feeding of Fenoxaprop-ethyl did not lead to an induction of foreign substance metabolism or to peroxisomal proliferation. More details are presented in the respective study report later in this section.

Organ weights: There was a statistically significant lowering of the relative liver weights in females at 10 and 40 ppm. This was considered to be a random occurrence since the control group showed a large number of mice with increased liver weights. All other organ weights corresponded closely to those of controls. The statistically significant increase of kidney weights observed at the 12 month interim sacrifice in females (40 ppm) could not be found at the 24 month sacrifice.

Table 129: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, absolute1 and relative organ weights

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Liver weight								
absolute (g)[1]	1.73	1.72	1.72	1.83	2.01	1.76	1.69	1.71
relative (% bw)	4.773	4.729	4.651	4.933	5.841	5.186	4.959*	5.017*
Kidneys weight								
absolute (g)[1]	0.60	0.61	0.61	0.63	0.48	0.46	0.48	0.47
relative (% bw)	1.663	1.667	1.662	1.709	1.418	1.358	1.400	1.395

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Histopathology: The histological examinations after 12 and 24 months showed that no morphologically detectable organ changes were caused by feeding of the test stubstance. No treatment-related effect was detected in the incidence or distribution of tumour types- see tables below. The most frequent tumours included: lymphoreticular tumours and pulmonary tumours in both male and female mice, adrenal cortical tumours in male mice, and ovarian tumours in female mice. There was an apparent increase in ovarian papillary cystadenomata in treated mice compared to controls. However, when this lesion was considered together with the incidence of cysts lined by hyperplastic epithelium, there was no increase any more. Both findings are characterised by a cyst lined by proliferative epithelium with differential diagnosis depending on the presence of a papillary projection into the cystic cavity, the identification of which frequently depends on the plane of section through a lesion.

Table 130: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, histopathology in females

	Dose group level (ppm)			
	Females			
	0	2.5	10	40
Ovarian papillary cystadenomata	1	4	2	7
Cysts lined by hyperplastic epithelium	4	2	0	1
Number of mice examined	45	50	48	49

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

Table 131:: Histopathology –neoplastic findings in mice at the study termination

Diet concentration (ppm)	**males**				**females**			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Total numer of animals examined	50	50	50	50	50	50	50	50
Lymphoretic tumours								
- Lymphosarcoma	9	6	7	11	12	9	16	14
- Lymphoid leukaemia	-	1	-	-	1	-	1	-
- Reticulum cell sarcoma	-	3	2	-	4	4	2	3
- Myeloid leukaemia	-	-	-	-	-	-	1	-
Lungs								
- Pulmonary adenoma	3	7	4	2	1	3	1	-
- multiple pulmonary adenomata	1	-	-	-	-	-	-	-
- Pulmonary adenocarcinoma	3	1	1	2	-	3	1	3
- multiple pulmonary adenocarcinomata	1	-	-	-	-	-	-	1
- Osteosarcoma	1	-	-	-	-	1	-	-
Lymph node								
- Haemangioma	-	-	-	-	-	1	-	-
Liver								
- benign liver cell tumour	-	-	-	-	-	-	-	-
- malign liver cell tumour	1	-	-	-	-	-	-	-
- Haemangioma	-	1	-	3	1	-	-	1
- multiple haemangioma	-	1	-	-	-	-	-	-
- Haemangiosarcomata	-	-	-	-	-	-	-	-
- multiple haemangiosarcomata	-	1	-	-	-	1	-	-
Spleen								
- Haemangiosarcoma	-	-	-	-	-	1	-	-
Testes								
- Gonadal atromal tumour (epididymes)	1	-	-	-				
- Interstitial cell adenoma	2	1	1	-				
- Malignant interstitial cell tumour	-	1	-	-				
- Haemangioma (epididymes)	-	-	-	1				
Uterus								
- Haemangioma					1	-	-	2
- Leiomyoma					2	1	-	-
- Polypoid adenoma					-	-	-	1
- Uterine adenocarcinoma					1	-	2	1
- Fibrosarcoma					1	-	1	-
Ovaries								
- Granulosa cell tumour					6	5	9	5
- two granulosa cell tumours					8	3	4	3
- Luteinised granulosa cell tumour					2	2	1	4
- two luteinised granulosa cell tumours					2	2	-	1
- Malignant granulosa cell tumour					-	-	-	1
- Tubular adenoma					5	4	5	5
- two tubular adenomata					1	-	1	1
- Arrhenoblastoma					1	-	-	-
- Papillary cystadenoma					1	4	2	6
- two papillary cystadenomata					-	-	-	1

Diet concentration (ppm)	males				females			
	0	2.5	10	40	0	2.5	10	40
- Anaplastic sarcoma					1	1	-	-
- Haemangioma					-	1	-	-
Adrenals								
- Phaeochromocytoma	1	1	-	-	-	-	-	-
- Adrenal cortical adenoma	8	12	4	7	-	1	-	-
- two adrenal cortical adenomata	2	-	1	1	-	-	-	-
- Adrenal cortical carcinoma	-	1	-	-	-	-	-	-
Pituitary								
- Pituitary adenoma	-	-	-	-	5	2	2	1
Stomach								
- Fibrosarcoma	-	-	1	-	-	-	-	-
- Anaplastic sarcoma	-	-	-	1	-	-	-	-
Duodenum								
- Polypoid adenoma	-	-	-	-	-	1	-	-
- Adenoma (Brunner's glands)	-	-	-	-	-	-	-	1
Skin								
- Squamous cell papilloma	-	-	1	-	-	-	-	-
- Squamous cell carcinoma	-	-	-	1	-	-	-	-
S/C mass								
- Subcutaneous haemangiosarcoma	1	-	-	-	-	-	1	-
- Mammary adenocarcinoma	-	-	-	-	3	4	1	1
- Osteosarcoma	-	-	-	-	-	-	-	1
- Subcutaneous fibrosarcoma	-	-	-	-	-	-	-	1
Adipose tissue								
- Haemangiosarcoma	-	-	-	-	-	-	1	-
Vagina								
- Fibrosarcoma					-	-	-	1

Conclusion:

The slight increase of relative kidney weights which was found in females at the top dose after 12 months of treatment could not be observed at the final sacrifice after 24 months. Investigation of hepatic enzyme levels at 24 months gave no indication of an induction of foreign substance metabolism or peroxisomal proliferation. After 24 months treatment, relative liver weights were decreased in females at 10 and 40 ppm, which was considered a random finding due to a large number of control animals showing high liver weights. No difference between control and treated animals were observed regarding mortality and histopathological findings.

The overall NOAEL of the carcinogenicity study (24 months) in NMRI mice is considered to be 40 ppm (equivalent to 5.48 mg/kg bw/d for males and 6.54 mg/kg bw/d for females). No carcinogenic effects were induced by Fenoxaprop-ethyl.

Hoe 33171 – active ingredient technical (Code Hoe: 33171 0H AS201). Chronic feeding study in mice (Interim killing after 12 months)

Reference: *Donaubauer et al*, 1983c; Doc. No. A29695 / Hoechst Report No. 83.0654

Guideline: OECD guideline 451 (adopted 1981); EPA guideline 83-2 (1982)

Deviations: Histopathology was not performed on sternum and femur.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to Donaubauer et al., 1985c, in this section

Findings of the 12 month interim sacrifice (the results refer to an animal number of 10/sex/group):

Behaviour and general health conditions: Throughout the study the behaviour remained unaffected and clinical signs could not be observed.

Body weight: There were no statistically significant deviations of the body weight of treated animals when compared to controls.

Table 132: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 12 month interim sacrifice, body weight data

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Initial body weight (g)	21	22	22	22	21	20	20	20
Terminal body weight (g)	34	34	37	35	30	30	31	30

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

Food consumption: Food consumption, both absolute and relative, at all concentration levels corresponded to that of the controls.

Hematology: There were no statistically significant changes observed.

Clinical chemistry: There were no statistically significant changes observed.

Hepatic enzyme levels: After 12 months of the study, feeding of Fenoxaprop-ethyl did not lead to an induction of foreign substance metabolism or to peroxisomal proliferation. More details are presented in the respective study report later in this section.

Organ weights: Kidney weights, both absolute and relative, showed a dose-related increase in both sexes, with statistical significance in the females of the 40 ppm group. However, no histopathological correlate was found, and the effect was not found at the subsequent sacrifice after 24 months of treatment.

Table 133: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 12 month interim sacrifice, absolute[1] and relative organ weights

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Liver weight								
absolute (g)[1]	1.59	1.47	1.72	1.70	1.44	1.45	1.50	1.44
relative (% bw)	4.657	4.333	4.688	4.827	4.820	4.859	4.862	4.852
Kidneys weight								
absolute (g)[1]	0.55	0.56	0.62	0.63	0.42	0.42	0.44	0.45
relative (% bw)	1.620	1.663	1.704	1.774	1.398	1.423	1.440	1.515*

* ($p < 0.05$); significantly different from controls
[1] no statistical analysis was performed on absolute organ weights

Histopathology: The histological examinations after 12 and 24 months showed no morphologically detectable organ changes.

Conclusion:

Please see overall conclusion at the beginning of this section, Ref.: Donaubauer et al., 1985(c), Doc. No. A30816, Hoechst Report No. 85.0046

Supplement to Report No. 83.0654. Hoe 33171 – active ingredient technical. Chronic feeding study in mice (interim killing at 12 months). Determination of hepatic enzyme levels

Reference: *Donaubauer et al*, 1984b; Doc. No. A29696 / Hoechst Report No. 84.0782 Amendment to Report No. 84.0782, *Leist et al*., 1987, Doc. No. A36268 / Hoechst Report No. 87.1225

Guideline: OECD guideline 453 (adopted 1981); EPA guideline 83-5 (1982)

Deviations: Histopathology was not performed on the required three section levels of the spinal cord and on parathyroids. These parameters do not limit the validity and acceptability of the results.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Please refer to *Donaubauer et al*., 1985c, in this section

Findings (the findings are generally related to an animal number of 10 / sex / dose group):

Of the foreign substance metabolism enzymes, the three mixed-function oxidases (aminopyrine N-demethylase, anisic acid ester O-demethylase, ethoxycoumarin O-deethylase) showed no increase. However, there was a statistically significant increase of cytochrome c reductase at 10 ppm (males) and 40 ppm (males, females), for which the reasons are unclear. With regard to the two glucuronyl transferases, there were statistically significant increases of enzyme I in the males and of enzyme II in the females; however, these increases were not dose-related. Catalase activities were not increased in treatment groups, and therefore peroxisomal proliferation was excluded by the authors. At the lowest concentration (2.5 ppm), lactate dehydrogenase was increase in females and decreased in males. Since neither changes were dose-related, these enzyme acitivities were not attributed to the test substance.

Table 134: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 12 month interim sacrifice, special biochemical investigations of hepatic enzyme levels

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Aminopyrine N-demethylase (U/g liver)	0.326	0.338	0.304	0.375	0.225	0.183	0.195	0.192

	Dose group level (ppm)							
	Males				Females			
	0	**2.5**	**10**	**40**	**0**	**2.5**	**10**	**40**
Anisic acid ester O-demethylase (U/g liver)	0.0706	0.0571	0.0402*	0.0555	0.0336	0.0204	0.0272	0.0292
Ethoxycoumarin O-deethylase (U/g liver)	0.0603	0.0661	0.0606	0.0673	0.0654	0.0653	0.0734	0.0661
Cytochrome c-reductase (U/g liver)	0.84	3.28	3.99*	4.29*	4.65	4.28	4.83	6.24*
Lipoperoxidation (E/g liver)	3.79	3.89	4.20	4.23	3.24	4.31	3.73	3.26
Glucuronyltransferase I (U/g liver)	0.182	0.253*	0.230	0.221*	0.281	0.296	0.289	0.294
Glucuronyltransferase II (U/g liver)	0.406	0.430	0.470	0.473	0.429	0.636*	0.603*	0.613*
Catalase (R/g liver)	4137	3323	2694	2070	2478	1954	713*	1902
ALP (U/g liver)	1.19	1.16	1.15	1.24	1.50	1.53	1.60	1.44
Glycerophosphate dehydrogenase (U/g liver)	15.1	13.5	11.1	11.4	11.6	14.6	12.8	9.9
LDH (U/g liver)	202	127*	112*	131*	142	186*	151	139
Malate enzyme (U/g liver)	0.717	0.607	0.951	0.968	0.719	0.555	0.746	0.878

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

Conclusion:

No increase of mixed-function oxidases occurred. However, cytochrom c reductase was significantly increased at 10 ppm (males only) and 40 ppm (both sexes). There was no increase of catalase so that peroxisomal proliferation was excluded.

Fenoxaprop-ethyl – substance technical (Code Hoe 033171 00 ZD96 0005). Carcinogenicity study in mice

Reference: *Troschau G.*, 1996; Doc. No. A57500 / Hoechst Report No. 96.0880
Supplement to Report No. 96.0880, *Durchfeld-Meyer B.*, 1996; Doc. No. A58176
Addendum. *Durchfeld-Meyer B.*, 1997; Doc. No. A58838

Guideline: OECD guideline 451 (1981); EPA guideline 83-2 (revised 1984); Jap. MAFF 59 NohSan No. 4200 (1985)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

50 male and 50 female NMRI mice (strain: NMRKf(SPF71), source: Hoechst) per dose group were treated with 0, 40, 115 or 320 ppm of Fenoxaprop-ethyl by oral feed for 24 months, which corresponds to 0, 5.67, 16.59 or 44.63 mg/kg bw/d in males and 0, 6.83, 19.44 or 53.68 mg/kg bw/d in females. At the start of the study the mice were about 5 – 6 weeks old and had a mean body weight of 22.1 g (males) and 20.8 g (females). The test substance (Code: Hoe 033171 00 ZD96 0005) had a purity of 96.8% according to certificate of analysis No. 4663 (1991). The standard pulverized diet Altromin-1321 and the test substance were premixed at 4-week intervals. The final feed mixes were prepared in 4-week intervals from the respective

premixes, adding the necessary amount of standard diet to the premix. Homogeneity and active ingredient content of the Fenoxaprop-ethyl in the diet was confirmed for each feed mix.

Behaviour, general health conditions and mortality were observed twice daily. Animals were examined monthly for neurological disturbances, impairment of dental growth and changes in the eyes and the oral mucosa. Body weights and food consumption were determined once weekly. Palpation of skin for nodules was done monthly, from month 6 onwards. Hematology was performed on non-starved animals. Blood samples were taken after 12 and 18 months from the first 10 males and 10 females per group for differential blood count only. After 24 months, blood samples were taken from the first 20 males and 20 females per group, and from intercurrently sacrificed animals as far as possible on the killing day. For these animals, hematological examinations comprised erythrocyte count, haemoglobin, hematocrit, total leucocyte count, platelet count, differential blood count, reticulocyte count, Heinz bodies, methaemoglobin, MCV, MCH and MCHC. Autopsy was performed on all animals and included macroscopic examination of integument, orifices, eyes and internal organs. The weights of the following organs were determined in all animals: heart, lungs, liver, kidneys, spleen, brain, testes and ovaries. Histopathology included heart, lungs, liver, kidneys, spleen, brain, testes, ovaries, aorta, bone marrow, both eyes with optic nerves, diaphragm, epididymides, oesophagus, femur, gallbladder, intestine (duodenum, jejunum, ileum, cecum, colon, rectum), lymph nodes (iliacal, mesenteric and cervical), medulla oblongata, nasal septum, pancreas, pituitary, prostate, salivary glands (parotid and mandibular), sciatic nerve, seminal vesicle, skeletal muscle, skin with mammary gland, spinal cord, sternum, stomach (fundus and prepyloric region), thymus, thyroid / parathyroid, tongue, trachea, urinary bladder, uterus and vagina. Statistical evaluation was performed on the following parameters: body weight, erythrocyte count, haemoglobin, hematocrit, MCV, reticulocyte count, leucocyte count, thrombocytes, and all absolute and relative organ weights and mortality.

Findings:

Behaviour and general health conditions: Throughout the study the behaviour and general health conditions remained unaffected. An increased incidence of swollen (inflated) abdomen was noted in both sexes at 115 ppm and above from study week 55 onwards, which was considered to be related to the intake of test substance.

Table 135: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, clinical signs

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Swollen (inflated) abdomen	3/50	1/50	7/50	13/50	8/50	6/50	15/50	14/50

Mortality: The incidence of intercurrent deaths or animals which had to be killed in extremis was comparable in all study groups.

Table 136: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, mortality rates

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320

	Dose group level (ppm)							
	Males				Females			
	0	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Treatment periods								
Week 1 – 26	3	1	1	0	1	1	0	0
Week 27 – 54	4	6	2	2	1	3	3	0
Week 55 – 78	1	1	6	1	6	7	7	6
Week 79 – 105	6	5	5	11	18	9	12	20
Total mortality	14	13	14	14	26	20	22	26
Total mortality (%)	28	26	28	28	52	40	44	52

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

Palpation of skin for nodules: Palpation of skin for nodules and masses did not reveal treatment-related pathological findings.

Body weight: Up to and including the highest dose level of 320 ppm the body weight gains were not adversely affected. However, the body weight gains particularly of the animals from the highest dose group were higher to a minimal degree (<10%) as compared to controls. Although these changes occasionally attained statistical significance during the study, a direct relationship to the test article appears doubtful. It may be assumed that this finding indirectly results from increased liver weights.

Table 137: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, body weight data

	Dose group level (ppm)							
	Males				Females			
	0	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Initial body weight (g)	22.4	22.1	21.7	22.0	20.9	20.7	20.9	20.8
Terminal body weight (g)	37.8	38.4	37.5	38.9	32.8	33.2	34.9	35.9

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

Food consumption: Food consumption, both absolute and relative, was comparable in all dose groups as compared with the controls.

Hematology: Evaluation of white cell count parameters at the study end (only week 105) pointed to tendencies (not statistically significant) towards increased neutrophils and decreased lymphocytes at the top dose. However, taking into consideration the wide variation between the highest and lowest value per group, these findings were not considered to be related to consumption of test substance. Altogether, evaluation of haematological parameters did not reveal any toxicological relevant findings.

Organ weights: Absolute and relative liver weights in males were dose-dependently increased: the absolute weights showed a statistically significant increase at 320 ppm and relative weights at 115 and 320 ppm. Females showed nearly the same tendency as males, but less pronounced and statistically not significant. Kidney weights were slightly increased in both sexes of the highest dose group. Although no histological correlate was observed, this change was considered to be test-article related. An increase in absolute heart weights (males, 320 pm) and decrease in relative lung weights (females, 115 ppm) were considered to be incidental.

Table 138: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, absolute and relative organ weights

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Liver weight								
absolute (g)	1.87	1.94	2.06	2.34*	1.78	1.76	1.90	2.13
relative (% bw)	4.92	5.03	5.47*	6.01*	5.36	5.28	5.45	5.99
Kidneys weight								
absolute (g)	0.58	0.61	0.58	0.64*	0.43	0.44	0.46	0.50*
relative (% bw)	1.54	1.58	1.56	1.66*	1.31	1.33	1.33	1.42

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

Macroscopic examination: At necropsy dose-related macroscopic findings were detected in the livers of both sexes and in the adrenal glands of males from the 320 ppm group. A brown or olive discoloration occurred in the liver, and in some males, nodules were observed. The latter finding corresponded mainly with hepatocellular neoplasms. The adrenal glands in some male animals were enlarged, which corresponded mainly to an adenoma of the subcapsular cells of type B.

Table 139: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, macroscopic findings

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Liver								
- discolored	-	2	7	28	6	4	8	17
- nodular changed	1	2	-	5	1	1	3	3
- nodules	-	-	2	3	-	-	1	-
Adrenals								
- enlargement	4	8	8	13	4	-	4	-

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

Histopathology: non-neoplastic findings:

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 necroses 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.

Table 140: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, non-neoplastic findings

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320

	Dose group level (ppm)							
	Males				Females			
	0	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Non-neoplastic liver findings								
Hypertrophy – diffuse	-	4	31**	46**	-	5*	4	39**
– cellular	-	1	4	-	-	-	2	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
( ) number of animals without liver tumours

Histopathology: neoplastic findings:
Liver: 30% of the males and 2 % of the females of the 320 ppm group showed hepatocellular tumours (predominantely adenomas). Additionally, 3 basophilic and 3 eosinophilic foci (6% respectively) were detected in the liver of the males and 1 basophilic focus in one female. At 115 ppm, a minimal increase in adenomas (2) and carcinomas (1) without statistical significance occurred in male mice. Additionally, two males showed basophilic foci. No compound-related tumours or pre-neoplastic lesions were detected in the 40 ppm group. The first hepatocellular neoplasms were detected after a period of 15.5 months.

Based on these findings, life-feeding of Fenoxaprop-ethyl at a dietary level of 320 ppm caused a significant increase in liver tumours in male mice. Very slight to minimal increased liver tumours were found in females at 320 ppm and in males at 115 ppm which cannot be excluded to be treatment-related, taking into consideration the historical incidences of the corresponding neoplastic and pre-neoplastic lesions. Foci of cellular alterations are very rare in the mouse liver and were considered to be compound-related and preneoplastic lesions.

Overall tumour incidences as well as liver tumour incidences can be found in the tables below.

Table 141:: Histopathology – benign neoplastic findings in mice at the study termination

	Males				Females			
Diet concentration (ppm)	**0**	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Benign neoplasms								
Heart - Schwann. endocard.b.	--	--	--	1 (50)	--	--	--	--
Lungs - Adenoma bronch. alv. - Haemangioma	6 (50) -	7 (50) -	9 (50) -	4 (50) -	3 (49) -	3 (50) 1 (50)	2 (50) -	4 (50) -
Forestomach - Pappiloma squamous	--	--	--	--	--	--	1 (24)	--
Duodenum -Adenoma	--	1 (9)	1 (7)	1 (38)	--	1 (11)	--	--
Liver -Haemangioma - Adenoma hepatocell.	0 1 (50)	1 (49) 1 (49)	1 (50) 2 (50)	- 12 (50)	1 (49) -	- -	- -	1 (50) -
Pancreas - Islet-cell adenoma - Adenoma acinar cell	1(50) -	- -	- -	- -	- -	- -	- -	- 1 (48)
Kidneys - adenoma	--	--	1 (50)	--	--	--	--	--
Testes - Leydig cell tumor	1 (50)	1 (26)	3 (27)	1 (50)				
Epididymides - Schwannoma	--	--	--	1 (50)				
Prostate - Adenoma	--	--	--	1 (50)				
Seminal vesicles - Leiomyoma	--	--	1 (20)	--				
Ovaries - Luteoma - Tum.sex cord stromal - Tum. granulosa c. ben. - Thecoma - Adenoma tubulostrom. - Cystadenoma - Haemangioma					4 (49) 7 (49) 6 (49) 1 (49) 2 (49) 6 (49) 1 (49)	3 (37) 2 (37) 5 (37) 2 (37) 2 (37) 5 (37) -	2 (37) 2 (37) 3 (37) - 1 (37) 5 (37) 1 (37)	5 (48) 2 (48) 7 (48) - 2 (48) 8 (48) 1 (48)
Uterus - Polyp stromal - Polyp glandular - Haemangiom - Fibroma - Leiomyoma - Granular cell tumour					3 (49) 1 (49) 3 (49) - 2 (49) 4 (49)	2 (34) 3 (34) - - - 1 (34)	3 (38) - 2 (38) - - 1 (38)	5 (50) 2 (50) 2 (50) 1 (50) 1 (50) 4 (50)
Pituitary gland - Adenoma pars distal. - Adenoma pars interm.	- -	- -	- -	- -	3 (37) 1 (37)	- -	- -	1 (39) -
Thyroid gland - Adenoma c-cell - Adenoma follicular cells	1 (47) -	- -	- -	- 2 (47)	- -	- -	- -	- -
Parathyroid glands - Adenoma	1 (39)	-	-	1 (39)	-	-	1 (15)	1 (43)

	Males				**Females**			
Diet concentration (ppm)	**0**	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Adrenal cortex								
- Adenoma cortical	3 (50)	4 (49)	4 (50)	1 (49)	2 (48)	-	1 (22)	-
- Adenoma subcap. mix.	1 (50)	-	2 (50)	-	-	-	-	-
- Adenoma subcap. A c.	1 (50)	-	-	1 (49)	-	-	-	-
- Adenoma subcap. B c.	11 (50)	11 (49)	15 (50)	21 (50)	-	-	-	-
Adrenal medulla								
- benign medullar tumor	2 (50)	1 (47)	-	-	-	-	-	-
Thymus								
- Thymoma	-	-	-	-	1 (39)	-	1 (16)	1 (34)
Mesent. Lymph node								
- Hemangioma	-	-	1 (18)	1 (44)	1 (40)	1 (28)	1 (24)	3 (46)
Harderian glands								
- Adenoma	-	-	1 (1)	1 (3)	1 (1)	-	-	3 (4)
Skin								
- Haemangioma	-	-	-	1 (50)	-	-	-	-
- Tumour hair foll. ben	-	-	-	-	-	1 (21)	-	-
Bone								
- Ossifying fibroma	-	-	1 (1)	1 (1)	-	-	-	-

Table 142: Histopathology – benign neoplastic findings in mice at the study termination

	Males				Females			
Diet concentration (ppm)	**0**	**40**	**115**	**320**	**0**	**40**	**115**	**320**
Malign neoplasms								
Lungs - Carcinoma bronch. al.	5 (50)	7 (50)	4 (50)	2 (50)	1 (49)	-	1 (50)	3 (50)
Forestomach - Carcinoma squamous	-	-	-	-	-	-	1 (24)	-
Rectum - Adenocarcinoma	-	-	-	-	-	-	1 (12)	-
Liver - Hepatocellular carcinoma - Hepatoblastoma - Haemangiosarcoma	- - -	- - -	1 (50) - -	4 (50) 1 (50) -	- - -	- - -	- - 1 (49)	1 (50) - -
Urinary bladder - Leiomyosarcoma	-	-	-	-	-	-	-	1 (43)
Pancreas - Carcinoma islet cell	-	-	1 (14)	-	-	-	-	-
Ovaries - Granulosa C. tumor - Haemangiosarcoma					1 (49) 1 (49)	1 (37) -	2 (37) -	- -
Uterus - Adenocarcinoma - Leiomysarcoma - Schwannoma - Sarcoma endom. strom.					4 (49) - 1 (49) 1 (49)	1 (34) 1 (34) 3 (34) 1 (34)	1 (38) 1 (38) 4 (38) -	- 2 (50) - 1 (50)
Testes - Carcinoma Leydig cell	-	-	-	1 (50)				
Adrenal Medulla - Tumour medullary	-	-	-	-	1 (47)	-	1 (23)	1 (45)
Hemolymphoret. System - Malignant lymphoma - Leukemia granulocyt. - Tumor mast cell - Histiocytic sarcoma	15 (50) - 1 (50) 1 (50)	13 (21) 1 (21) - -	10 (16) - - -	5 (50) - 1 (50) 4 (50)	20 (49) - - -	16 (28) - - -	20 (30) - - -	13 (50) - - 1 (50)
Spleen - Haemangiosarcoma - Sarcoma NOS	- -	- -	- -	1 (50) 1 (50)	1 (46) -	- -	- -	- -
Thymus - Thymoma	1 (32)	-	-	-	-	-	-	-
Mesent. lymph node - Haemangiosarcoma	-	-	-	1 (44)	-	-	-	-
Harderian glands - Adenocarcinoma	-	-	-	1 (5)	-	1 (1)	-	1 (4)
Mammary gland - Adenocarcinoma - Adenocanthoma	- -	- -	- -	- -	- 1 (35)	1 (11) -	1 (18) -	1 (35) -
Skin - Malignant schwannoma - Fibrosarcoma - Carcinoma basal cell - Haemangiosarcoma	1 (50) 1 (50) - 1 (50)	1 (15) - - 2 (15)	- - - -	- - 1 (50) -	1 (48) - - -	- - - -	- - - -	- - - 1 (49)
Body cavities - Leiomyosarcoma	-	-	-	1 (50)	-	-	-	-
Bone - Osteosarcoma	-	-	-	-	-	1 (1)	-	-

Table 143: 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	1	1	2	12**	-	-	-	-
% hepatocellular adenoma	2.0	2.0	4.0	24	-	-	-	-
% historical control range	1.2 (0 – 3.0)				0.2 (0 – 4.0)			
Hepatocellular carcinoma	-	-	1	4	-	-	-	1
% hepatocellular carcinoma	-	-	2.0	8.0	-	-	-	2.0
% historical control range	0.8 (0 – 2.0)				0.2 (0 – 1.0)			
Animals with tumours	1	1	3	15**	-	-	-	1
% animals with tumours	2.0	2.0	6.0	30	-	-	-	2.0

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

In the adrenal glands, adenomas of the subcapsular cells of type B occurred with a greater frequency in males at the high dose (320 ppm), compared with the controls, however, since the incidence of males at the high dose with this lesion (42.9%) is well within the equivalent historical control data range (19.6 - 52.3%), this finding was considered not to be treatment-related.

Table 144: Carcinogenicity study of Fenoxaprop-ethyl in NMRI mice 24 month sacrifice, neoplastic findings, adrenals

	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	11	11	15	21*	-	-	-	-
% subcapsular adenoma, type B	22	22.5	30	42.9	-	-	-	-
% historical control range	32.3 (19.6-52.3)				-			

* (p< 0.05); significantly different from controls

Conclusion:

Target organs identified in this carcinogenicity study were the liver and the kidney. A brown discoloration of the liver and an increase in liver weight was observed from 115 ppm onwards. Fenoxaprop-ethyl caused hepatocellular tumours (predominantely adenomas) in 30 % of the male animals receiving 320 ppm. In females at 320 ppm and males at 115 ppm, a low rate of tumours occurred so it was not clear if these findings were treatment-related. Hepatocellular hypertrophy and degenerative liver lesions were noted with dose-related incidences and severities predominantely in males at 115 and 320 ppm. Peroxisome proliferation is discussed as a non-genotoxic mechanism for the hepatocellular carcinogenesis, which is highly species-specific for rodents.

Kidney weights were slightly increased in both sexes of the 320 ppm group, however without any histological correlate. The rate of subcapsular adenomas of the adrenal was increased in males of the highest dose group; however this finding was within the range of historical controls and therefore not considered treatment-related.

The NOAEL for NMRI mice in this carcinogenicity study 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:

Toxicological testing of Hoe 33171 – active ingredient technical (Code: Hoe 033171 0H ZC94 0001) by repeated oral administration to beagle dogs for 2 years

Reference: *Brunk et al*.; 1985; Doc. No. A31854 / Hoechst Report No. 85.0073
Amendment to Report No. 85.0073, 1987, Doc.No. A37103
Explanatory supplement to Report No. 85.0073, *Ebert et al*., 1987, Doc. No. A37042

Guideline: No guideline is mentioned in the study report. However, the study design is similar to OECD Guideline 452 (adopted 1981).

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

6 male and 6 female Beagle dogs per dose group (strain: BEAK, source: Hoechst) received diets containing 0, 3, 15 or 75 ppm Fenoxaprop-ethyl for two years (equivalent to 0.2, 1.1 or 5.2 mg/kg bw/d in males and 0.18, 0.9 or 4.6 mg/kg bw/d in females). At the start of the study the dogs had a mean age of 11 months and a mean weight of 13.3 kg (males) or 11.9 kg (females). The test substance (Hoe 033171 0H ZC94 0001) had a purity of 94 % (according to certificate of analysis dated 27 April 1982) and was premixed with cornmeal. Portions of the premixes were stirred daily into the diet. Homogeneity and stability of the mixture of test substance in the food were checked once every three months.

Viability, clinical signs, behaviour and food consumption were checked daily. Body weights were recorded weekly. Additional investigations were performed before first dosing, then once every 3 months and before study termination: neurological status, ophthalmoscopic examinations, hearing test, dental and visible mucous membranes inspections. Blood samples were collected from fasted animals before the study, after approximately 6 weeks, at 3 monthly intervals, and before the termination of the study. The haematological examinations covered haemoglobin, erythrocyte count, leukocyte count, hematocrit, reticulocytes, Heinz bodies, differential blood count, thrombocytes, prothrombin time and methaemoglobin. Clinical chemistry included sodium, potassium, inorganic phosphorus, uric acid, total bilirubin, direct bilirubin, creatinine, glucose, urea nitrogen, calcium, chloride, iron, cholesterol, triglycerides, total lipids, total protein, electrophoresis, ASAT, ALAT, ALP and LDH. The 24-hour urine was collected from each animal at the same times when blood samples were taken. The following parameters were determined at urinalysis: appearance, color, pH, protein, glucose, haemoglobin, bilirubin, ketone bodies, specific gravity, urinary sediment and urobilinogen. A liver function test (BSP, bromsulphthalein sodium test) and a renal function test (PSP, phenolsulfonphthalein test) were performed before the start of the study, at three-monthly intervals and before the termination of the study. All animals were sacrificed on the day after the final application. Dissection and macroscopic examination were performed directly after sacrifice. The weights of the following organs were recorded: heart, lungs, liver, kidneys, spleen, brain, pituitary, pancreas, ovaries, testes, adrenals, thyroids, thymus, prostate and uterus. Histopathological examinations were performed on the following organs: heart, lungs, liver, kidneys, spleen, adrenals, thyroid, parathyroid, pancreas, thymus, pituitary, cerebral cortex, brain stem, cerebellum (cortex and marrow), medulla oblongata,

eyes with optic nerve, urinary bladder, testes, ovaries, epididymides, uterus, prostate, stomach (fundus and prepyloric region), duodenum, jejunum, ileum, cecum, colon, rectum, gall bladder, tonsils, salivary glands (parotid and submandibular), lymph nodes (cervical and iliac), esophagus, trachea, aorta (thoracic), diaphragm, skeletal muscle (psoas), skin and mammary glands, and bone marrow (middle sternal segment).

Findings:

Mortality / Clinical Signs: No deaths occurred and no animal had to be sacrificed intercurrently. The dogs of all groups remained in good health.

Food consumption: No substance-related inhibition of food intake was observed.

Body weight: In the main study report, statistical analysis was performed on pooled body weights for males and females. According to these calculations, a significant reduction of body weight was observed for the high dose group. In an amendment (Doc. No. A37103) to the study report, statistical analysis was conducted for males and females separately. Significance was found for males at 15 ppm and females at 75 ppm. However, males at 15 ppm showed a lower initial body weight than males from the control or other treatment groups so that the reduction of body weight at 15 ppm was considered to be not related to treatment.

Table 145: Chronic toxicity study of Fenoxaprop-ethyl in Beagle dogs 24 month sacrifice, body weight data

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Initial body weight (g)	13.6	13.6	12.5	13.5	12.1	12.0	11.7	12.0
Terminal body weight (g)	17.1	16.5	15.2*	15.5	15.9	15.0	15.1	14.0*

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

No substance-related changes were noted regarding behaviour, neurological status, ophthalmoscopy, hearing, teeth and visible mucous membranes.

Hematology, clinical chemistry and urinalysis: At the beginning and throughout the study various statistical significancies were observed between control and treatment groups. These statistical differences were in general transient, not dose-related and described to be within the physiological range of biological variation and therefore considered not to be of toxicological relevance. Some of the statistical significancies are presented in the following table.

Table 146: Chronic toxicity study of Fenoxaprop-ethyl in Beagle dogs 24 month sacrifice, haematology and clinical chemistry findings

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Hematology								
Erythrocytes (10^{12}/L)	7.74	7.49	7.50	6.80*	7.29	7.21	7.36	6.74
Haemoglobin (g/L)	183	175	174	157*	172	167	173	158
Hematocrit (unity)	0.55	0.52	0.52	0.48*	0.52	0.50	0.52	0.47
Reticulocytes (unity)	0.012	0.008	0.008	0.006*	0.010	0.006	0.008	0.005*
Thrombocytes (10^9/L)	326	337	382	369	356	407	362	443*
Clinical chemistry								
Cholesterol (mmol/L)	3.89	3.63	3.53	3.73	4.81	6.51*	4.62	5.48
Triglycerides (mmol/L)	0.38	0.22	0.47	0.42	0.46	0.62	0.57	0.76*

	Dose group level (ppm)							
	Males				Females			
	0	**3**	**15**	**75**	**0**	**3**	**15**	**75**
Total lipids (g/L)	5.30	6.36	5.62	6.54*	6.73	6.83	6.42	6.42
ASAT (U/L)	13	13	18*	19*	11	13	15*	16*
ALAT (U/L)	32	17*	27	21	16	17	20	16
LDH (U/L)	94	90	56*	100	81	108	71	154*

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

Liver and renal function tests: None of the measured parameters indicated impairment of hepatic or renal function.

Organ weight analysis: Some statistical significancies were found especially at the high dose level. However, the author states that these organ weight changes were attributable to inadequate exsanguinations or, in the case of uterus and ovaries, to oestrus phase.

Table 147: Chronic toxicity study of Fenoxaprop-ethyl in Beagle dogs 24 month sacrifice, absolute and relative organ weights

	Dose group level (ppm)							
	Males				Females			
	0	**3**	**15**	**75**	**0**	**3**	**15**	**75**
Liver weight								
absolute (g)	495	545	528	504	453	525	531	530
relative (% bw)	2.903	3.307	3.488*	3.256	2.858	3.503	3.536	3.821*
Lungs weight								
absolute (g)	137.5	133.2	129.0	149.7	127.2	130.5	124.8	128.3
relative (% bw)	0.807	0.807	0.850	0.968*	0.803	0.872	0.832	0.930*
Brain weight								
absolute (g)	88.0	86.5	85.3	88.0	80.2	83.7	80.2	81.5
relative (% bw)	0.515	0.527	0.564	0.569	0.507	0.559	0.535	0.591*
Thyroid weight								
absolute (g)	723	780	753	885	756	815	715	826
relative (% bw)	0.0042	0.0047	0.0050	0.0057*	0.0048	0.0054	0.0047	0.0059
Ovaries weight								
absolute (g)	-	-	-	-	1279	1825	2099	2268*
relative (% bw)					0.0080	0.0123	0.0139	0.0165*
Uterus weight								
absolute (g)	-	-	-	-	10.8	19.3	29.2*	25.2*
relative (% bw)					0.067	0.130	0.192*	0.182*

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

Macroscopic examination: Autopsy revealed no substance-related organ changes.

Histopathological examination: Administration of the test substance over 2 years resulted in no discernible organ lesions at any of the dose levels.

Conclusion:

A reduction of body weight was observed at the high dose level of 75 ppm. Furthermore, some organ weights were increased at this dose level (liver, lungs, thyroid, brain) which was attributed to inadequate exanguinations by the study author. However, a relation to treatment cannot be excluded. Therefore, the NOAEL for Beagle dogs after 2 year oral application of Fenoxaprop-ethyl 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).

4.10.1.2 Carcinogenicity: inhalation

No data

4.10.1.3 Carcinogenicity: dermal

No data

4.10.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.10.3 Other relevant information

See 4.12.1.3 Specific investigations: other studies

4.10.4 Summary and discussion of carcinogenicity

No long term toxicity or carcinogenicity study has been performed with Fenoxaprop-P-ethyl. Therefore information on long term toxicity and carcinogenicity was bridged from studies with Fenoxaprop-ethyl.

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 noticed in form of decreased total cholesterol and total lipid levels, which appeared consistently at the highest dose level of 180 ppm. Slight reductions of 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 of organ weight together with distension of the sinuses of the zona reticularis and medulla was 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. Preneoplastic changes consisting of hepatocellular hypertrophy and degenerative liver lesions were noted with dose-related incidences and severities predominantely in males at 115 and 320 ppm. In the high dose study, Fenoxaprop-ethyl caused carcinogenicity in the liver of mice. Hepatocellular tumours (predominantely adenomas) were observed in 30% of the male animals receiving 320 ppm. The rates of tumours in females at 320 ppm and males at 115 ppm were low when compared to controls therefore a relation to treatment remained unclear.

Peroxisome proliferation was shown as 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 G, 1993a). The electron microscopy examination showed there to be 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 – Special Investigations), these studies showed that catalase activity was increased in mice at 80 ppm onwards and in rats at 640 ppm onwards. This mode of action for the induction of hepatic tumours is highly species-specific for rodents.

In the adrenal glands, increase of 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 to be not treatment-related. Kidney weights were slightly increased in both sexes of the 320 ppm group, however 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 of 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 exanguinations 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 were found in NMRI mice due to a non-genotoxic mechanism in rodents (peroxisome proliferation).

4.10.5 Comparison with criteria

No long term study has been provided for fenoxaprop-P-ethyl. However, the chronic/carcinogenicity studies performed with fenoxaprop-ethyl have been used as bridging data 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 in increased incidences in mice but were shown to be due to a highly species-specific mechanism of peroxisome proliferation. No carcinogenic potential was observed in the other species.

Relevance of peroxisome proliferation for human health

Rodent hepatocarcinogenesis has been evaluated to be induced by peroxisome proliferators (PPs) as initiators and promoters. The lack of initiating activity for even the most potent peroxisome proliferators suggests that neither direct nor indirect damage to DNA occurs in liver of rodents exposed to peroxisome proliferators. In contrast, several PPs have been described to exhibit tumour promoting activity but no direct DNA damage, what is consistent with the reversibility of effects of tumour promoters (Roberts, 1999a; Doc. No.: C032167; Huber *et al*., 1996a; Doc. No.: C032177).

In common with other classes of non-genotoxic carcinogens, there are remarkable species differences in response to PPs. Humans respond to the fibrate hypolipidaemic PPs via a reduction in serum cholesterol but appear refractory to the adverse effects of PPs such as hepatic peroxisome proliferation, DNA synthesis and tumour formation. Hypothetically, PPARα expression levels are sufficient in humans to mediate hypolipidaemia, but too low for transcriptional regulation of full battery of genes associated with the adverse effects seen in rodents such as peroxisome proliferation, liver enlargement and tumours (Chevalier and Roberts, 1998a; Doc. No.: C032173). PPARαs are less abundant in human than in rodent liver, which has led to the suggestion that species differences result from quantitative differences in gene expression (Holden and Tugwood, 1999a; Doc. No.: C032171). A number of studies have shown that humans do not display the same range of PP-induced responses seen in rats and mice. The guinea pig and non-human primates also appear unaffected by PPs. It has been suggested that the relative amounts of PPARα mRNA differ between responsive and non responsive species since lower transcript levels are detected in human and guinea pig liver compared with rat and mice. On an average, it is estimated that human hepatocytes express PPARα at 5-10% of the levels found in rodent hepatocytes. Humans are still able to respond to PPs despite the low levels of mRNA by changes in serum lipid levels, i.e. there may be sufficient amounts of PPARα mRNA in human and guinea pig liver to maintain lipid homeostasis but not growth and peroxisome proliferation (Chevalier and Roberts, 1998a; Doc. No.: C032173; Holden and Tugwood, 1999a; Doc. No.: C032171).

Relevance assessment for fenoxaprop-P-ethyl

Although peroxisome proliferators can produce hepatocellular carcinoma in rodents, they are not considered to be genotoxic agents and do not bind covalently to DNA after *in vivo* administration to rats and mice. Generally PPs produce negative results in a wide range of short-term mutagenicity and genotoxicity tests. Since man is insensitive or unresponsive, at therapeutic or chemical exposure concentrations, to peroxisome proliferator-induced hepatic effects it is reasonable to conclude that the levels of exposure encountered to these non-genotoxic agents do not present a hepatocarcinogenic hazard to men. This conclusion is supported by the available epidemiological data (ECETOC, 1992; Doc. No.: A58049).

The same aspects apply to the carcinogenic potential of fenoxaprop-P-ethyl, which was investigated in life-span studies with rats and mice. Like other compounds, fenoxaprop-P-ethyl exhibited a hepatocarcinogenic potential as a results of peroxisome proliferation. The effective doses were 115 and 320 ppm (diet) in mice. However, with regard to the weight of the evidence of the oncogenic potential of fenoxaprop-P-ethyl, well-conducted epidemiological studies in *man* with peroxisome proliferators such as the hypolipidaemic drug clofibrate and other chlorophenoxy herbicides *failed to show significant hepatic peroxisome proliferation and gave no evidence of hepatocarcinogenicity*. Supporting views and expert opinions can be found in more recent scientific literature. In this connection, it is also worth noting that the industrial chemical Di(2-ethylhexyl)phthalate (DEHP) as a prominent representative of the hepatocarcinogenic peroxisomal proliferating compounds will *not be classified* or labelled as a carcinogenic substance in the European Community (Holden and Tugwood, 1999a; Doc. No.: C032171).

Therefore it is concluded that fenoxaprop-P-ethyl is unlikely to pose a carcinogenic risk to humans.

4.10.6 Conclusions on classification and labelling

No classification for carcinogenicity is proposed.

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.

4.11 Toxicity for reproduction

Table 148: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Fenoxaprop-P-ethyl			
Developmental toxicity study in rats (Wistar)	Maternal toxicity: - decreased food consumption - decreased body weight - reduced placentae weight - reduced heart weight Fetal toxicity (in presence of maternal toxicity): - embryonic death - reduced pup weight - reduced pup length - skeletal findings (delayed or non-ossification)* * only fetal finding observed at 32 mg/kg bw/d in absence of maternal effects	Dose levels: 0, 10, 32 and 100 mg/kg bw/d Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 10 mg/kg bw/d	*Baeder C. et al., 1985a*
Embryotoxicity and postnatal development study in rats (Wistar)	Maternal toxicity: - decreased food consumption - decreased body weight - slightly increased duration of gravidity Offspring toxicity: -	Dose levels: 0, 10, 32 and 100 mg/kg bw/d Maternal NOAEL: 32 mg/kg bw/d Offspring NOAEL: 100 mg/kg bw/d	*Pensler M. et al., 1987a*
Developmental toxicity study in rabbits (Himalayan)	Maternal toxicity: - decreased food consumption - decreased body weight gain during treatment period - slightly increased kidney weight Fetal toxicity: - slightly increased incidence of a 13th rib	Dose levels: 0, 10, 32 and 100 mg/kg bw/d Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 32 mg/kg bw/d	*Baeder C. et al., 1986a*
Fenoxaprop-ethyl (read across)			
Multi-generation study in rats (Wistar) (EPA guideline 83-3)	Parental: - organ weight changes (liver, kidney) - clinical chemistry parameters Offspring: - reduced body weight gain during lactation - organ weight changes (liver, kidney) - clinical chemistry parameters	Dose levels: 0, 5, 30 and 180 ppm Reproduction NOAEL: 180 ppm (8.77 – 35.98 mg/kg bw/d) Systemic parental NOAEL: 30 ppm (1.42 – 6.06 mg/kg bw/d) Systemic offspring NOAEL: 30 ppm (1.42 – 6.06 mg/kg bw/d)	*Becker H. et al., 1986a*

Fenoxaprop-ethyl (supportive information)			
Developmental toxicity study in rats (Wistar)	Maternal toxicity: - clinical signs (piloerection) - decreased food consumption - decreased body weight Fetal toxicity: - embryonic death - reduced pup weight - reduced pup length - slightly delayed ossification	Dose levels: 0, 10, 32 and 100 mg/kg bw/d Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 32 mg/kg bw/d	*Baeder C. et al., 1982a*
Embryotoxicity and postnatal development study in rats (Wistar)	Maternal toxicity: - decreased food consumption - decreased body weight - slightly increased duration of gravidity Offspring toxicity: - embryonic death	Dose levels: 0, 10, 32 and 100 mg/kg bw/d Maternal NOAEL: 32 mg/kg bw/d Offspring NOAEL: 32 mg/kg bw/d	*Baeder C. et al., 1986b*
Developmental toxicity study in rabbits (Himalayan)	Maternal toxicity: - decreased food consumption - body weight loss during the first week of treatment at 50 mg/kg bw/d and throughout treatment period at 200 mg/kg bw/d - decreased defecation only at 200 mg/kg: - reduced number of dams with live fetuses - increased abortions and early resorptions - macroscopic enlargement and increased organ weight of liver and spleen Fetal toxicity: - embryonic death - reduced pup weight - reduced pup length - increased incidence of a 13th rib Teratogenicity (in the presence of maternal mortality > 10%): - diaphragm hernias (3/28)	Dose levels: 0, 12.5, 50 and 200 mg/kg bw/d Maternal NOAEL: 12.5 mg/kg bw/d Fetal NOAEL: 50 mg/kg bw/d Teratogenicity NOAEL: 50 mg/kg bw/d	*Baeder C. et al., 1982b*
Developmental toxicity study in rabbits (Himalayan)	Maternal toxicity: - body weight loss during first week of treatment - decreased food consumption - decreased defecation - slightly increased number of resorptions sites Fetal toxicity: - reduced number of live fetuses/dam Teratogenicity: - diaphragm hernia (1/40 in the highest dose group)	Dose levels: 0, 2, 10 and 50 mg/kg bw/d Maternal NOAEL: 10 mg/kg bw/d Fetal NOAEL: 10 mg/kg bw/d	*Baeder C. et al., 1983*
Developmental toxicity study in mice (CD-1)	Maternal toxicity: - increased liver weight	Dose levels: 0, 2, 10 and 50 mg/kg bw/d	*James P. et al., 1983*

	Fetal toxicity: -	Maternal NOAEL: 10 mg/kg bw/d Fetal NOAEL: 50 mg/kg bw/d	
Developmental toxicity study in Cynomolgus monkeys (Macaca fascicularis)	*Supportive information only*	No NOAELs could be established due to limited study design	*Osterburg I., 1984*

4.11.1 Effects on fertility

4.11.1.1 Non-human information

No multigeneration study has been performed with Fenoxaprop-P-ethyl. For bridging of the data derived from studies conducted with Fenoxaprop-ethyl, results from short term toxicity studies and developmental toxicity studies are considered. These data show that the toxicological profiles are comparable.

A multigeneration study according to GLP and EPA guideline has been conducted with fenoxaprop-ethyl in Wistar rats. In this study there were no effect on reproduction parameters, fertility or offspring development observed even at the highest concentration used (180 ppm, equivalent to 8.77 – 35.98 mg/kg bw/d). Systemic toxicity was observed in both parents and offspring. Significant organ weight changes of the target organs liver and kidney were observed as well as changes in clinical chemistry parameters. These effects appeared predominantely and coincidentally at the highest dose group in parents and offspring. Furthermore, a slightly reduced body weight gain was noted in offspring during the period of lactation in the highest dose group. In conclusion, the NOAEL was 180 ppm (equivalent to 8.77 – 35.98 mg/kg bw/d) for reproduction and 30 ppm (1.42 – 6.06 mg/kg bw/d) for parental and offspring systemic toxicity.

4.11.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Developmental studies with **fenoxaprop-P-ethyl**:

Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Wistar rats following oral administration

Reference: *Baeder C. et al., 1985a;* Doc. No. A33810 / Hoechst Report No. 85.1239 Supplement to Report No. 85.1239, *Baeder Ch. et al., 1988a*; Doc. No. A37496 / Hoechst

Report No. 88.0094
Supplement to Report No. 85.1239, *Baeder Ch. et al., 1990a*; Doc. No. A42779 / Hoechst Report No. 90.0250

Guideline: No information on study guidelines is presented in the study report.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 20 – 23 female Wistar rats (Hoe WISKf(SPF71), source: Hoechst) were treated by oral gavage once daily on gestation days 7 to 16 with 0, 10, 32 or 100 mg/kg Fenoxaprop-P-ethyl (vehicle: sesame oil). At the beginning of the study the rats were 65 – 70 days old and had a mean bodyweight of 192 ± 14 g. According to certificate of analysis No. 02327 (1983), the test substance had a purity of 99 % (Code: Hoe 046360 0H ZB99 0002). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Throughout the study, behaviour and general health condition of the animals were observed daily, food intake continuously, and body weight gains once weekly and again one day after the final treatment. On gestation day 21, rats were sacrificed and caesarean section was performed. Live and dead fetuses, resorption sites, placentae, corpora lutea on the ovaries were counted and examined macroscopically. The diameters of the embryonic resorption sites and the weights of the placentae were determined. After staining of the uteri, implantation sites were counted. After removal from the uterus, fetuses were checked for viability, appearance and external anomalies. Bodyweights and crown-rump lengths were determined. About half of the fetuses from each litter and all fetuses found dead in utero were fixed and dissected and examined for stage of development and anomalies. The remaining fetuses were checked for organ anomalies. After caesarean section, dams were examined macroscopically. Heart, liver, kidneys and spleen were weighed.

Range finding study: Groups of three or two gravid Wistar rats were treated with doses of 50, 100 or 200 mg/kg bw on GD 7 – 16. This study showed that 50 mg/kg was tolerated by three dams without complications; however, the bodyweights of the foetuses delivered on day 21 appeared to be slightly reduced. Following administration of 100 mg/kg, one dam showed pilo-erection from days 17 to 19 of gravidity. Moreover, the foetuses of all three dams showed a slight reduction of bodyweights. Doses of 200 mg/kg resulted in pilo-erection from days 4 to 7 of treatment in both dams and caused a reduction of food intake and bodyweights. Apart from one stunted, live foetus with a diaphragmatic and an umbilical hernia, the uteri of the two dams contained only conceptuses under resorption. No further information regarding the range finding study was available in the study report.

Findings:

Maternal effects: No changes in behaviour or general health condition were noted. Pilo-erection was observed from gestation day 14 onwards in one dam of the 32 mg/kg group. In the 100 mg/kg group, increased urinary excretion was observed in 4 dams. In the 100 mg/kg group, food consumption was slightly reduced during treatment. After termination of the treatment the nutritive deficiency was compensated by a slight increase in food consumption. Dams of the 100 mg/kg group showed a retardation of bodyweight and body weight gains. For a more detailed evaluation of food consumption and body weight the reader is referred to the Addendum of the DAR. At autopsy of dams, no substance-related macroscopic findings were

noted. With regard to organ weights, heart weights were slightly reduced in dams of the 100 mg/kg group. Liver, kidney and spleen weights were comparable in all groups.

Table 149: Developmental toxicity study of Fenoxaprop-P-ethyl in Wistar rats: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw)				
GD 1 – 7	9.79	9.40	9.76	9.28
GD 7 – 14	7.96	7.44	7.58	5.42*
GD 14 – 17	7.58	7.45	7.35	7.53*
GD 17 – 21	8.34	8.54	8.58	9.46*
Body weight (g) GD 21	336	315*	323	292*
Body weight gain (g) GD 0 – 21[1)]	141[1)]	127[1)]	132[1)]	106[1)]
Heart weight of dams (g)	0.86	0.78	0.84	0.71*

GD: gestation day
* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed

Litter data / fetal parameters: 1/20 dams at 32 mg/kg and 2/20 dams at 100 mg/kg showed only empty implantation sites, resulting from premature death of the conceptuses shortly after implantation. The other 19 dams in the 32 mg/kg group carried fetuses to full term and there was no increase in the rate of dead conceptuses, whereas a slight increase was observed in the other 18 dams in the 100 mg/kg group. The finding at 32 mg/kg was initially considered to be substance-related due to very low historical incidence (1 out of 1275 dams); however, in supplement Doc. No. A34796 this finding was considered by the study director to be incidental due to the absence of this finding in a subsequent post-natal study conducted even at a dose of 100 mg/kg (Doc. No. A35687). The finding at 100 mg/kg was higher than any found in previous control data, so that in the supplement Doc. No. A34796 a substance-relationship was considered to be probable, despite the fact that no confirmation was obtained from the subsequent post-natal study.

The number of corpora lutea and the number of implantations in all treatment groups were comparable with those for the control dams. The litters of the dams in the 10 and 32 mg/kg groups were of the same size than those of the controls, while there was a slight reduction in the number of live fetuses in the 100 mg/kg group, due to an increase in embryonic death. The fetuses delivered in the 10 and 32 mg/kg groups were normally developed while fetuses at 100 mg/kg displayed reduced body weight and body length. Also, placenta weight was decreased in the 100 mg/kg group.

Skeletal and visceral examination: Skeletal examination revealed that there were more fetuses in all of the treatment groups with weaker ossification of cranial bones and os metacarpale 5 than in the control group. With regard to historical control data, the number of fetuses in the 10 mg/kg group showing delayed ossification of cranial bones, and also the number of fetuses in the 10 and 32 mg/kg groups in which ossification of os metacarpale 5 had not yet taken place, were considered as non-substance-related spontaneous occurrences in the supplement Doc. No. A34796.

In the 100 mg/kg group, one fetus (1 %) exhibited an abdominal fissure with protrusion of intestinal coils, and another fetus from another litter (0.9 %) showed multiple malformations

in the region of the cervical and thoracic vertebral column. As these findings occurred also spontaneously in historical control groups and were isolated to the 100 mg/kg group, a substance-relationship was considered hardly probable (supplement Doc. No. A42779).

Fragmented or dislocated vertebral centra were observed in one fetus (0.8 %) from the 10 mg/kg group and in four fetuses (3.6 %) out of two litters from the 100 mg/kg group. As such findings occurred also spontaneously in historical control data, the single finding at 10 mg/kg was considered to be incidental. However, the percentage of fetuses affected at 100 mg/kg was above the upper range of historical control data and a treatment relationship for this finding is likely (supplement Doc No. A42779).

In all groups individual or numerous fetuses exhibited longitudinally displaced, dysplastic, dislocated or fragmented sternebrae. These anomalies of the sternebrae appeared in two fetuses from the control group (1.5 %), three fetuses from the 10 mg/kg group (2.3 %), one fetus from the 32 mg/kg group (0.8 %) and 26 fetuses from the 100 mg/kg group (23.6 %). As the historical control range is from 0.9 % to 7.6 %, the findings at 100 mg/kg were considered to be substance-related. Both the sternal anomalies and the fragmented or dislocated vertebral centra observed in the 100 mg/kg group were considered as an expression of an embryotoxic, but not teratogenic effect (supplement Doc No. A42779).

No findings were noted at soft tissue examination.

Table 150: Developmental toxicity study of Fenoxaprop-P-ethyl in Wistar rats: Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Dams with live fetuses	20	20	19	18
Dams with empty implantation sites only	-	-	1	2
Mean number of live fetuses / dam	12.8	12.7	12.8	11.9
Mean pup weight (g)	3.5	3.2	3.3	2.9*
Crown rump length (cm)	3.6	3.5	3.6	3.2*
Mean placental weight (g)	0.49	0.50	0.47	0.41*
Skeletal examination (no. fetuses examined)	133	131	125	110
Dysplastic /dislocated sternebrae (%)	1.5	2.3	0.8	23.6*
Historical control data (Doc. No. A42779)	0.9 – 7.6 %			
Weak or non-ossification of at least 1 cranial bone (%)	19.5	30.5*[1)]	56.8*	65.5*
Historical control data (Doc. No. A37496) min. - max.	31 ± 9.6 % 13.1 – 56 %			
Non – ossification of one sternebrae (%)	5.3	5.3	8.0	56.4*
Non – ossification of one os metacarpale 5 (%)	23.3	33.6	36.8*[1)]	91.8*
Historical control data (Doc. No. A37496) min. – max.	38.3 ± 13.7 % 13.5 – 85.7 %			

* ($p < 0.05$); significantly different from controls
[1)] considered to be within the historical control range, supportive data are presented in supplement Doc. No. 37496

Conclusion:

The NOAEL for maternal toxicity in this study with Fenoxaprop-P-ethyl was considered to be 32 mg/kg bw/day based on decreased food consumption, body weight and reduced heart weights. Fetal toxicity was demonstrated by embryonic death, reduced pup weight and pup length at 100 mg/kg. Furthermore, skeletal findings at 32 and 100 mg/kg occurred leading to a NOAEL of 10 mg/kg bw/day for fetotoxic effects. No teratogenicity was observed.

Hoe 046360 – active ingredient technical (Code: Hoe 046360 0H ZC96 0002) Testing for embryotoxicity and effects on post-natal development in Wistar rats after oral administration

Reference: *Pensler M. et al., 1987a;* Doc. No. A35687 / Hoechst Report No. 87.0309 Supplement to Report No. 87.0309, *Baeder Ch. et al., 1990a*; Doc. No. A42781 / Hoechst Report No. 90.0251

Guideline: postnatal toxicity study, no guideline available; in the study report it is stated that the study was conducted according to OECD guideline 414

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

The aim of the study was to determine whether Fenoxaprop-P-ethyl impaired the postnatal development of offspring following repeated dosing during gravidity. Groups of 20 – 21 female Wistar rats (Hoe WISKf(SPF71), source: Hoechst) with an age of 65 – 70 days and a mean body weight of 190 ± 6.7 g were treated orally by gavage on gestation days 7 – 16 with 0, 10, 32 or 100 mg/kg Fenoxaprop-P-ethyl (vehicle: sesame oil). According to certificate of analysis No. 02912 (1985), the test substance had a purity of 95.6 % (Code: Hoe 046360 0H ZC96 0002). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Throughout the study, behaviour and general health condition of the animals were observed daily. Food consumption was checked during gravidity but not after delivery. Body weight gains were determined once weekly and again one day after the final treatment, and again after delivery.

All dams were allowed to deliver normally and rear their offspring for 21 days. Duration of gravidity and number of live and dead offspring were recorded. During the 21 day lactation period, the offspring was examined daily for viability and general behaviour. Body weights were determined on the day of delivery, on post natal days 4 and 7 and subsequently once weekly. For the examination of the physical development, the times of pinna separation, coat growth start, incisor eruption and eyelid opening were recorded. The dams and the offspring were sacrificed between days 21 and 23 after delivery. Macroscopical examination was performed in dams and offspring and organ weights of heart, liver, kidneys and spleen were recorded.

Findings:

Maternal effects: No treatment-related clinical signs were observed in the dams of all groups. The increased urinary excretion observed in one dam at 32 mg/kg and two dams at 100 mg/kg

was considered to be spontaneously. Slight reduction of food consumption and body weight gains were observed during the treatment period in the 100 mg/kg group. After delivery, the dams started to develop normal bodyweight again.

At autopsy of the dams, no treatment-related changes could be found. The heart, liver, kidney and spleen weights of the dams treated with the test substance were comparable to those of the controls.

Table 151: Developmental and postnatal toxicity study of Fenoxaprop-P-ethyl in Wistar rats: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw) GD 0 – 7 GD 7 – 17 GD 17 – 21	 9.9 8.2 8.6	 9.8 8.2 8.3	 9.6 7.8 8.6	 9.6 6.8* 9.4*
Body weight gain (g) GD 0 – 21[1)]	138[1)]	136[1)]	129[1)]	116[1)]

GD: gestation day
* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed on body weight gain; statistical analyses were performed on medians and showed significant differences between control and 100 mg/kg group

Litter data / fetal parameters: The duration of gravidity in all three treatment groups was 22 – 24 days which is normal for this strain of rat. However, it was noticeable that a larger number of dams in the 100 mg/kg group did not deliver until the 23rd day of gravidity or during the following night, whereas most of the dams from the other groups delivered during the night from the 22nd to the 23rd day of gravidity. There was no difference in any other litter parameter. The litter size of all groups was comparable with previous control values. No increase in the incidence of dead conceptuses or supernumerary implantation sites could be found at any of the three dosage levels. The physical development (pinna separation, coat growth start, incisor eruption and eyelid opening) and viability of the offspring of all groups remained within the range of historical control values, even though the offspring from the 100 mg/kg group had gained rather less weight than those from the other groups. In contrast to the earlier embryotoxicity study in Wistar rats (Doc. No. A33810), the offspring from the 100 mg/kg dose group were not retarded. This may possibly be attributable to the fact that the weight deficit was compensated by the slightly longer gravidity.

Examination for external anomalies: Toe anomalies and ingrowing of both forelimbs into the skin fold of the upper arm was observed in two pups at 10 mg/kg, one still-born pup at 32 mg/kg, and one pup at 100 mg/kg. Similar anomalies, in combination with hematocysts or hematomas, had been occurring sporadically in a number of rat fetus studies in the same performing laboratory. For this reason and due to the fact that these were isolated findings without any dose relation it was considered unlikely by the study authors that there was a causal connection with the administration of the test substance (supplement Doc. No. A42781).

Macroscopical examination of offspring: At autopsy of the offspring, no treatment-related changes could be found. The heart, liver, kidney and spleen weights of the pups treated with the test substance were comparable to those of the controls.

Table 152: Developmental and postnatal toxicity study of Fenoxaprop-P-ethyl in Wistar rats:
Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Duration of gravidity (days)	22.5	22.3	22.5	22.8
Dams with live fetuses	20	20	20	20
Dams with empty implantation sites only	-	-	-	-
Mean number of live fetuses / dam	12.8	12.6	12.3	12.8
Number of offspring by group	255	252	247	255
Mean offspring weight (g) at birth[1)] Mean offspring weight (g) on day 21[1)]	5.8[1)] 36.1[1)]	5.5[1)] 35.6[1)]	5.6[1)] 38.2[1)]	5.5[1)] 34.8[1)]
Survival rate (%) day 21	95.6	98.4	98.7	98.0
Morphological anomalies in offspring				
External anomalies: Toe anomalies	0	2 (1)[2)]	1 (1)[2)]	1
Historical control data (Doc. No. A42781)	0 – 2.1 % in 1986			

($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed on mean body weight; however, statistical analyses were performed on medians and showed no significant differences between control and treatment groups
[2)] in brackets: number of animals with toe anomalies together with ingrowing of both forelimbs into the skin fold of the upper arm

Conclusion:

On the basis of the results of this study with Fenoxaprop-P-ethyl, the maternal NOAEL was considered to be 32 mg/kg bw/day due to reductions of food consumption and body weight and a slightly increased duration of gravidity. As no significant effects on the fetuses and the postnatal development were observed in this study, the NOAEL for offspring toxicity was considered 100 mg/kg bw/d.

Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration

Reference: *Baeder C. et al., 1986a;* Doc. No. A33302 / Hoechst Report No. 86.0488

Guideline: No information on study guidelines is presented in the study report.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

15 gravid female Himalayan rabbits (Hoe HIMK(SPFWiga), source: Hoechst) were treated by oral gavage once daily on gestation days 7 to 19 with 0, 10, 32 or 100 mg/kg Fenoxaprop-P-ethyl (vehicle: sesame oil). At the beginning of the study the rabbits were about 7 months old and had a mean bodyweight of 2525 ± 173 g. According to certificate of analysis No. 02327

(1983), the test substance had a purity of 99 % (Code: Hoe 046360 0H ZB99 0002). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Throughout the study, behaviour and general health condition of the animals were observed daily, food intake continuously, and body weight gains on gestation days 0, 7, 14, 20 and 29. On gestation day 29, rabbits were sacrificed and pups delivered by caesarean section. After opening of the uterus, the live and dead fetuses, resorption sites, placentae, and corpora lutea on the ovaries were counted and examined macroscopically. The diameters of the embryonic resorption sites and the weights of the placentae were determined. After removal from the uterus, the fetuses were checked for viability, appearance, external anomalies and bodyweights. The live fetuses were then reared for 24 hours in an incubator at a temperature of 32°C and a relative humidity of 60 %. A record was kept of the fetuses which died during this time. After this 24 h period the fetuses were subjected to autopsy and checked for skeletal and internal anomalies. After caesarean section, dams were examined macroscopically. Heart, liver, kidneys and spleen were weighed.

Range finding study: Groups of three gravid Himalayan rabbits were treated with doses of 10, 50, 100 or 200 mg/kg bw/d on GD 7 – 19. This study showed that 10, 50 and 100 mg/kg were tolerated without complications by both dams and fetuses. Following administration of 200 mg/kg, all three dams showed a slight bodyweight reduction during the treatment period. One dam had slightly retarded and severely stunted dead fetuses together with normally developed fetuses. The fetuses of the other two dams of this group were unimpaired.

Findings:

Maternal effects: No changes in behaviour or general health condition were noted. In the 100 mg/kg group, food consumption was slightly reduced which was also manifested in reduced faecal excretion. Food consumption could not be determined regularly for all of the dams, since a number of animals scattered their feed out of the racks. Additionally, a stagnation of body weight gain during the treatment period was observed in dams receiving 100 mg/kg. For a more detailed evaluation of food consumption and body weight the reader is referred to the Addendum of the DAR.

At autopsy of dams, no substance-related macroscopic findings were noted. Kidney weights were found to be slightly increased in dams of the 100 mg/kg group compared to controls and to previous control values. The weights of liver and spleen were also slightly increased at 100 mg/kg, however, these findings were considered not to be related to treatment as the values were within the range of historical control data.

Table 153: Developmental toxicity study of Fenoxaprop-P-ethyl in Himalayan rabbits: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Body weight gain (g) GD 7 – 20[1)] Body weight gain (g) GD 20 – 29[1)]	101 177	107 153	96 175	-3 197
Kidney weight of dams (g) Liver weight of dams (g) Spleen weight of dams (g)	15.54 55.12 0.55	15.52 55.17 0.62	15.80 57.11 0.56	16.85* 59.71 0.68*

GD: gestation day
* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed

Litter data / fetal parameters: One dam of the 10 mg/kg delivered prematurely and one dam in the 100 mg/kg group aborted. One female each in the 32 and 100 mg/kg groups had no fetuses but only implantation sites in the uterus. However, the study authors judged these findings to be spontaneous, as the historical control rates of the laboratory showed that premature deliveries occurred occasionally at a rate of up to 2/15 animals and abortions at a rate of up to 3/15 animals. Furthermore, there was no increase of these findings at higher doses.

Administration of the test substance had no effect on the intra-uterine development of the fetuses. They were normally developed and showed no differences in body weights or body lengths as compared with controls. The placentae of the live fetuses in all of the groups showed no macroscopic abnormalities and were normal in weight. The survival rate of the fetuses during the first 24 hours after delivery in the incubator showed no differences compared to controls.

Skeletal and visceral examination: Morphological examination of the progeny revealed no increase in the incidence of malformations in any of the three treated groups. All observed effects in control and treatment groups were considered to be spontaneous and not related to treatment by the study authors as the effects occurred only sporadically and without dose-relation. However, when the incidence of an anlage of a short or normally sized 13th rib is compared to historical control data from the same laboratory, a fetotoxic effect seems possible. In the Hoechst study report No. 667/82 (Baeder C. et al., 1982b; Doc. No. A24756) the incidence of previous controls was presented to be 0 – 10.2 %, which is lower than the rate of 13.5 % observed in this study. A relation to treatment therefore cannot be ruled out. No increased frequency of delayed skeletal ossification was observed.

Table 154: Developmental toxicity study of Fenoxaprop-P-ethyl in Himalayan rabbits: Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Pregnant dams	15	15	15	15
Dams with premature delivery	-	1	-	-
Dams with abortion or only early resorptions	-	-	1	2
Dams with live fetuses	15	14	14	13
Mean number of live fetuses/dam	5.9	5.4	5.6	5.2
Mean pup weight (g)	44.1	44.1	44.1	43.0
Crown rump length (cm)	9.6	9.8	9.7	9.8
Mean placental weight (g)	5.73	5.94	5.93	6.05
Body cross section, no. of fetuses examined	40	34	35	31
Umbilical hernia with protrusion of hepatic tissue (%)	-	-	1 2.9	-
Skeletal examination, no. of fetuses examined	48	41	43	37
Anlage of a short or normally sized 13th rib, uni- or bilateral (%)	1 2.1	-	1 2.3	5 13.5

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

Conclusion:

The NOAEL for maternal toxicity in this study with Fenoxaprop-P-ethyl was considered to be 32 mg/kg bw/day based on slightly decreased food consumption, stagnation of body weight gains during the treatment period, and slightly increased kidney weights observed at 100 mg/kg. Regarding fetal toxicity, the only effect observed was a very slight increase in the incidence of a 13th rib in the highest dose group when compared to previous control data presented in the Hoechst study report No. 667/82 (Baeder C. et al., 1982b; Doc. No. A24756), leading to a NOAEL for fetal toxicity of 32 mg/kg. No teratogenicity was observed in this study.

Supportive information

Developmental studies with **fenoxaprop-ethyl**:

An oral embryotoxicity study of Hoe 33171 0H AT204 in Wistar rats

Reference: *Baeder C. et al., 1982a;* Doc. No. A26170 / Hoechst Report No. 613/82

Guideline: No information on study guidelines is presented in the study report.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Fenoxaprop-ethyl was administered to groups of 20 female Wistar rats (Hoe WISKf(SPF71), source: Hoechst) by oral gavage on gestation days 7 to 16. Animals were approximately 70 days old and had an average body weight of 185 ± 13 g. The test substance was dissolved in sesame oil and administered in doses of 0, 10, 32 and 100 mg/kg. An additional group of females received 100 mg/kg in order to clarify the results obtained at 32 and 100 mg/kg. The test substance (Hoe 33171 0H AT204) had a purity of 93.0 % according to certificate of analysis No. 01711, 1982. The stability of the test substance preparations was guaranteed by analytical analysis.

Throughout the study, behaviour and general health condition of the animals were observed daily, food intake continuously, and body weight gains once weekly and again one day after the final treatment. On gestation day 21, rats were sacrificed and caesarean section was performed. Live and dead fetuses, resorption sites, placentae and corpora lutea on the ovaries were counted and examined macroscopically. The diameters of the embryonic resorption sites and the weights of the placentae were determined. After staining of the uteri, implantation sites were counted. After removal from the uterus, fetuses were checked for viability, appearance and external anomalies. Bodyweights and crown-rump lengths were determined. About half of the fetuses from each litter and all fetuses found dead in utero were fixed and dissected and examined for stage of development and anomalies. The remaining fetuses were checked for organ anomalies. After caesarean section, dams were examined macroscopically. Heart, liver, kidneys and spleen were weighed.

Range finding study: Groups of three Wistar rats were treated by oral gavage with doses of 10, 32 or 100 mg/kg bw on GD 7 – 16. In that study, 10 and 32 mg/kg were tolerated without complications by the dams and fetuses. The 100 mg/kg dosage led to slight signs of intoxication

in the dams and a reduction in the body weight of fetuses. In a further orientational study on 20 dams, 32 mg/kg did not impair the health of the dams or the intra-uterine development of the fetuses either.

Findings:

Maternal effects: Administration of 100 mg/kg led to piloerection in 5 dams of the 100 mg/kg group which appeared between gestation days 12 and 16 and lasted for 1 – 9 days. One dam from the additional 100 mg/kg group showed also piloerection from gestation day 13 – 21. Feed consumption and body weight were slightly decreased at 100 mg/kg.

The autopsy of dams revealed no treatment-related changes. The weights of heart, liver, kidneys and spleen were within the range of controls.

Table 155: Developmental toxicity study of Fenoxaprop-ethyl in Wistar rats: Maternal effects

	Dose group level (mg/kg bw/day)				
	0	**10**	**32**	**100**	**100 (repetition)**
Food consumption (g/100g bw)					
GD 1 – 7	9.73	9.41	9.86	9.79	9.39
GD 7 – 14	7.67	7.50	7.59	6.46*	5.54*
GD 14 – 17	7.65	7.48	7.64	6.92*	5.90*
GD 17 – 21	8.16	8.18	8.30	8.47	8.77*
Body weight (g) GD 21	317	313	308	299*	285*
Body weight gain (g) GD 0 – 21[1)]	127[1)]	125[1)]	126[1)]	115[1)]	105[1)]

GD: gestation day
* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed

Litter data / fetal parameters: 3/20 dams at 100 mg/kg and 1/20 dams of the repetition group had no live fetuses but only implantation sites in the uterus. These can be attributed to early embryonic death shortly after implantation or to undetected abortion. The fetuses delivered alive in the 100 mg/kg groups showed a slightly reduced body weight and body length. Also, the placentae of these groups had lower weights than in controls. The incidence of dead fetuses was not increased in any treatment group. Embryonic resorption sites did not occur more often in the dams which carried fetuses than in the control group.

Skeletal and visceral examination of offspring: Ossification of the skeleton in the fetuses from the 100 mg/kg group was slightly retarded which was particularly evident from the cranium and from the deficient ossification of the sternebrae and the fifth metacarpal.

Deformities of the head were found in one fetus at 32 mg/kg and three fetuses at 100 mg/kg. Of those fetuses, one at 32 mg/kg and one at 100 mg/kg also exhibited abnormalities in the vertebral column and the ribs. One fetus at 100 mg/kg had an abdominal fissure. Diaphragmatic hernia was found at both skeletal and body cross-section investigations. The total numbers of animals affected were one fetus from each of the control, 10 mg/kg and 30 mg/kg group and in two fetuses of the 100 mg/kg group. Bending of the scapula was found in two fetuses from the 10 mg/kg group, one fetus from the 32 mg/kg group and three fetuses from the control group. Two of the three latter mentioned control fetuses also showed shortening of one humerus. The repetition group in which additional 20 dams were treated with 100 mg/kg was conducted to check if those results were reproducible. In the repetition

group, a diaphragmatic hernia was found in two fetuses, a bending of one scapula in two fetuses, and a shortened humerus in one of the latter two fetuses. However, no fetuses exhibited an abdominal fissure or deformities of the head. The findings of the repetition group showed that the deformities of the head found in the first 100 mg/kg group and the abdominal fissure could not be reproduced. The numbers of fetuses affected by diaphragmatic hernias and deformities of the scapulae and humeri were not greater in the repetition group than in the first 100 mg/kg group (diaphragmatic hernia) and the control group (deformities of the scapulae and humeri). With regard to the diaphragmatic hernias, the fact that this deformity affected 1 – 2 fetuses from each of the 5 groups in the study means that the rate of incidence in the various groups is between 0.4 and 1.0 %. Although the formation of diaphragmatic hernias rarely occurs spontaneously, this abnormality has been observed in 5 previous Hoechst control studies. In these studies, the highest frequency of occurrence found was 2 from 216 fetuses, corresponding to a rate of 0.9 %.

Table 156: Developmental toxicity study of Fenoxaprop-ethyl in Wistar rats: Maternal and developmental effects

	Dose group level (mg/kg bw/day)				
	0	**10**	**32**	**100**	**100 (repetition)**
Dams with live fetuses	20	20	20	17	19
Dams with empty implantation sites only	0	0	0	3	1
Mean number of live fetuses / dam	11.6	12.0	11.6	12.0	11.3
Mean pup weight (g)	3.34	3.26	3.25	2.97*	2.85*
Crown rump length (cm)	3.61	3.60	3.59	3.53	3.47*
Mean placental weight (g)	0.49	0.50	0.50	0.46	0.44*
Diaphragmatic hernia total number (%)	1 (0.43 %)	1 (0.41 %)	1 (0.43 %)	2 (0.98 %)	2 (0.93 %)
Skeletal examination (no. fetuses examined)	120	127	120	106	115
Deformities of the head	1	-	-	3	-
Abdominal fissure	-	-	-	1	-
Scapula bent costally, one or both sides, humerus shortened, one side	2	-	-	-	1
Scapula bent costally, one or both sides	1	2	1	-	1

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

Conclusion:

The NOAEL for maternal toxicity in this study with Fenoxaprop-ethyl was considered to be 32 mg/kg bw/day based on clinical signs and a decrease in food consumption and body weight. Fetal toxicity was demonstrated in the highest dose group of 100 mg/kg by embryonic death, reduced pup weight and pup length, and a slightly delayed ossification, leading to a NOAEL of 32 mg/kg bw/day for fetotoxic effects. No teratogenicity was observed.

Hoe 033171 – active ingredient technical (Code: Hoe 033171 0H ZD98 0001) Testing for embryotoxicity and effects on postnatal development in Wistar rats following oral administration

Reference: *Baeder C. et al., 1986b;* Doc. No. A35783 / Hoechst Report No. 86.0133

Guideline: postnatal toxicity study, no guideline available; in the study report it is stated that the study was conducted according to OECD guideline 414

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

The aim of the study was to determine the effect of Fenoxaprop-ethyl on postnatal development of offspring following repeated dosing during gravidity. 20 female Wistar rats (Hoe WISKf(SPF71), source: Hoechst) per group were treated by oral gavage on gestation days 7 – 16 with 0, 10, 32 or 100 mg/kg Fenoxaprop-ethyl (vehicle: sesame oil). The animals were 65 – 70 days old and had a mean bodyweight of 194 ± 12.8 g. According to certificate of analysis No. 03098 (1985), the test substance had a purity of 97.9 % (Code: Hoe 033171 0H ZD98 0001). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Throughout the study, behaviour and general health condition of the animals were observed daily. Food consumption was checked during gravidity but not after delivery. Body weight gains were determined once weekly and again one day after the final treatment, and again after delivery.

All dams were allowed to deliver normally and rear their offspring for 21 days. Duration of gravidity and number of live and dead offspring were recorded. During the 21 day lactation period, the offspring was examined daily for viability and general behaviour. Body weights were determined on the day of delivery, on post natal days 4 and 7 and subsequently once weekly. For the examination of the physical development, the times of pinna separation, coat growth start, incisor eruption and eyelid opening were recorded. The dams and the offspring were sacrificed between days 21 and 23 after delivery. Macroscopical examination was performed and organ weights of heart, liver, kidneys and spleen were recorded in dams and offspring.

Findings:

Maternal effects: The only treatment-related sign of intolerance was piloerection in 4 dams of the highest dose group. The dams of the 100 mg/kg group showed a very slight tendency to reduced food consumption during the treatment period, but by the end of the study the animals had made up for the deficit by increased food consumption. Regarding body weights, a slight retardation was noted at 100 mg/kg during the treatment period, but body weights developed normally again after delivery.

At autopsy of the dams, no treatment-related changes could be found. The heart, liver, kidney and spleen weights of the dams treated with the test substance were comparable to those of the controls.

Table 157: Developmental and postnatal toxicity study of Fenoxaprop-ethyl in Wistar rats:
Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw) GD 0 – 7 GD 7 – 17 GD 17 – 21	 8.5 6.9 7.5	 8.1 6.7 7.5	 8.2 6.3* 7.7	 8.5 5.9* 8.6*
Body weight (g) GD 7 – 17 (mean) GD 0 – 21 (mean)	245 276	249 289	241 275	233* 276

GD: gestation day
* ($p < 0.05$); significantly different from controls

Litter data / fetal parameters: The duration of gravidity in all three treatment groups was 22 – 24 days which is normal for this strain of rat. However, it was noticeable that a larger number of dams in the 100 mg/kg group did not deliver until the 23rd day of gravidity or during the following night, whereas most of the dams from the other groups delivered during the night from the 22nd to the 23rd day of gravidity. One dam of the 100 mg/kg group had only implantation sites in the uterus and no fetuses. Regarding other litter parameters, there was no difference between control and treatment groups. The viability and physical development (pinna separation, coat growth start, incisor eruption and eyelid opening) of the offspring were not impaired by treatment. The bodyweights of the treated offspring at birth and during lactation were comparable with those of the control animals.

Examination for external anomalies: According to the study author no treatment-related findings were noted in any of the dose groups. With regard to the toe anomalies observed on one fore limb of one pup in the 32 mg/kg group, and also on the hind limbs of three pups in the 100 mg/kg group which died postnatally, it was pointed out that similar anomalies had already been occurring for some time in connection with hematocysts or hematomas in a number of in-house studies with rat fetuses. Furthermore, one pup of the controls also exhibited a hematoma in one hind foot, even though there were no recognizable toe anomalies.

Macroscopical examination of offspring: No signs of any damage to the internal organs were found. The heart, liver, kidney and spleen weights of the pups treated with the test substance were comparable to those of the controls.

Table 158: Developmental and postnatal toxicity study of Fenoxaprop-ethyl in Wistar rats:
Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Duration of gravidity (days)	22.5	22.5	22.5	22.9
Dams with live fetuses	20	20	20	19
Dams with empty implantation sites only	0	0	0	1
Mean number of live fetuses / dam	12.0	13.4	12.2	12.1

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Mean offspring weight (g) at birth[1)] Mean offspring weight (g) on day 21[1)]	5.61[1)] 36.6[1)]	5.62[1)] 32.8[1)]	5.65[1)] 35.5[1)]	5.65[1)] 34.6[1)]
Survival rate (%) day 21	91.6	95.3	88.1	91.3

* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed on mean body weight

Conclusion:

In this study with Fenoxaprop-ethyl, the maternal NOAEL was considered to be 32 mg/kg bw/d based on a slight decrease in food consumption and body weight and a slightly increased duration of gravidity at 100 mg/kg bw/d. Also in the highest dose group, embryonic death occurred in one dam as evidenced by empty implantation sites leading to a NOAEL for the offspring of 32 mg/kg bw/d. No other effects on offspring and postnatal development were noted.

An oral embryotoxicity study of Hoe 33171 active ingredient (technical grade, Code: Hoe 33171 0H AT204) in Himalayan rabbits

Reference: *Baeder C. et al., 1982b;* Doc. No. A24756 / Hoechst Report No. 667/82

Guideline: No information on study guidelines is presented in the study report.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Fenoxaprop-ethyl was administered to 15 gravid female Himalayan rabbits per group (Hoe HIMK(SPFWiga), source: Hoechst) by oral gavage once daily on gestation days 7 to 19 at doses of 0, 12.5, 50 or 200 mg/kg bw/day (vehicle: sesame oil). The rabbits had an initial age of 9 - 11 months and a mean initial bodyweight of 2688 ± 207 g. According to certificate of analysis No. 01711 (1981), the test substance had a purity of 93 % (Code: Hoe 33171 0H AT204). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

During the study, the animals´ behaviour and general health condition were assessed daily, their food intake was checked continuously, and body weight development was checked once a week in the first three weeks and then at a 9-day interval. On gestation day 29, rabbits were sacrificed and pups delivered by caesarean section. After opening of the uterus, the live and dead fetuses, resorption sites, placentae, and corpora lutea on the ovaries were counted and examined macroscopically. The diameters of the embryonic resorption sites and the weights of the placentae were determined. After removal from the uterus, the fetuses were checked for viability, appearance, external anomalies and bodyweights. The live fetuses were then reared for 24 hours in an incubator at a temperature of 32°C and a relative humidity of 60 %. A record was kept of the fetuses which died during this time. After this 24 h period the fetuses were subjected to autopsy and checked for skeletal and internal anomalies. After caesarean section, dams were examined macroscopically. Heart, liver, kidneys and spleen were weighed.

Range finding study: Groups of 2 – 4 Himalayan rabbits received single daily doses of 3, 10, 32, 100, 200 or 400 mg/kg bw on gestation days 7 – 19. The doses up to and including 100 mg/kg were tolerated by the dams and the fetuses without complication. The 200 mg/kg dose led to a slight reduction in body weight of the dams and also the fetal weight. In the 400 mg/kg dose group one dam refused to eat after beginning of treatment and obviously starved to death after eleven dose administrations. The second dam of this group had a markedly reduced food intake and subsequent weight loss and showed vaginal bleeding after ten and eleven dose administrations. The animal was therefore sacrificed and autopsy showed only embryonic primordia in resorption.

Findings:

Maternal effects: In the 12.5 mg/kg group, a dam died on gestation day 16. No effects were observed in the 50 mg/kg group. In the 200 mg/kg group, two dams died on gestation days 17 and 18, respectively. In addition to these findings, reduced defecation was noted in 4 dams of the controls, three dams at 12.5 mg/kg, 8 dams at 50 mg/kg, and all 15 dams at 200 mg/kg, during treatment period. The feed intake was reduced in the 50 mg/kg group and extremely reduced in the 200 mg/kg group. On conclusion of treatment, the dams again consumed normal quantities of food. It was not possible to determine exactly the feed intake of all dams since some scattered their feed from the racks. In addition, there was a reduction in water intake in one dam receiving 50 mg/kg and 2 dams receiving 200 mg/kg. The body weight development in the surviving dams from the 12.5 group corresponded to that of controls, whilst there was a body weight loss between GD 7-14 at 50 mg/kg and a very marked body weight loss throughout the treatment period at 200 mg/kg. Overall, between GD 0-29 was 58% of the control value at 50 mg/kg and 28% of the control value at 200 mg/kg. The effect on body weight was correlated with reduced feed intake and reduced defecation at the two highest dose levels.

The macroscopical examination revealed enlargement of liver and spleen in some of the dams receiving 200 mg/kg. Liver and spleen weight were increased at 200 mg/kg.

Table 159: Developmental toxicity study of Fenoxaprop-ethyl in Himalayan rabbits: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**12.5**	**50**	**200**
Pre-terminal deaths	-	1	-	2
Reduced defecation	4	3	8	15
Food con (g/100 g/day) GD 0-7	2.80	2.78	2.83	3.05
Food con (g/100 g/day) GD 7-14	2.30	2.87	1.45	0.57
Food con (g/100 g/day) GD 14-20	2.15	2.11	1.64	0.14
Food con (g/100 g/day) GD 20-29	2.63	2.59	2.59	3.62
Body weight (g) GD 0	2611	2659	2691	2646
Body weight (g) GD 7	2647	2664	2707	2648
Body weight (g) GD 14	2653	2676	2670	2452
Body weight (g) GD 20	2673	2723	2695	2351
Body weight (g) GD 29	2833	2862	2820	2710
Body weight gain (g) GD 0-7	36	5	16	2
Body weight gain (g) GD 7-14	6	12	-37	- 196
Body weight gain (g) GD 14-20	20	47	25	- 101
Body weight gain (g) GD 0-29	222	203	128	63
(% control)	-	(91)	(58)	(28)

	Dose group level (mg/kg bw/day)			
	0	**12.5**	**50**	**200**
Liver weight of dams (g) Spleen weight of dams (g)	53.51 0.61	55.69 0.72	56.66 0.72	63.54* 1.09*

GD: gestation day
* ($p < 0.05$); significantly different from controls

Litter data / fetal parameters: In the 12.5 mg/kg group, one dam gave birth prematurely on gestation day 29 and another exhibited only implantation sites in the uterus. Two dams of the 50 mg/kg group showed only implantation sites. In the 200 mg/kg group, one dam gave birth prematurely on gestation day 24, three dams aborted between gestation days 19 and 23, and another dam showed only implantation sites. The effects at 12.5 and 50 mg/kg were considered to be within the normal range, while a relation to treatment was suggested for the 200 mg/kg group. The number of corpora lutea, the number of implants and live fetuses per dam in the various dose groups were within the limits of previously obtained control values. The fetuses of the 200 mg/kg group were slightly underdeveloped showing reduced body weight and body length. The number of embryonic resorptions in the dams which carried live fetuses full term did not differ from those in dams from the control group. The placental weight was slightly reduced at 200 mg/kg. After 24 hours rearing in the incubator, the survival rate of the fetuses of the 200 mg/kg group was reduced compared to controls.

Skeletal and visceral examination: In the 200 mg/kg group, three of the full term fetuses from three different litters and one of the fetuses aborted on the 20th day of pregnancy of another dam showed anomalies in the form of diaphragmatic hernia. The number of fetuses displaying such diaphragmatic hernia gives a percentage occurrence of 10.7 %. In previous examinations of 32 control groups conducted in the same laboratory, only one such hernia had been encountered which represents a spontaneous rate of 0 – 1.3 %. One of the previously mentioned fetuses in this group also showed an umbilical hernia.

Skeletal examination showed an increased incidence of the 13th rib anlage in the 200 mg/kg group. 13 fetuses (46.4 %) showed the 13th rib anlage which was distributed between 7 out of 10 litters. This was a marked increased compared to previous controls, where the incidence was 0 – 10.2 %. Additionally, a 13th rib anlage was also found in four fetuses which were stunted, prematurely born or aborted dead. The incidence of this finding was slightly higher in the 12.5 mg/kg (3 fetuses; 7.5%) and 50 mg/kg (4 fetuses; 9.8 %) dose groups, compared with concurrent control value (1 fetus; 2.0 %), but clearly within the control historical control range (0 – 10.2 %), particularly at 12.5 mg/kg. In addition, no treatment-related incidence in this finding was observed in a subsequent study (*Baeder C. et al., 1983;* Doc. No. A29690) up to and including a dose level of 50 mg/kg. In any case, this finding is classed as a variation which commonly occurs spontaneous in control animals with no adverse consequences. In isolation, 13th rib anlage could be regarded as a non adverse finding at 12.5 mg and 50 mg/kg.

All other anomalies and variations observed in the treatment groups were considered to be spontaneous.

Table 160: Developmental toxicity study of Fenoxaprop-ethyl in Himalayan rabbits: Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**12.5**	**50**	**200**
Pregnant dams	15	15	15	15
Dams which died prematurely	-	1	-	2
Dams which delivered prematurely	-	1	-	1
Dams with abortion or only early resorptions	-	1	2	4
Dams with live fetuses	15	12	13	8
Mean number of live fetuses/dam	6.1	5.4	5.2	5.6
Mean pup weight (g)	43.5	44.6	43.6	35.3*
Crown rump length (cm)	9.8	9.7	9.8	9.2*
Mean placental weight (g)	5.68	5.80	5.79	5.08*
Survival rate after 24 hours (%)	92.5	95.3	92.2	61.2*
Morphological examination (fetuses examined)	54[1)]	44[2)]	50[3)]	42[4)]
Diaphragmatic hernia / no. examined (%)	-	-	-	3/28 10.7
Anlage of a short or normally sized 13th rib, uni- or bilateral / no. examined (%)	1/50 2.0	3/40 7.5	4/41 9.8	13/28 46.4
Morphological examination in stunted, prematurely born or aborted dead fetuses	*4*	*4*	*9*	*14*
Diaphragmatic hernia / no. examined	-	-	-	*1/14*
Anlage of a short normally sized 13th rib, uni- or bilateral / no. examined	-	-	-	*4/14*

* ($p < 0.05$); significantly different from controls
[1)] of which 4, [2)] of which 4, [3)] of which 9 and [4)] of which 14 stunted, prematurely born or aborted dead fetuses are not included in the calculation

Conclusion:

The administration of Fenoxaprop-ethyl resulted in a NOAEL for maternal toxicity of 12.5 mg/kg bw/day based on reduced food intake and body weight gain during treatment, with an actual loss of body weight between GD 7-14, and reduced defecation at 50 mg/kg. At the highest dose group of 200 mg/kg, additional findings such as reduced number of dams with live fetuses, increased incidence of dams with abortions or early resorptions, and decreased placental weight were recorded. Furthermore, liver and spleen were enlarged in some animals and mean weights of these organs were increased at 200 mg/kg.

Fetuses receiving 200 mg/kg showed a reduced body weight and body length, and a reduced survival rate after 24 hours. Furthermore, fetuses of this dose group showed diaphragm hernias and an increased incidence of a 13th rib. Diaphragmatic hernias were regarded as anomalies while the presence of a 13th rib anlage was regarded as an effect due to fetotoxicity. The NOAEL for fetal toxicity and teratogenicity therefore is 50 mg/kg.

Hoe 33171 - active ingredient technical (Code: Hoe 033171 0H ZC96 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration

Reference: *Baeder C. et al., 1983;* Doc. No. A29690 / Hoechst Report No. 83.0516

Guideline: No information on study guidelines is presented in the study report.

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

Groups of 15 gravid female Himalayan rabbits (Hoe HIMK(SPFWiga), source: Hoechst) were treated with Fenoxaprop-ethyl by oral gavage once daily on gestation days 7 to 19 at doses of 0, 2, 10 or 50 mg/kg bw/day (vehicle: sesame oil). The rabbits had an initial age of 9 - 10 months and a mean initial bodyweight of 2646 ± 184 g. The test substance (Code: Hoe 033171 0H ZC96 0002) had a purity of 96.2 % according to certificate of analysis No. 02183 (1983). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Throughout the study, behaviour and general health conditions of the animals were observed daily, food intake continuously, and body weight gains in the first three weeks once a week and then after a nine day interval. On gestation day 29, all dams were sacrificed and caesarean section was performed. After opening of the uterus, the live and dead fetuses, the conceptuses under resorption, the placentae and the corpora lutea on the ovaries were counted and examined macroscopically. The bodyweight of the fetuses, the diameter of the conceptuses under resorption and the weight of the placentae were measured. The fetuses were checked for appearance and overt anomalies, and the reared for 24 hours in an incubator at a temperature of 32°C and a relative atmospheric humidity of 60 %. A record was kept of the fetuses which died during this period. After this 24 h period the fetuses were subjected to autopsy and checked for skeletal and internal anomalies. After caesarean section, dams were examined macroscopically. Heart, liver, kidneys and spleen were weighed.

Findings:

Maternal effects: One dam of the 50 mg/kg group was sacrificed during the study due to vaginal haemorrhage (abortion) on gestation days 21 and 22. During the treatment period, dams with decreased amounts of excrements were found in all groups: two dams each in the control and 2 mg/kg group, four in the 10 mg/kg group, and eight in the 50 mg/kg group. Food intake in dams receiving 50 mg/kg was decreased during the first week of treatment, which correlated with a body weight loss during this phase of the study. The food intake and body weight gain subsequently returned to normal. Food intake could not be determined in all animals because a number of them scattered their feed from the racks.

Autopsy of the dams resulted in no changes in the internal organs which might be ascribed to administration of the test substance. Heart, liver, kidney and spleen weights were comparable in all groups.

Table 161: Developmental toxicity study of Fenoxaprop-ethyl in Himalayan rabbits: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Pre-terminal deaths	-	-	-	1[1)]
Reduced defecation	2	2	4	8
Food con (g/100 g/day) GD 0-7	2.81	2.88	2.90	2.93
Food con (g/100 g/day) GD 7-14	2.45	2.28	2.47	1.75
Food con (g/100 g/day) GD 14-20	2.43	2.13	2.34	2.53
Food con (g/100 g/day) GD 20-29	2.68	2.60	2.68	2.64
Body weight (g) GD 7	2710	2642	2681	2687
Body weight (g) GD 14	2720	2634	2684	2652
Body weight (g) GD 20	2780	2692	2745	2737
Body weight (g) GD 29	2934	2812	2903	2865
Body weight gain (g) GD 7-14	10	- 8	3	- 35
Body weight gain (g) GD 0-29	262	192	253	198
(% control)	-	(73%)	(97%)	(76%)

* ($p < 0.05$); significantly different from controls
[1)] The animal was sacrificed because of vaginal bleeding on gestation days 21 and 22 (abortion)

Litter data / fetal parameters: One dam each in the 2 and 10 mg/kg groups had only implantation sites or conceptuses under resorption. One dam of the 50 mg/kg aborted (vaginal haemorrhage) and then was sacrificed. All of these findings were considered to be within the spontaneous rate as they occurred with comparable frequency in almost every test for embryotoxicity in rabbits. The number of corpora lutea and the number of implantations remained for all groups within the limits of previous control values. On the contrary, litter sizes for the dams of the 50 mg/kg group were lower than historical control values though no statistical significant difference was found compared with the control group. Also, a relatively high resorption rate was found in the high dose group which exceeded the limit of the previous spontaneous rate. It was assumed that 50 mg/kg is a borderline dose for fetotoxicity. The live fetuses showed normal development and their body weights and body lengths corresponded to those of the control fetuses. The placentae showed no abnormalities either macroscopically or in regard to weight. The viability of the fetuses in the first 24 hours after delivery remained unaffected by treatment.

Skeletal and visceral examination: A single case of diaphragmatic hernia was found in the 50 mg/kg dose group. No increase in the incidence of a 13th rib was found in this study.

Table 162: Developmental toxicity study of Fenoxaprop-ethyl in Himalayan rabbits: Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Pregnant dams	15	15	15	15
Dams with abortions or only early resorptions	-	1	1	1
Dams which delivered prematurely	-	-	-	-
Dams with live fetuses	15	14	14	14

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Mean number of live fetuses/dam	5.7	5.1	6.6	5.1[1)]
Mean number of resorption sites	1.13	0.79	0.36	1.64[1)]
Mean pup weight (g)	43.1	45.3	44.4	44.8
Crown rump length (cm)	9.6	9.7	9.8	9.8
Mean placental weight (g)	6.05	6.11	5.91	6.09
Survival rate after 24 hours (%)	97.8	89.0	97.4	92.3
Morphological examination (fetuses examined)	49[1)]	42[2)]	52[3)]	42[4)]
Diaphragmatic hernia / no. examined (%)	-	-	-	1/40 2.5
Anlage of a short or normally sized 13th rib, uni- or bilateral / no. examined (%)	1 2.1	4 10.0	1 2.0	2 5.0

* ($p < 0.05$); significantly different from controls
[1)] outside the normal range of previous controls
[1)] of which 1 and [2-4)] of which 2 stunted or dead fetuses are not included in the calculation

Conclusion:

The NOAEL for maternal toxicity in this rabbit developmental toxicity study with Fenoxaprop-ethyl was 10 mg/kg bw/d based on a loss in body weight, reduced food intake and defecation during the first week of treatment, and an increased number of resorptions sites compared to historical controls, though the latter finding was statistically not significant when compared to concurrent controls, at a dose level of 50 mg/kg bw/d. Regarding fetuses, a slightly reduced number of live fetuses per dam was observed, which again was statistically not significant but outside the range of previous controls. A single case of diaphragmatic hernia was found in the 50 mg/kg dose group. Though the incidence of this finding was low (2.5 %), it cannot be excluded that it was caused by treatment with the test substance. The NOAEL for fetotoxicity and teratogenicity therefore is 10 mg/kg bw/d.

A study of the effect of the active ingredient Hoe 033171 technical on pregnancy of the mouse (Code: Hoe 033171 0H ZC96 0002)

Reference: *James P. et al., 1983;* Doc. No. A30282 / Huntingdon Research Centre plc, Report No. HST 221/222-R/83666

Guideline: EPA, section F. Hazard Evaluation, Humans and domestic animals section 83-3 (Teratology study)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

The effects of Fenoxaprop-ethyl on pregnancy and fetal development were tested in CD-1 mice (source: Charles River UK Limited, Manston Road, Margate, Kent). Groups of 30 mice were

mated and checked for the presence of a vaginal plug, which was considered as gestation day 0. The test substance was dissolved in sesame oil and administered by oral gavage on gestation days 6 – 15 at doses of 0, 2, 10 and 50 mg/kg bw/d. According to certificate of analysis No. 02183 (1983), the purity of the test substance was 96.2 %. The solutions were made daily and dosed on the day of preparation.

Clinical signs were checked daily. All animals were weighed on gestation days 0, 1, 3, 6, 8, 10, 14 and 17. On day 17.5 of pregnancy the dams were sacrificed by cervical dislocation and examined for macroscopic pathological changes in maternal organs. The liver was weighed. The ovaries and uteri were immediately examined to determine the number and distribution of live fetuses, the number of embryonic deaths, the individual fetal body weight and fetal malformations. Fetuses were examined for visceral and skeletal abnormalities.

Range finding study: In this study groups of 10 female CD-1 mice were treated with doses of 0, 12.5, 25 or 50 mg/kg bw/d by oral gavage on gestation days 6 – 15. There were no clinical signs or deaths attributed to treatment. No effect on food consumption or body weight gain was observed. Absolute liver weight was slightly increased with dose. Occasional females had total resorption but treatment with the test substance had no apparent effect on litter parameters. Autopsy revealed one fetus with a kinked tail in the 25 mg/kg group.

Findings:

Maternal effects: There were no clinical signs of reaction to treatment, no mortalities and no apparent effect on body weight gain. Among females with live young, relative liver weight was significantly increased at 50 mg/kg while at 2 and 10 mg/kg it was only marginally higher than the control value. At autopsy of dams, no abnormalities related to treatment were found.

Table 163: Developmental toxicity study of Fenoxaprop-ethyl in CD-1 mice: Maternal effects

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Number of animals	21	26	23	26
Terminal body weight (g)	50.74	51.14	51.00	53.10
Liver weight absolute (g) relative to body weight	2.407 2.430	2.469 2.482	2.482 2.500	3.022 2.952**

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

Litter data / fetal parameters: Occasional females had total resorption (one in the control and the 2 mg/kg group, two in the 10 mg/kg group) but there was no relation to treatment as assessed by litter size, sex ratios, fetal loss and mean pup weight.

Skeletal and visceral examination of offspring: Neither the type nor the distribution of malformations and anomalies observed indicated any obvious association with treatment.

Table 164: Developmental toxicity study of Fenoxaprop-ethyl in CD-1 mice: Maternal and developmental effects

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Dams with sperm/pregnant	22/30	27/30	25/30	26/30

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Dams with total resorptions	1	1	2	-
Dams with live fetuses	21	26	23	26
Mean number of live fetuses/dam[1)]	11.8	11.3	11.7	12.1
Embryonic deaths[1)]	0.8	1.1	0.8	0.8
Post implantation loss[1)]	6.2	10.4	6.3	6.1
Mean pup weight (g)	1.04	1.07	1.07	1.05
Fetuses with malformations / no. examined (%)	6/227 2.6	3/268 1.1	5/247 2.3	4/288 1.3
Fetuses with visceral anomalies / no. examined (%)	5/110 4.3	4/133 3.3	3/123 2.7	5/138 3.6
Fetuses with skeletal anomalies / no. examined (%)	5/111 4.6	12/132 11.0	6/119 5.1	11/146 7.3
Fetuses with unossified sternebrae / no. examined (%)	4/111 3.7	3/132 4.0	4/119 3.5	4/146 2.4

* ($p < 0.05$); significantly different from controls
[1)] includes only animals with live young at termination

Conclusion:

Treatment with Fenoxaprop-ethyl at a dose level of 50 mg/kg bw/d resulted in an increase in liver weight in dams leading to a NOAEL for maternal toxicity of 10 mg/kg bw/d. No effect on fetuses was observed at any dose resulting in a NOAEL for fetotoxicity of 50 mg/kg bw/d. There was no teratogenicity observed.

Hoe 033171, technical grade (Code: Hoe 033171 0H ZC96 0002), oral embryotoxicity study in the Cynomolgus monkey

Reference: *Osterburg I., 1984;* Doc. No. A29702 / Hazleton Laboratories Deutschland GmbH, Report No. 245-169/6
Supplement to Doc. No. A29702, Hazleton Laboratories Deutschland GmbH, 1984

Guideline: no

GLP: yes

Due to missing concurrent controls, the study is of limited validity. Furthermore, only three fetuses were available for morphological examination of the high dose group.

Material and Methods:

The objective of this study was to assess the potential of Fenoxaprop-ethyl to affect the embryonic and fetal development in Cynomolgus monkeys. The non-human primate (Cynomolgus monkey, macaca fascicularis) was selected for this study because of similarities with humans in reproduction physiology during pregnancy. The monkeys were obtained from the breeding station at Hazelton Research Primates (Reston, Virginia, USA) and were sexually

mature. The body weight of the animals was between 2.4 and 4.7 kg. The animals were acclimatised to the laboratory for a minimum of 3 weeks prior to the starting of mating. Female animals were mated with untreated fertile males one or two days before the theoretical middle of the menstrual cycle. The day on which the vaginal smear showed the presence of sperm was taken as day 0 of pregnancy. Pregnancy of the females was checked on gestation days 18 and 19. On day 20, pregnant females were allocated to study groups and treated with Fenoxaprop-ethyl from gestation day 20 – 50 by oral gavage. The animals then were maintained without treatment until day 100 of gestation when caesarean section was performed.

The test substance (vehicle: sesame oil) was administered at doses of 10 and 50 mg/kg bw/d to 23 and 11 pregnant females, respectively. Control animals referred to in this study were taken as a collection from historical controls from the years 1982 - 1985. The purity of the test substance (Code: Hoe 033171 0H ZC96 0002) was 96.2 % according to certificate of analysis no. 02183.

All animals were examined at least once daily for clinical signs, behavioural change, food intake, feces and vaginal bleeding. Blood samples were taken on gestation days 20, 27, 34, 41, 48, 55, 69 and 83 for determination of alkaline phosphatase (ALP), aspartate amino transferase (ASAT), alanine amino transferase (ALAT), cholesterol, triglycerides and total lipids. The body weight of each pregnant animal was recorded on days 20, 27, 34, 41, 48, 55, 62, 69, 76, 83, 90 and 97. On gestation day 100 the fetuses were removed by caesarean section. The pregnant females were examined for pathological changes macroscopically during caesarean section as far as possible. The fetuses were weighed, sexed, measured and examined for external abnormalities. A full necropsy was performed on each fetus with macroscopic and microscopic visual inspection of all organs. The liver, spleen, kidneys, adrenals, lungs, heart, thymus, eyes, brain, testes, ovaries and uterus were weighed. The carcass of each fetus was processed and stained for examination of skeletal and visceral defects.

Findings:

Maternal effects: In the low dose group (10 mg/kg), two females with positive pregnancy tests were found not to be pregnant. No placental signs could be detected therefore the pregnancy tests were considered as false positive. In both dose groups, clinical signs were limited to reduced food intake and / or slight diarrhea observed in all females mainly during the treatment period. Occasional vomiting was not considered to be treatment-related since these were isolated events. In the high dose group (50 mg/kg), 5 of 11 females died, 4 females during the dosing period and 1 female four days after the treatment period. The necropsy showed the following findings: nephritis (female no. 4204), tubular nephrosis (female no. 4171), enteritis and hemorrhagic ulcera in the stomach (female no. 4266), chronic nephropathy and hemorrhagic ulcera in the stomach (female no. 4182) and pneumonia and slight enteritis (female no. 4121).

The mean values of cholesterol, triglycerides and total lipids, calculated from pregnant animals with live fetuses, were markedly reduced between days 20 to 83 of gestation. The other parameters (ALP, ASAT, ALAT) did not reveal a treatment-related effect.

Table 165: Developmental toxicity study of Fenoxaprop-ethyl in Cynomolgus monkeys: Maternal effects

	Dose group level (mg/kg bw/day)	
	10	**50**
Mortality	-	5 / 11
Reduced food intake and / or diarrhea	21 / 21	11 / 11

	Dose group level (mg/kg bw/day)	
	10	**50**
Body weight (kg) Day 20 (beginning of treatment) Day 48 (close to end of treatment) Day 100 (terminal body weight)	 3.3 3.2 3.9	 3.7 3.5 4.3
Body weight gain (Days 20 – 100, kg)	0.6	0.6
Cholesterol (mg/dl) Day 20 (beginning of treatment) Day 48 (close to end of treatment) Day 83 (no treatment)	 161.33 116.43 74.50	 126.39 82.62 60.97
Triglycerides (mg/dl) Day 20 (beginning of treatment) Day 48 (close to end of treatment) Day 83 (no treatment)	 65.80 41.69 33.91	 55.93 38.88 29.68
Total lipids (g/L) Day 20 (beginning of treatment) Day 48 (close to end of treatment) Day 83 (no treatment)	 7.16 5.85 4.43	 4.67 3.17 3.80

Litter data / fetal parameters: At 10 mg/kg, 5 females aborted on days 30, 31, 53, 57 and 60 of gestation, respectively. At 50 mg/kg, 2 females aborted during the treatment period and a third female with an injury to the right hindleg aborted after the treatment period. Regarding the rates of abortions, a supplement to the study report was prepared including historical control data (Supplement to Doc. No. A29702, Hazleton Laboratories Deutschland GmbH, 1984). In this document, data from 15 studies involving 151 pregnant females (*Macaca fascicularis*) were presented. Of these 151 females, 27 aborted which results in a mean abortion rate of 17.9 %. The range of abortions therefore laid between 0 – 40 %, reflecting a high range of variability within the control data. Considering the historical control data, the abortions observed in the actual study (23.8 % in the 10 mg/kg; 27.3 % at 50 mg/kg) were within the range observed in previous studies. However, due to high variations in the controls it remains difficult to judge if abortions observed in this study were treatment-related or not.

For all other parameters, historical control data was used wich was collected during a period of three years from obviously four different studies. In this historical control studies, 36 fetuses were examined.

In the actual study, the mean fetal weight was 108.7 g at 10 mg/kg and therefore slightly lower than in the historical controls (116.9 g). This decrease was mainly due to one fetus which was extremely reduced in weight (75.6 g). The other fetuses were all within the range of historical controls. In the 50 mg/kg dose group, the mean fetal body weight was 118.6 g which is very close to the mean of historical controls. In the other parameters measured (distance coccyx to head, tip of nose to back of head, front to back of head, width of head, and distance between the eyes) there were no differences found between treatment groups and historical controls. Regarding organ weights, there was no treatment-related effect found in any organ. All values were within the range of historical controls.

Skeletal and visceral examination of offspring: External, visceral and skeletal findings were observed in both treatment groups and historical controls at comparable incidences. However, there was considerable variation in the different studies used for historical control data

especially regarding skeletal findings. The external findings were non specific mainly affecting the tail. Visceral findings were limited to adrenals reduced in size and skeletal findings mainly consisted in uneven thickness of ribs.

Table 166: Developmental toxicity study of Fenoxaprop-ethyl in Cynomolgus monkeys: Maternal and developmental effects

	Dose group level (mg/kg bw/day)		
	10	**50**	**Historical controls**
Females with positive pregnancy test	23	11	151
Pregnant females	21	11	-
Mortality	-	5	-
Dams with abortions (%)	5 (23.8 %)	3 (27.3 %)	27 (17.9 %) (range 0 – 40 %)
Dams with live fetuses	16	3	124
Number of live fetuses	16	3	36
Mean fetal weight (g)	108.7 (range 94 – 153)	118.6 (range 76 – 128)	116.9 (range 102 – 129)
Fetuses with external findings (%)	3 (19 %)	1 (33 %)	6 (17 %)
Fetuses with visceral findings (%)	2 (13 %)	-	3 (8 %)
Fetuses with skeletal findings (%) *- Undeveloped or uneven thickness of 1 or 2 ribs (%)* *- Non ossified sternebrae or vertebra (%)*	11 (69 %) *10 (62.5 %)* *1 (6.3 %)*	2 (67 %) *2 (67 %)* -	22 (61 %) *15 (42 %)* *9 (25 %)*

Conclusion:

In the high dose group (50 mg/kg), clear maternal toxicity was observed resulting in mortality of five from eleven treated females. Slight diarrhea and / or a reduction of food intake were noted in all treated animals from both the 10 mg/kg and the 50 mg/kg group. Also, clinical chemistry parameters were affected in both dose groups as shown by reduction of cholesterol, triglycerides and total lipid levels during the treatment period. 5 of 21 females aborted in the 10 mg/kg group and 3 of 6 surviving females aborted in the 50 mg/kg group. Though the incidence of abortion is within the range of the historical controls, a relation to treatment cannot be ruled out because of the wide range of variation in historical control data (rates of 0 – 40 %).

Regarding fetotoxicity or teratogenicity it has to be kept in mind that due to maternal mortality and abortions, only 3 fetuses were available for investigations in the high dose group. Furthermore, historical control data used for fetal parameters showed high variation in skeletal findings, which makes it very difficult to evaluate the results of the study. However, there was some indication of an increase in the incidence of undeveloped or uneven thickening of the ribs in both dose groups.

Due to a missing concurrent control group and a very small number of fetuses in the high dose group it is not possible to establish NOAELs for maternal and fetal toxicity. The study therefore is of limited value and supplementary information only.

4.11.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.11.3 Other relevant information

4.11.4 Summary and discussion of reproductive toxicity

No multigeneration 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 with comparable effect levels, it was considered justified to use the multigeneration 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/day whereas the reproductive NOAEL was 8.77 mg/kg bw/day.

Developmental toxicity studies with **Fenoxaprop-P-ethyl** have been carried out in rats and rabbits. All of the studies were performed according to GLP, and, when applicable, close to international guidelines though that was not 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 weight and heart weight was reduced. These findings were confirmed in the embryo- and postnatal toxicity study in Wistar rats, when a decrease in food consumption, a decrease in body weight and a slightly increased duration of gravidity was noted at 100 mg/kg. Fetal toxicity was demonstrated by embryonic death, reduced pup weight and pup length at 100 mg/kg. An increased rate of weak or non-ossification of at least 1 cranial bone was already observed at 32 mg/kg bw/d which was considered to be a treatment-related fetal development effect. However, since the incidence (56.8%) was only marginally outside the historical control range (min. 13.1 – max. 56%) and in the absence of any other fetal 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 fetal toxicity. For the notifier this argumentation is 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 PRAPeR expert meeting No. 19 (26-30.3.2007) the relevant developmental NOAEL was agreed to be 10 mg/kg bw/d and the maternal NOEAL 32 mg/kg bw/d. An embryotoxicity study in Himalayan rabbits also showed maternal toxicity at the dose level of 100 mg/kg resulting in decreased food consumption, decreased body weight gain during treatment period, and slightly increased kidney weights. With respect to fetotoxicity, the only effect observed was an increase of 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, when applicable, close to international guidelines though that was not stated in most of the study reports. With the exception of the study in monkeys, all studies are scientific valid and acceptable.

The developmental study in Wistar rats showed maternal toxicity at the highest dose level of 100 mg/kg. Clinical signs (piloerection) and a decrease in food consumption and body weight were noted in the dams. Results of the embryo- and postnatal toxicity study in Wistar rats confirm these findings, as similar maternal toxic effects like decreased food consumption and body weight, and a slightly increased duration of gravidity were observed at the same dose level. Fetotoxicity 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 treatment animals; no relation to treatment was considered as the incidences were within the historical control range. Deformities of the head which were found in one fetus at 32 mg/kg and three fetuses at 100 mg/kg 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, postnatal 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, and in the second study 2, 10 and 50 mg/kg. At the highest dose level of 200 mg/kg, excessive maternal toxicity was observed resulting in a reduced number of dams with live fetuses, an increase of abortions and early resorptions, and a macroscopic enlargement and increased organ weight of liver and spleen. A decreased number of resorption sites and of live fetuses per dam was observed at 50 mg/kg 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 of body weight during the treatment period, and a decreased defecation were noted at 50 and 200 mg/kg. Embryonic death, reduced pup weight and reduced pup length were observed at 200 mg/kg, as well as an increased incidence of a 13^{th} rib, all demonstrating embryotoxicity at this dose level. Furthermore, the incidence of diaphragmatic hernias was increased at 200 mg/kg (3 of 28 fetuses, 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 (1 of 40 fetuses, 2.5 %). It remains questionable if the single case of diaphragmatic hernia found at 50 mg/kg bw/d in the second study was related to treatment. In conclusion, in the first study maternal NOAEL can be set at 12.5 mg/kg bw/d while the fetal NOAEL is 50 mg/kg bw/d, in the second study the NOAEL for maternal and fetal toxicity is 10 mg/kg bw/d.

An embryotoxicty 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 fetotoxicity or teratogenicity was observed. The NOAEL for maternal toxicity is 10 mg/kg bw/d, while the NOAEL for fetal toxicity is 50 mg/kg bw/d.

A developmental toxicity study in Cynomolgus monkeys is of limited validity as no concurrent controls were used and the historical control data showed high variations.

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 fetuses were available in this dose group for evaluation of fetotoxicity or teratogenicity. Further maternal toxicity effects observed were slight diarrhea 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 fetuses, relatively high rates of undeveloped or uneven thickening of the ribs were observed in both dose groups. Taken together, it is not possible to finally evaluate this study for maternal and fetal toxicity and teratogenicity. Therefore, no NOAELs were established.

4.11.5 Comparison with criteria

No adverse effects on reproduction parameters, fertility or offspring development were observed in a multigeneration study conducted in rats with fenoxaprop-ethyl.

In the developmental rat study with fenoxaprop-P-ethyl, the maternal NOAEL was 32 mg/kg bw/day based on decreased body weight gain. In foetuses, weak or non-ossification of at least one cranial bone was statistically increased at 32 mg/kg bw/day, affecting 56.8% of the fetuses, slightly above the historical control data (min. 13.1 – max 56%) and at 100 mg/kg bw/day, affecting 65.5% of the fetuses. At 10 mg/kg bw/day weak or non-ossification of at least one cranial bone was (non statistically significant) increased, affecting 30.5% of the fetuses, which is slightly below the mean of the historical control data (31 ± 9.6%) and therefore within the range of normal variability. For weak or non-ossification of at least one cranial bone the litter incidence is increased at the two high doses (32 and 100 mg/kg bw/d) but not at the low dose (10 mg/kg bw/d). The clear foetal NOAEL was 10 mg/kg bw/day. The findings occurred in absence of maternal toxicity (maternal NOAEL is 32 mg/kg bw/d), therefore the severeness of the effect was discussed at the PRAPeR 19 meeting (mammalian toxicology), whether it is non-ossification or delayed ossification in the light of classification with R 63. Thereby the experts agreed to highlight the concern about the developmental effects with the proposal Toxic to Repr. cat.3, R63?.

The reason for proposing R63? in the peer review was that in the first rat study conducted by Baeder et al., 1985a, in foetuses, weak or non-ossification of at least one cranial bone was statistically increased at 32 mg/kg bw/day, affecting 56.8% of the fetuses in the absence of maternal toxicity, which is slightly above the historical control data (min. 13.1 – max 56%). Furthermore it was pointed out at the PRAPeR 19 meeting that in rats and rabbits effects of abdominal fissure and diaphragmatic and umbilical hernia were observed.

In the view of the dossier submitter the increase in weak or non-ossification of at least one cranial bone in the absence of maternal toxicity was only minimally (56.8 versus 56%) above the historical control. This finding is a common spontaneously occurring variant finding and reflects a slight delay in development with no long term consequences. In the absence of other fetal findings at 32 mg/kg bw/d, according to the notifier this dose level could be considered to be a NOAEL for fetal toxicity. A NOAEL of 32 mg/kg bw/d for maternal and fetal toxicity for fenoxaprop-P-ethyl would also be consistent with that derived for fenoxaprop-ethyl. Furthermore another rat study is available showing as well effects on the cranial ossification, which are obviously not dose related and are within the historical control range.

In the first rat study conducted by Baeder et al., 1985a in the 100 mg/kg group, one foetus (1 %) exhibited an abdominal fissure with protrusion of intestinal coils, and another foetus from another litter (0.9 %) showed multiple malformations in the region of the cervical and thoracic vertebral column. As these findings occurred also spontaneously in historical control groups

and were isolated to the 100 mg/kg group, a substance-relationship was considered hardly probable.

In a range finding study in rats, groups of three or two gravid Wistar rats were treated with doses of 50, 100 or 200 mg/kg bw on GD 7 – 16. Doses of 200 mg/kg resulted in pilo-erection from days 4 to 7 of treatment in both dams and caused a reduction of food intake and bodyweights. Apart from one stunted, live foetus with a diaphragmatic and an umbilical hernia, the uteri of the two dams contained only conceptuses under resorption. Historical control data (5 previous studies) for diaphragmatic hernia are available for a rat study conducted with fenoxaprop-ethyl in 1982 in the same laboratory by the same study author. Since the years where the studies were conducted are in the same time frame (1982 versus 1985) this data can be used as historical control data for the range finding study. The highest frequency of diaphragmatic hernia occurrence was found in 2 from 216 foetuses, corresponding to a rate of 0.9%. It is not possible to calculate a rate for the dose finding study as there is no information available on the total number of foetuses, but considering the total number of diaphragmatic and umbilical hernia it is likely that this finding is within the historical control range. Furthermore this finding occurred at a dose level, where all other foetuses were aborted and no signs of either diaphragmatic or umbilical hernia were shown in the main rat studies. Therefore this isolated finding is considered to be incidental.

In a developmental study with fenoxaprop-P-ethyl in rabbits, the maternal and foetal NOAELs were 32 mg/kg bw/day. 1/35 (2.9%) foetuses in the 32 mg/kg bw/day group developed umbilical hernia. No umbilical hernias were found in the other dose groups tested (0, 10 and 100 mg/kg bw/day). No historical control data are available. No increase in abortions which could mask teratogenicity was observed. Therefore it is considered likely that this isolated, not dose related finding is incidentally.

4.11.6 Conclusions on classification and labelling

No classification for fertility effects is proposed.

No classification for developmental effects is proposed.

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 13th 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.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

According to the available acute, subchronic and chronic studies, there was no indication of a neurotoxic potential (neither neurobehavioural changes nor any morphological changes in the CNS or in the peripheral nerves).

4.12.1.2 Immunotoxicity

According to the available acute, subchronic and chronic studies, there was no indication of an immunotoxic potential.

4.12.1.3 Specific investigations: other studies

Table 167: Summarised results of hepatic enzyme studies with Fenoxaprop-P-ethyl

Study; Reference	Dose levels	Effects
Wistar rat, 28 days oral *Suter P., Luetkemeier H., 1987b*	0, 20, 80, 320, 1280 and 5120 ppm / diet (equivalent to 0, 2, 6, 26, 95 and 126 mg/kg bw/d in males; 0, 2, 6, 28, 94 and 144 mg/kg bw in females)	- 5120 ppm: animals killed in extremis on study day 9 (no analytic measurements) - increased N-demethylase in females at 320 and 1280 ppm - increased GSH and total glutathione in males at 320 and 1280 ppm - <u>increased catalase activity at 1280 ppm in both sexes (↑ 81% in males, ↑ 126% in females)</u>
Wistar rat, 13 weeks oral *Tennekes H., Luetkemeier H., 1987*	0, 10, 80 and 640 ppm / diet (equivalent to 0, 0.7, 5.8 and 49.0 mg/kg bw/d in males; 0, 0.8, 6.3 and 51.8 mg/kg bw/d in females)	- increased Cytochrom P-450 in males at 80 and 640 ppm - decreased N-demethylase in all male dose groups and increased N-demethylase in females at 640 ppm - decreased GSH and increased GSSG levels at 640 ppm - <u>increased catalase activity at 640 ppm (↑ 27% in males, ↑ 14% in females)</u>

Study; Reference	Dose levels	Effects
NMRI mouse, 28 days oral *Suter P., Luetkemeier H., 1987c*	0, 20, 80, 320 and 640 ppm / diet (equivalent to 0, 3, 14, 56 and 260 mg/kg bw/d in males; 0, 4, 16, 61 and 280 mg/kg bw/d in females)	- decreased cytochrome P-450 and increased GSH and total glutathione in males at 640 ppm - increased catalase activity at 80 ppm (males, ↑ 55%) and above (↑ 184% in males and 115% in females at 320 ppm, ↑ 194% in males and 206% in females at 640 ppm)
NMRI mouse, 13 weeks oral *Suter P., Luetkemeier H., 1987d*	0, 10, 80 and 640 ppm / diet (equivalent to 0, 1.4, 11.9, 100.8 mg/kg bw/d in males; 0, 2.0, 16.5 and 122.4 mg/kg bw/d in females)	- increased cytochrome P-450 activity in males at 640 ppm - increased N-demethylase activity in females at 640 ppm - increased catalase activity at 640 ppm in both sexes (↑ 217% in males and ↑ 308% in females)
Beagle dog, 28 days oral *Sachsse K. et al., 1987c*	0, 80, 320 and 1280 ppm / diet (equivalent to 0, 3.3, 13.0 and 67.9 mg/kg bw/d in males; 0, 3.7, 14.9 and 56.1 mg/kg bw/d in females)	- no enzymatic change could be detected (only 1 dog/sex/dose) (catalase activity not determined)
Beagle dog, 13 weeks oral *Sachsse K. et al., 1987d*	0, 80, 400 and 2000 ppm / diet (equivalent to 0, 3.0, 15.6 and 77.7 mg/kg bw/d in males; 0, 3.2, 16.2 and 83.4 mg/kg bw/d in females)	- decreased N-demethylase activity in males at 2000 ppm (catalase activity not determined)

Hoe 046360 Technical. 28-day dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver

Reference: *Suter P., Luetkemeier H.;* 1987(b); Doc. No. A36955 / RCC Project No. 060636

Guideline: not applicable

GLP: yes, deviation: the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.

In this study special investigations on liver enzymes were performed which is supplementary to the 28-day repeated dose toxicity study in Wistar rats (Suter P., Luetkemeier H., 1987(a); Doc. No. A36568)

Material and Methods:

Groups of 5 male and 5 female Wistar rats (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 20, 80, 320, 1280 or 5120 ppm Fenoxaprop-P-ethyl equivalent to 0, 2, 6, 26, 95 or 126 mg/kg bw/d in males and 0, 2, 6, 28, 94 or 144 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the rats were about 6 weeks old and weighed 138 – 167 g (males) and 130 – 145 g (females). Diets were prepared twice

monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450, N-demethylase, glutathione and catalase was removed from all animals scheduled for necropsy after 28 days of treatment. The sections were weighed and rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were investigated: cytochrome P-450, N-demethylase (females only), reduced glutathione (GSH), oxidized glutathione (GSSG), total glutathione (GSH+GSSG) and catalase.

Findings:

All animals of the highest dose group (5120 ppm) were sacrificed in extremis on treatment day 9 as they displayed severe signs of toxicity like emaciation, ruffled fur and a curved position. No analytical measurements were performed in this dose group.

Hepatic enzyme determination: A moderately increased N-demethylase activity was noted for females at 320 and 1280 ppm. Due to an analytical error, no data were obtained for N-demethylase for male rats. A repeat analysis was not performed because of the limited amount of sample available for analysis. GSH and total glutathione levels were increased in males receiving 320 and 1280 ppm, while GSSG levels were increased in females receiving 1280 ppm. A marked increase of catalase activity was measured in both sexes at 1280 ppm.

Table 168: 28 day feeding study in Wistar rats with Fenoxaprop-P-ethyl
Hepatic enzyme determination after 28 days

	Dose group level (ppm)									
	Males					**Females**				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Cytochrome P-450 (nmol/g)	20.1	17.6	18.7	22.9	23.2	15.0	14.2	13.9	14.9	13.9
N-demethylase (nmol/min/g)	n.d.	n.d.	n.d.	n.d.	n.d.	125	134	157	194*	167*
Glutathione										
(µmol/g)	3.28	3.44	3.99	4.76*	5.89*	3.77	4.03	3.81	4.72	4.60
-reduced (GSH)	0.98	1.05	0.92	0.80	1.15	0.74	0.78	0.79	0.80	1.07*
-oxidized (GSSG)	4.26	4.49	4.91	5.55*	7.04*	4.51	4.81	4.60	5.52	5.66
-total (GSH+GSSG)										
Catalase (k/g)	176	205	164	224	318*	87	66	68	86	197*

* ($p < 0.05$); significantly different from controls (Dunnett-test)
n.d. not determined

Conclusion:

The analysis of liver tissue revealed neither clear induction of the drug-metabolizing system nor depletion of glutathione (GSH). Determination of catalase which is an enzymic marker of peroxisome proliferation showed a distinct increase at a dose level of 1280 ppm.

Hoe 046360 Technical. 13-week dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver

Reference: *Tennekes H., Luetkemeier H.*; 1987; Doc. No. A36954 / RCC Project No. 060671

Guideline: not applicable

GLP: yes

In this study special investigations on liver enzymes were performed which is supplementary to the 13-week repeated dose toxicity study in Wistar rats (Tennekes H. et al., 1987; Doc. No. A36566)

Material and Methods:

Groups of 10 male and 10 female Wistar rats (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 10, 80 or 640 ppm Fenoxaprop-P-ethyl equivalent to 0, 0.7, 5.8 or 49.0 mg/kg bw/d in males and 0, 0.8, 6.3 or 51.8 mg/kg bw/d in females. The reversibility of treatment-related changes was studied with 10 additional animals/sex in the control and the 80 ppm and 640 ppm treatment groups over a 4-week recovery period. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the rats were about 6 weeks old and weighed 143 – 172 g (males) and 128 – 153 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450, N-demethylase, glutathione and catalase was removed from all animals scheduled for necropsy after 13 and 17 weeks of treatment. The sections were weighed and rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were investigated: cytochrome P-450, N-demethylase, reduced glutathione (GSH), oxidized glutathione (GSSG), total glutathione (GSH+GSSG) and catalase.

Findings:

Hepatic enzymes after 13 weeks: There was a slight increase in cytochrome P-450 content for males receiving 80 and 640 ppm. The activity of N-demethylase was decreased in males of all treated groups, and increased in females receiving 640 ppm. A decreased GSH level was observed only in males of the 640 ppm group, while slightly increased GSSG levels were noted for both sexes of the same dose group. Catalase was slightly increased only in males receiving 640 ppm.

Hepatic enzymes after 17 weeks: Liver N-demethylase activities remained slightly reduced for males receiving 80 and 640 ppm, and slightly increased for females receiving 640 ppm. Liver glutathione levels (GSH as well as GSSG) were slightly increased for recovery females receiving 80 and 640 ppm. Furthermore, catalase activity was found to be slightly increased for females of the 640 ppm group.

Table 169: 13 week feeding study in Wistar rats with Fenoxaprop-P-ethyl
Hepatic enzyme determination after treatment (13 w) and recovery (17 w)

	Dose group level (ppm)							
	Males				**Females**			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Cytochrome P-450 (nmol/g)								
13 weeks	16.7	17.1	20.0*	21.7*	14.9	15.1	15.7	15.7
17 weeks	18.6	n.d.	17.6	17.0	12.7	n.d.	14.3*	12.8
N-demethylase (nmol/min/g)								
13 weeks	404	324*	320*	285*	175	174	196	216*
17 weeks	431	n.d.	372*	328*	167	n.d.	183	217*
GSH (µmol/g)								
13 weeks	1.23	0.95	0.92	0.45*	0.85	0.42	0.93	0.73
17 weeks	1.66	n.d.	1.40	1.41	0.67	n.d.	1.24	1.33*

	Dose group level (ppm)							
	Males				Females			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
GSSG (µmol/g)								
13 weeks	1.39	1.13	1.63	1.79*	1.09	1.02	1.15	1.44*
17 weeks	1.33	n.d.	1.40	1.03	1.08	n.d.	1.70*	2.25*
Total glutathione (µmol/g)								
13 weeks	2.58	2.05	2.55	2.16	1.96	1.46	2.10	2.21
17 weeks	2.98	n.d.	2.80	2.45	1.80	n.d.	2.94*	3.58*
Catalase (k/g)								
13 weeks	143	127	110*	182*	88	74	63*	100
17 weeks	115	n.d.	108	115	60	n.d.	67	88*

* ($p < 0.05$); significantly different from controls (Dunnett-test)
n.d. not determined

Conclusion:

At 640 ppm, changes in glutathione levels and a slight increase in cytochrome P-450 were noted pointing to increased drug metabolism. Furthermore, activity of catalase was elevated in males receiving 640 ppm which could be a sign for induction of peroxisome proliferation at this dose level.

Hoe 046360 Technical. 28-day dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver

Reference: *Suter P., Luetkemeier H.*; 1987(c); Doc. No. A36958 / RCC Project No. 060647

Guideline: not applicable

GLP: no information on GLP is presented in the study report

In this study special investigations on liver enzymes were performed which is supplementary to the 28-day repeated dose toxicity study in NMRI mice (Suter P. et al.; 1987(b); Doc. No. A36557).

Material and Methods:

Groups of 5 male and 5 female NMRI mice (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 20, 80, 320 or 1280 ppm Fenoxaprop-P-ethyl equivalent to 0, 3, 14, 56 or 260 mg/kg bw/d in males and 0, 4, 16, 61 or 280 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the mice were about 6 weeks old and weighed 25 - 30 g (males) and 20 - 25 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450, N-demethylase, glutathione and catalase was removed from all animals scheduled for necropsy after 28 days of treatment. The sections were weighed and rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were investigated: cytochrome P-450, N-demethylase, reduced glutathione (GSH), oxidized glutathione (GSSG), total glutathione (GSH+GSSG) and catalase.

Findings:

Hepatic enzyme determination: There was a slightly decreased cytochrome P-450 content observed for males receiving 1280 ppm. At the same dose level, GSSG levels were slightly decreased in females and GSH and total glutathione levels were slightly increased in both sexes. For catalase activity, a significant increase was demonstrated in males at 80 ppm and above, as well as in females at 320 ppm and above. Due to limited amount of sample available for analysis, not all N-demethylase assays could be performed for some animals.

Table 170: 28 day feeding study in NMRI mice with Fenoxaprop-P-ethyl
Hepatic enzyme determination after 28 days

	Dose group level (ppm)									
	Males					**Females**				
	0	**20**	**80**	**320**	**1280**	**0**	**20**	**80**	**320**	**1280**
Cytochrome P-450 (nmol/g)	25.8	16.5*	22.3	23.1	17.0*	20.2	17.4	16.8	19.2	18.4
N-demethylase (nmol/min/g)	174	164	174	147	118	n.d.	162	142	168	n.d.
Glutathione (µmol/g)	7.65	7.29	7.11	7.87	9.71*	7.69	5.89*	6.68	6.29*	8.98
-reduced (GSH)	1.65	1.60	1.59	1.34	1.62	1.56	1.24	1.40	1.29	1.17*
-oxidized (GSSG)	9.29	8.89	8.70	9.21	11.33	9.24	7.13*	8.08	7.59*	10.16
-total (GSH+GSSG)					*					
Catalase (k/g)	125	161	192*	353*	367*	119	124	126	256*	365*

* ($p < 0.05$); significantly different from controls (Dunnett-test)
n.d. not determined

Conclusion:

No induction of drug metabolizing enzyme (cytochrome P-450) and no depletion of glutathione (GSH) were found in this study. Catalase was markedly increased in males (80 ppm onwards) and females (320 ppm onwards) indicating induction of peroxisome proliferation.

Hoe 046360 Technical. 13-week dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver

Reference: *Suter P., Luetkemeier H.*; 1987(d); Doc. No. A36960 / RCC Project No. 060660

Guideline: not applicable

GLP: yes

In this study special investigations on liver enzymes were performed which is supplementary to the 28-day repeated dose toxicity study in NMRI mice (Suter P. et al.; 1987(b); Doc. No. A36557).

Material and Methods:

Groups of 10 male and 10 female NMRI mice (source: Kleintierfarm Madoerin AG, CH) received a diet containing 0, 10, 80 or 640 ppm Fenoxaprop-P-ethyl equivalent to 0, 1.4, 11.9 or 100.8 mg/kg bw/d in males and 0, 2.0, 16.5 or 122.4 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At the beginning of the study the mice were about 6 weeks old and weighed 26 – 32 g (males) and 22 – 30 g (females). Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450 and catalase was removed from 5 scheduled animals per group and sex with the lowest identification numbers. For N-demethylase and glutathione determinations, liver samples were taken from 5 scheduled animals per group and sex with the highest identification numbers, at necropsy. Due to the limited amount of sample available for analysis, not all parameters could be assayed in some animals. In the case of the male mice of the 640 ppm dose group, additional samples were available from animals with the lowest identification numbers. Accordingly, supplementary unscheduled glutathione measurements were made with these animals. The sections were weighed, rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were assessed: cytochrome P-450, N-demethylase, reduced glutathione (GSH), oxidized glutathione (GSSG), total glutathione (GSH+GSSG) and catalase.

Findings:

Hepatic enzyme determination: In the high dose group (640 ppm), increased cytochrome P-450 levels in males, elevated N-demethylase activity in females, and increased catalase activities in both sexes were measured. Not all parameters could be assessed in all animals.

Table 171: 13 week feeding study in NMRI mice with Fenoxaprop-P-ethyl
Hepatic enzyme determination after 13 weeks

	Dose group level (ppm)							
	Males				**Females**			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Cytochrome P-450 (nmol/g)	14.8	16.8	18.9	20.6*	15.7	13.5	15.2	19.0
N-demethylase (nmol/min/g)	238	230	301	244	285	272.1	214	577*
Glutathione (µmol/g)								
-reduced (GSH)	1.62	0.41*	1.78	1.78	n.d.	n.d.	1.34	2.18
-oxidized (GSSG)	1.53	1.54	1.65	1.66	n.d.	n.d.	1.33	1.27
-total (GSH+GSSG)	3.15	1.94*	3.42	3.44	n.d.	n.d.	2.66	3.45
Catalase (k/g)	127	129	130	400*	68	101	78	279*

* ($p < 0.05$); significantly different from controls (Dunnett-test)
n.d. not determined

Conclusion:

The analysis of liver tissue revealed an induction of the drug-metabolizing system for N-demethylase in females at 640 ppm. However, there was no change in the cytochrome P-450 content or any depletion of GSH observed. An increased amount of cytochrome P-450 was observed in males receiving 640 ppm, but again, no changes in glutathione levels were observed. A marked increase in catalase activity was noted at 640 ppm in both sexes, pointing to induction of peroxisome proliferation.

Hoe 046360 Technical. 28-day dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver

Reference: *Sachsse K. et al.*; 1987(c); Doc. No. A36957 / RCC Project No. 060658

Guideline: not applicable

GLP: yes, deviation: the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.

In this study special investigations on liver enzymes were performed which is supplementary to the 28-day repeated dose toxicity study in Beagle dogs (Sachsse K. et al.; 1987(a); Doc. No. A36558).

Material and Methods:

One male and one female Beagle dog (source: Kleintierfarm Madoerin AG, CH) per dose group were administered Fenoxaprop-P-ethyl in the diet for 4 weeks. The dose groups were 0, 80, 320 and 1280 ppm which was equivalent to 0, 3.3, 13.0 and 67.9 mg/kg bw/d in males and 0, 3.7, 14.9 and 56.1 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At delivery from the breeder the dogs were about 4 – 5 months old and weighed 4.4 – 7.2 kg (males) and 4.8 – 5.4 kg (females). The acclimation period was 4 weeks and 4 days under test conditions after veterinary examination. Diets were prepared at the beginning of the study and after 2 weeks, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450, N-demethylase and glutathione determinations was removed from all animals scheduled for necropsy after 28 days. The sections were weighed, rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were assessed: cytochrome P-450, N-demethylase, reduced glutathione (GSH), oxidized glutathione (GSSG) and total glutathione (GSH+GSSG).

Findings:

Hepatic enzyme determination: The analysis of liver tissue indicated no obvious changes after 28 days of treatment. However, it should be noticed that there was only one animals/sex/dose evaluated in this study.

Table 172: 28 day feeding study in Beagle dogs with Fenoxaprop-P-ethyl
Hepatic enzyme determination after 28 days

	Dose group level (ppm)							
	Males				**Females**			
	0	**80**	**320**	**1280**	**0**	**80**	**320**	**1280**
Cytochrome P-450 (nmol/g)	7.2	10.8	9.2	8.8	10.0	10.4	11.6	10.4
N-demethylase (nmol/min/g)	n.d.	n.d.	n.d.	n.d.	129	107	125	111
Glutathione (µmol/g)								
-reduced (GSH)	4.16	7.15	3.87	5.17	5.74	6.17	6.36	6.54
-oxidized (GSSG)	0.36	0.48	0.30	0.44	0.55	0.55	0.45	0.40
-total (GSH+GSSG)	4.52	7.63	4.17	5.61	6.29	6.72	6.81	6.94

n.d. not determined

Conclusion:

No change in enzyme values could be detected in this study with single animals/sex/dose group.

Hoe 046360 Technical. 13 week dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver

Reference: *Sachsse K. et al.*; 1987(d); Doc. No. A36959 / RCC Project No. 060682

Guideline: not applicable

GLP: yes

In this study special investigations on liver enzymes were performed which is supplementary to the 13 week repeated dose toxicity study in Beagle dogs (Sachsse K. et al.; 1987(b); Doc. No. A36617).

Material and Methods:

Four Beagle dogs/sex/dose group (source: Kleintierfarm Madoerin AG, CH) were administered Fenoxaprop-P-ethyl in the diet for 13 weeks. The dose groups were 0, 80, 400 and 2000 ppm which was equivalent to 0, 3.0, 15.6 and 77.7 mg/kg bw/d in males and 0, 3.2, 16.2 and 83.4 mg/kg bw/d in females. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % (according to certificate of analysis No. 02912). At delivery from the breeder the dogs were about 4 – 6 months old and weighed 4.1 – 8.6 kg (males) and 4.2 – 6.8 kg (females). The acclimation period was 5 weeks and 4 days under test conditions. Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Hepatic enzyme determination: A section of liver tissue for the analysis of cytochrome P-450, N-demethylase and glutathione determinations was removed from all animals scheduled for necropsy after 13 weeks. The sections were weighed, rinsed in ice-cold saline (0.9 % NaCl) solution, blotted dry and immediately frozen in liquid nitrogen, and stored at -20 degrees centigrade until analysis. The following parameters were assessed: cytochrome P-450, N-demethylase, reduced glutathione (GSH), oxidized glutathione (GSSG) and total glutathione (GSH+GSSG).

Findings:

Hepatic enzyme determination: A decrease in N-demethylase activity was observed in males receiving 2000 ppm. Data was lost for some glutathione determinations in females.

Table 173: 13 week feeding study in Beagle dogs with Fenoxaprop-P-ethyl
Hepatic enzyme determination after 13 weeks

	Dose group level (ppm)							
	Males				**Females**			
	0	**80**	**400**	**2000**	**0**	**80**	**400**	**2000**
Cytochrome P-450 (nmol/g)	9.8	10.3	9.4	7.5	9.2	9.4	8.5	8.1
N-demethylase (nmol/min/g)	116	114	77	43*	101	124	115	109
Glutathione (µmol/g)								
-reduced (GSH)	3.75	2.97	3.77	4.22	4.02	-[1])	-[1])	2.69
-oxidized (GSSG)	2.10	1.99	1.82	1.73	1.02	-[1])	-[1])	1.68
-total (GSH+GSSG)	5.85	4.95	5.59	5.95	5.04	-[1])	-[1])	4.36

* ($p < 0.05$); significantly different from controls (Dunnett-test)
[1]) data was lost

Conclusion:

N-demethylase activity was decreased in males receiving 2000 ppm. This was discussed to reflect an impairing effect on metabolizing enzymes, although a parallel decrease of cytochrome P-450 was not observed, nor were changes observed for glutathione.

Table 174: Summarised results of a 13 week combination toxicity study with Fenoxaprop-P-ethyl and the safener mefenpyr-diethyl

Study; Reference	Dose levels	NOAEL	Relevant effects for setting the NOAEL
Wistar rat 13 weeks oral *Schmid H. et al.; 1996*	0+0, 10+5, 80+40 and 640+320 ppm / diet (equivalent to 0+0, 0.74+0.37, 5.79+2.89 and 48.20+24.10 mg/kg bw/d in males; 0+0, 0.81+0.41, 6.39+3.20 and 50.89+25.45 mg/kg bw/d in females)	10+5 ppm (♂:0.74+0.37 mg/kg bw/d; ♀: 0.81+0.41 mg/kg bw/d)	- haematology, clinical chemistry and urinalysis findings - increased organ weights (liver) - hepatocellular hypertrophy

13-week oral toxicity (feeding) study with Hoe 046360 + Hoe 107892 (2:1) in the rat. Influence of the coadministration of Hoe 107892 on the toxicological profile of Hoe 046360

Reference: *Schmid H. et al.*; 1996; Doc. No. A57200 / RCC Project No. 610121

Guideline: OECD Guideline 408 (1981), EPA Guideline 82-1 (1984), EEC Directive 87/302/EEC B.p.8 (1988), MAFF Guideline 59 NohSan No. 4200 (1985)

GLP: yes

The study is scientific valid and acceptable.

Material and Methods:

The purpose of this oral toxicity study was to investigate the influence of coadministration of the safener Hoe 107892 on the toxicological profile of Fenoxaprop-P-ethyl (Hoe 046360). In the present study, a mixture of Hoe 046360 + Hoe 107892 (ratio 2:1) was administered to rats in their feed for a period of 13 weeks. The study design, dosing levels, the biological test system as well as the experimental conditions were selected to comply as far as possible with the earlier 13-week feeding study in rats with Hoe 046360 alone (Tennekes H. et al.; 1987; Doc. No. A36566) to permit the detection of even minor changes in the toxicological profile of Hoe 046360.

Groups of 10 male and 10 female Wistar rats (source: BRL Biological Research Ltd., Fuellinsdorf, CH) received a diet containing 0+0 ppm, 10+5 ppm, 80+40 ppm or 640+320 ppm Fenoxaprop-P-ethyl + Hoe 107892 over a period of 3 months. At delivery of the test animals, the rats were about 4 weeks old and weighed 61 - 91 g (males) and 57 - 81 g (females). The intake of test substance is listed in the following table:

Table 175: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Intake of test substance (g)

	Dose group level (ppm)							
	Males				**Females**			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Hoe 046360 (g)	-	0.74	5.79	48.20	-	0.81	6.39	50.89
+	+	+	+	+	+	+	+	+
Hoe 107892 (g)	-	0.37	2.89	24.10	-	0.41	3.20	25.45

The purity of Fenoxaprop-P-ethyl (Code: Hoe 046360 00 ZC97 0002) was 96.1 % (according to certificate of analysis No. AZ 05581) and the purity of the safener Hoe 107892 (Code: Hoe 107892 00 ZC97 0001) was 94.5 % (according to certificate of analysis No. AZ 05815). Hoe 046360 + Hoe 107892 were dissolved in acetone and mixed with microgranulated food. The stability of the test substances in the diet were checked by chemical analysis for each preparation before and during the study.

Viability and clinical signs were checked at least once daily. Food consumption and body weight were recorded weekly. Ophthalmoscopic examinations were performed on all animals at pretest and at week 13.

At the end of treatment (13 weeks), blood samples were taken after a fasting period of 18 hours. At the same point of time urine was collected during the 18-hour fasting period. Hematology consisted of erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, reticulocyte fluorescence ratios (high, middle, low), nucleated erythrocytes – normoblasts, total leukocyte count, differential leukocyte count, red cell morphology, thromboplastin time and partial thromboplastin time. In clinical chemistry the following parameters were assessed: glucose, urea, creatinine, uric acid, total and direct bilirubin, total lipids, total cholesterol, triglycerides, HDL-cholesterol, HDL-phospholipids, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatine kinase (CK), alkaline phosphatase (ALP), gamma-glutamyl-transferase (γ-GT), calcium, phosphorus, sodium, potassium, chloride, total protein and protein electrophoresis. Urinalysis included 18-hour volume, specific gravity, osmolality, color, appearance, pH, protein, glucose, ketone, bilirubin, blood, urobilinogen and urine sediment.

All animals were weighed and necropsied. Descriptions of all macroscopic findings were recorded. The following organ weights were recorded: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid and thymus. The following organs were examined histopathologically in the animals of the control and 640+320 ppm dose group: adrenal glands, aorta, bone (femur with joint, sternum), bone marrow (sternum, femur), brain, epididymides, esophagus, exorbital lacrimal glands, eyes, Harderian glands, heart, kidneys, large intestine, larynx, liver, lungs, lymph nodes (mandibular, mesenteric), mammary gland area, optic nerves, ovaries, pancreas, parathyroid glands, pituitary gland, prostate, salivary glands (mandibular, sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, vagina and all gross lesions. From the rats of the low and intermediate dose groups, only brain, heart, liver, pancreas, kidneys, testes, ovaries, adrenal glands, and all gross lesions were examined microscopically.

Findings:

Mortality / Clinical Signs: All animals survived their assigned study period. There were no clinical signs which could be attributed to treatment. The few clinical signs noted during the course of the study were those commonly seen in rats of this strain and age. These signs comprised alopecia, scars and crusts. One male of the controls, 3 females of the controls, 1 female at 80+40 ppm and 2 females at 640+320 ppm were affected.

Food consumption: Food consumption was slightly reduced for both sexes at 640+320 ppm.

Body weight: Body weight was moderately lower in males at 640+320 ppm and slightly lower in females at 640+320 ppm. Statistical significance was attained from week 3 in males and from week 4 in females, and persisted throughout the study.

Table 176: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Group food consumption and mean body weight after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	10+5	80+40	640+320	0	10+5	80+40	640+320
Food consumption (g/d)	22.0	23.1	21.2	18.4	15.4	15.4	15.1	13.4
Body weight on day 1 (g)	125	129	126	125	105	109	106	108
Body weight on day 85 (g)	375	409	377	302**	225	227	225	197**

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

Ophthalmoscopic examinations: There were no treatment-related changes observed. The few findings observed were within the normal range of biological variation and comprised corneal opacities and persistent papillary membranes. The frequency or group distribution did not distinguish treated groups from controls.

Hematology: A marginal decrease in the haemoglobin concentration, hematocrit and platelet count, as well as a slight increase in the HFR reticulocyte fluorescence ratio was observed in males receiving 640+320 ppm. In addition, a slightly prolonged thromboplastin time was noted in males of this dose group and a slightly shorter thromboplastin time in females at 80+40 ppm and 640+320 ppm. All other statistical differences were considered to be incidental and of normal biological variation for rats of this strain and age.

Table 177: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Relevant haematology findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	10+5	80+40	640+320	0	10+5	80+40	640+320
Hemoglobin (mmol/L)	10.3	10.1	10.0	9.8*	10.1	10.2	10.1	9.9
Hematocrit (L/L)	0.48	0.48	0.47	0.47*	0.47	0.47	0.47	0.46
Platelets (g/L)	925	881	860	799*	857	834	879	806
High reticulocyte fluorescence ratio (%)	6.4	6.5	10.0	11.6*	9.2	7.4	9.7	9.7
Thromboplastin time (sec)	12.4	12.8**	12.5	13.1**	13.3	13.4	12.7**	12.6**

* ($p< 0.05$); ** ($p< 0.01$); significantly different from controls (Dunnett-test or Steel-test)

Clinical chemistry: The assessment of biochemical data indicated treatment-related effects on the following parameters: decreased glucose and creatinine levels in males at 640+320 ppm; increased uric acid level in males at 640+320 ppm; decreased total bilirubin level in females at 10+5 ppm and in both sexes at 80+40 ppm and 640+320 ppm; decreased direct bilirubin level in females in all dose groups; decreased total cholesterol level in males at 640+320 ppm; decreased HDL-cholesterol level in males at 80+40 ppm and 640+320 ppm; decreased HDL-phospholipid level in males at 640+320 ppm; increased ASAT and LDH activity in males at 640+320 ppm; increased ALP activity in both sexes at 640+320 ppm; increased phosphorus and sodium levels in both sexes at 640+320 ppm; decreased total protein level in males at 640+320 ppm, and slight changes in some plasma protein fractions in both sexes at 80+40 ppm and/or 640+320 ppm. This was characterized primarily by an increased albumin fraction, decreased alpha 1-globulin, alpha 2-globulin and beta globulin fractions, and increased albumin to globulin ratio.

Table 178: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Relevant clinical chemistry findings after 13 weeks

	Dose group level (ppm)							
	Males				**Females**			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Glucose (mmol/L)	5.42	5.75	5.13	4.76**	5.16	5.57	5.15	4.71
Creatinine (µmol/L)	37.6	34.7	34.0	32.9*	43.8	42.9	42.3	40.4
Uric acid (µmol/L)	10.7	10.7	12.2	13.8**	25.3	24.3	26.1	26.3
Total bilirubin (µmol/L)	2.8	2.9	2.4**	2.4**	3.4	3.0**	2.7**	2.6**
Direct bilirubin (µmol/L)	0.7	0.8	0.6	0.7	1.1	0.8**	0.8**	0.8**
Total cholesterol (mmol/L)	1.81	1.57	1.55	0.80**	1.71	1.69	1.74	1.54
HDL cholesterol (mmol/L)	1.37	1.25	1.08**	0.43**	1.36	1.43	1.50	1.25
HDL phospholipid (mmol/L)	1.21	1.14	1.08	0.71**	1.51	1.53	1.55	1.44
ASAT (µkat/L)	1.21	1.24	1.21	1.43**	1.15	1.13	1.21	1.28
LDH (µkat/L)	1.43	1.35	1.25	2.02**	1.41	1.21	1.45	1.63
ALP (ukat/L)	2.66	2.68	2.43	4.61**	1.09	1.05	1.22	1.89**
Phosphorus (mmol/L)	1.91	2.01	1.83	2.06*	1.33	1.49	1.39	1.62*
Sodium (mmol/L)	138.9	138.1	140.0	140.9**	138.3	138.8	139.7	141.4*
Total protein (g/L)	68.7	69.3	67.7	64.4**	71.7	70.3	71.2	70.1
Albumin (g/L)	31.3	31.2	32.1	36.6**	34.0	34.3	36.3*	37.3**
Alpha 1-globulin (g/L)	19.4	18.7	18.9	15.6**	18.8	18.4	17.5	16.9**
Alpha 2-globulin (g/L)	4.6	5.0	3.4**	1.8**	4.5	4.1*	3.7**	3.0**
Sum of beta globulins (g/L)	11.8	12.5	11.8	9.0**	12.2	11.2*	11.4	10.7**
Albumin / globulin ratio	0.84	0.82	0.90*	1.32*	0.91	0.96	1.04*	1.14*

* ($p < 0.05$); ** ($p < 0.01$); significantly different from controls (Dunnett-test or Steel-test)

Urinalysis: Urinalysis data indicated slight ketonuria in males at 80+40 ppm and 640+320 ppm, slight bilirubinuria and urobilinogenuria in males at 640+320 ppm as well as deep yellow urine coloration. The ketonuria was considered a secondary effect of the treatment (fatty acid metabolism) and not of biological variance. Increased urine volume and pH, decreased specific gravidity and osmolality in females at 640+320 ppm were discussed to be within the normal range of biological variation.

Table 179: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Relevant urinalysis findings after 13 weeks

	Dose group level (ppm)							
	Males				**Females**			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Ketone (score 0/3)[1]	1	1	2*	2*	0	0	1	0
Bilirubin (score 0/3)[2]	0	0	0	1*	0	0	0	1
Urobilinogen (Score 0/4)[3]	0	0	0	2*	1	1	0	1

* ($p < 0.05$); significantly different from controls (Steel-test)
[1] 0 = negative; 1 = 1.5 mmol/L; 2 = 5.0 mmol/L; 3 ≥ 15.0 mmol/L
[2] 0 = negative; 1 = 17 µmol/L; 2 = 50 µmol/L; 3 ≥ 100 µmol/L
[3] 0 = normal; 1 = 17 µmol/L; 2 = 68 µmol/L; 3 = 135 µmol/L; 4 ≥ 203 µmol/L

Organ weight analysis: There were no effects on organ weights in the low and intermediate dose group. At 640+320 ppm, liver weight (absolute, relative to body weight and relative to brain weight) was increased for both sexes with males being more affected than females. All other statistically significant findings noted in this dose group were considered to be due to the lower terminal body weight and not to reflect direct effects of the test substances.

Table 180: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Organ weight findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	10+5	80+40	640+320	0	10+5	80+40	640+320
Liver								
absolute (g)	8.88	9.62	9.33	10.91**	5.91	6.02	6.34	6.66*
relative to body weight (%)	2.52	2.48	2.61	3.85**	2.90	2.92	3.09	3.69**
relative to brain weight (%)	435	461	450	525**	307	311	333	345
Kidney								
absolute (g)	2.17	2.35	2.33	2.30	1.44	1.47	1.45	1.51
relative to body weight (%)	0.62	0.61	0.65	0.81**	0.71	0.71	0.71	0.84**
relative to brain weight (%)	107	113	112	111	75	76	76	78

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

Macroscopic examination: In the 640+320 ppm group, dark brown discoloration of the liver was noted in 8 of 10 males and 4 of 10 females. This finding was not present in any rat of the other dose groups.

Histopathological examination: Hepatocellular hypertrophy was noted in 8 males at 80+40 ppm and 3 females and all males at 640+320 ppm. In 8 males at 640+320 ppm, this hypertrophy was diffuse and slight in severity, whereas in the remaining animals this change was centrilobular and ranged from minimal to slight in severity. Inflammatory foci were noted in most rats of all groups with similar incidence and severity. In kidneys, corticomedullary mineralization was noted in all females of all groups. The mean severity grade of this mineralization was 2.3 in the controls, 2.6 in the low dose group, 1.7 in the intermediate dose group, and 1.5 in the high dose group. The incidences and severity were within the normal historical range.

Table 181: Combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats: Macroscopic and microscopic findings after 13 weeks

	Dose group level (ppm)							
	Males				Females			
	0	10+5	80+40	640+320	0	10+5	80+40	640+320
Macroscopic examination								
Liver								
Dark brown discoloration	-	-	-	8/10**	-	-	-	4/10*
Histopathological examination								
Liver								
Hepatocellular hypertrophy:								
- diffuse	-	-	-	8/10	-	-	-	-
- centrilobular	-	-	8/10	2/10	-	-	-	3/10

* ($p < 0.05$); ** ($p < 0.01$); significantly different from controls (Fischer´s Exact-test)

Conclusion:

In this combination study with Hoe 046360 (Fenoxaprop-P-ethyl) and the safener Hoe 107892, treatment-related effects were observed at the intermediate and high dose level. Reductions of food consumption and body weight as well as findings in haematology were noted only at the high dose level of 640+320 ppm. Effects on the liver as demonstrated by changes in lipid parameters and liver enzyme activity, ketonuria, increased organ weight, discoloration and cellular hypertrophy were already noted at the intermediate dose level of 80+40 ppm.

The NOAEL is considered to be 10+5 ppm Fenoxaprop-P-ethyl + Hoe 107892 (equivalent to 0.74+0.37 mg/kg bw/d in males and 0.81+0.41 mg/kg bw/d in females).

4.12.1.4 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.12.2 Summary and discussion

Determinations of liver enzymes in repeated dose studies with Fenoxaprop-P-ethyl

Activity and amount of hepatic enzymes were determined in 28 day and 13-week studies in rats, mice and dogs. These investigations were additionally performed to the respective repeated dose toxicity studies which were evaluated in the chapter 4.7 Repeated dose toxicity.

Drug-metabolizing enzymes (Cytochrome P-450, N-demethylase) and glutathione were changed, if at all, only at high dose levels and not always in a consistent manner, giving only weak indication of an induction of the hepatic drug-metabolizing system. In contrast, catalase activity was clearly increased in mice at 80 ppm onwards, pointing to induction of peroxisome proliferation. In rats, elevation of catalase activity was observed at higher doses (640 ppm onwards). In dogs, catalase activity was not determined.

Combined repeated dose toxicity study of the active ingredient Fenoxaprop-P-ethyl and the safener mefenpyr-diethyl in the rat

In this combination study with fenoxaprop-P-ethyl and the safener mefenpyr-diethyl in Wistar rats, treatment-related effects were observed at the intermediate (80+40 ppm) and high dose level (640+320 ppm). Reductions of food consumption and body weight as well as findings in haematology were noted only at the high dose level. Effects on the liver as demonstrated by changes in lipid parameters and liver enzyme activity, ketonuria, increased organ weight, discoloration and cellular hypertrophy were already noted at the intermediate dose level. The results of this 13-week combination toxicity study suggested that the toxicological profile of fenoxaprop-P-ethyl was qualitatively not changed by co-administration of the safener mefenpyr-diethyl. The effects on food consumption and body weight at the top dose, the slight findings in haematology at the top dose, the changes in lipid parameters and the slight ketonuria found predominantely in males from the intermediate dose onwards, and the changes in parameters indicative of liver toxicity such as an increased organ weight and ALP activity observed in this study corresponded to a high degree to those observed in a previous study (Tennekes H. et al.; 1987; Doc. No. A36566) when fenoxaprop-P-ethyl was administered alone. The increases of kidney weights which were observed in the previous study with administration of fenoxaprop-P-ethyl alone as well as in the combination study were considered to be probably related to the reduction of body weight at the top dose. Only the histopathological examinations suggested a quantitative increase in hepatotoxicity in the combination study, however in a slight pathological degree. While hepatocellular hypertrophy was noted at 80+40 ppm (males) and 640+320 ppm (both sexes) in the combination study, this effect was only observed at 640 ppm fenoxaprop-P-ethyl in the previous study. Since there was a 10-year time interval between both studies, this difference in effect was discussed to be reflective of a change in the sensitivity of the rat strain.

4.12.3 Comparison with criteria

See chapter 4.7 Repeated dose toxicity and 4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE) as well as 4.10 Carcinogenicity.

4.12.4 Conclusions on classification and labelling

No classification for other effects is proposed.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 182: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Hydrolysis Guideline: OECD 111; 92/69/EEC, Part C.7; US-EPA OPPTS 835.2110	DT50 Fenoxaprop-P-ethyl: pH 4: 2.8 d at 25 °C pH 5: 19.2 d at 25 °C pH 7: 23.2 d at 25 °C pH 9: 0.69 d at 25 °C		van der Gaauw, A. (2002)
Hydrolysis Guideline: OECD 111; 92/69/EEC, Part C.7	DT50 Fenoxaprop-P: pH 5: 26.8 d at 25 °C pH 7: 182.7 d at 25 °C pH 9: 33.5 d at 25 °C		Schollmeier M.; Eyrich U. (1993)
Photolysis Guideline: OECD Photodegradation of Chemicals in Water, Part A, 1992; US/EPA, N §161-2,1982	pH 5 (sterile buffer): 57.5 d pH 6.8 (distilled water): 104.7 d pH 9 (natural surface water): 7.2 d [1)]		Schwab, W. (1993c)
Biological degradation	No data submitted, substance considered not ready biodegradable.		
Water/Sediment Study Guideline: EEC 95/36/EC; USEPA, N § 162-4; BBA IV, 5-1; PMRA (1991)	DT50/DT90 total system: Fenoxaprop-P-ethyl: S1 (sand), pH 7.3: 0.1d/0.4d S2 (silt loam). pH 6.8: 0.1d/0.3d Fenoxaprop-P: S1: 13d/43.3d S2: 6.9d/22.8d	U-^{14}C-chlorophenyl labelled Fenoxaprop-P-ethyl	Tarara G. (2000)
Water/Sediment Study Guideline: EEC 95/36/EC; USEPA, N § 162-4; BBA IV, 5-1; PMRA (1991)	DT50/DT90 total system: Fenoxaprop-P-ethyl: S1 (loamy sand), pH 6.6: 0.16d/0.54d S2 (clay). pH 8.0: 0.29d/0.96d Fenoxaprop-P: S1: 40d/133d S2: 39d/129d	Test item: U-^{14}C-dioxyphenyl labelled Fenoxaprop-P-ethyl	Fitzmaurice (2004)

Aerobic degradation in soil Tthe rate of egradation was tested for Fenoxaprop-P-ethyl (or Fenoxaprop-ethyl) with 6 soils	<u>Study No.1 (four soils)</u> Fenoxaprop-P-ethyl DT50: 0.48 d (arithm. Mean), pH 5.2 – 5.8, temp. 20-22°C Acid: DT50: 7.5 d (arithm. Mean), pH 5.2 – 5.8, temp. 20-22°C Study No.2 (one soils) Fenoxaprop-P-ethyl DT50: 0.65 d, pH 5.8, temp. 20-22°C Acid: DT50: 20 d, pH 5.8, temp. 20-22°C Study No.3 (two soils) Fenoxaprop-ethyl (racemic miture): DT50: < 1 d, pH 6.9 and 7.0), temp. 20-22°C Acid: DT50: 22.3 and 7.9 d, pH 6.9 and 7.0), temp. 20-22°C	Test item: chlorophenyl-labelled Fenoxaprop-P-ethyl. The experimental obtained data from the aerobic soil degradation stuty were calculated using the RMS (single 1st order, over the wohl time range of the study) Test item: chlorophenyl-labelled Fenoxaprop-P-ethyl. The experimental obtained data from the aerobic soil degradation stuty were calculated using the RMS (single 1st order kinetics) Test item: dioxihenyl-labelled racemic miture. The experimental obtained data from the aerobic soil degradation stuty were calculated using the RMS (single 1st order kinetics)	”not stated”

1) Water dissolved photosensitizers (indirect photolysis) in combination with alkaline conditions (hydrolysis) resulted in rapid degradation

5.1.1 Stability

Hydrolysis

Reference: van der Gaauw, A. (2002): [^{14}C]-Fenoxaprop-P-ethyl: Hydrolysis at five different pH values. Report No. 815670

Fenoxaprop-P-ethyl was found to be sensitive towards abiotic hydrolytical processes under the conditions of sterile aqueous buffer hydrolysis testing at 25 °C. The rate of hydrolysis was higher at pH 4 and 9 than at pH 5 and 7. The corresponding DT_{50} values have been estimated to 2.8 d (pH 4), 19.2 d (pH 5), 23.2 d (pH 7) and 0.6 d (pH 9).
The Benzoxazolone AE F054014 was formed as major product at all pH-values tested. While this compound was nearly exclusively formed under acidic conditions of pH (*i.e.* 4 and 5), its formation was paralleled under neutral to alkaline conditions (pH 7 and 9) by ester hydrolysis to Fenoxaprop-P AE F088406 as an additional major product.
Hydrolysis thus proceeds either *via* split of the ether bond in the central position of the molecule to form Benzoxazolone AE F054014 and *via* hydrolysis at the ester function to result in the formation of Fenoxaprop-P AE F088406. Fenoxaprop-P AE F088406 may be hydrolysed at the ether function in a next step to form Benzoxazolone AE F054014.

Fenoxaprop-P-ethyl was shown to be sensitive towards abiotic hydrolysis under acidic and basic conditions. However,half-lives of more than 16 days have been determined at pH 5 and 7. The hydrolysis data are therefore not applied for the purpose of classification.

Reference: Schollmeier M.; Eyrich U. (1993): Determination of the abiotic hydrolysis as a function of pH according to OECD Guideline No. 111 and EEC Guideline C.7. Hoe 088406 (Fenoxaprop-P). Report No. CP93/009

Fenoxaprop-P AE F088406 was found to be hydrolytically stable at pH 7 at 20 °C or 25 °C to result in estimated DT_{50}-values of 319.6 d (20°C) and 182.7 d (25°C).
Hydrolysis of Fenoxaprop-P AE F088406 was enhanced under acidic (pH 5) and alkaline conditions (pH 9) to result in DT_{50}-values of 43.1 d (pH 5) and 66.2 d (pH 9) at 20 °C.
Benzoxazolone AE F054014 was observed as the major product of abiotic hydrolysis.

The results of the test indicate potential of Fenoxaprop-P AE F088406 showed for abiotic hydrolysis under environmentally relevant acidic and alkaline conditions of pH.

Photolysis in water

Reference: Schwab, W. (1993c): Photodegradation of Fenoxaprop-P-ethyl in surface water, sterile buffer and distilled water. Report No. CB 91/035.

In sterile aqueous buffer solution of pH 5 phototransformation of Fenoxaprop-P-ethyl was moderate as it is indicated by a DT_{50}-value of 57.5 d[1].

In distilled water of pH 6.8 Fenoxaprop-P-ethyl was stable to photolysis (DT_{50}: 104.7 d)[2].

[1] Mean value of two replicates

[2] Mean value of two replicates

In surface water samples degradation of Fenoxaprop-P-ethyl was most rapid (DT_{50}: 7.2 d)[3]. Degradation in surface water was the result of indirect photolysis caused by water-dissolved photosensitizers. Indirect photolysis was paralled by hydrolysis to form rapidly Fenoxaprop-P AE F088406 and the Benzoxazolone AE F054014 due to the alkaline conditions of pH. Additionally, the phenol-type compound AE F040356, the Hydroxybenzoxazolone AE 0316854, a number of short chained aliphatic carboxylic acids were identified as primary products of indirect photolytical transformation. Finally, carbon dioxide was detected as a result of ultimate degradation.

The mean quantum yield Φ for direct photolysis was determined to 5.11×10^{-6} in sterile buffer and 2.88×10^{-6} in distilled water. No quantum yield was determined in surface water due to the hydrolysis and indirect photolysis.

Direct photolysis does not contribute significantly to the elimination of Fenoxaprop-P-ethyl from the surface water environment.
Combined processes of hydrolysis and indirect photolysis may contribute to a moderate extent to the elimination of Fenoxaprop-P-ethyl from natural surface waters. It should be noted that degradation under the conditions of this test was slow when being compared to the results of simulation tests with natural water in the dark demonstrating fast biotic hydrolysis at the ester funtion (see Section 5.1.2.3).

Photolysis on soil surfaces

Reference: Sarafin, R.; Jordan, H.-J. (1989a): Photodegradation on soil, Hoe 033171-^{14}C (Fenoxaprop-ethyl). Report No. CB 071/88

Phototransformation of Fenoxaprop-ethyl on the surface of a sterilised soil was found to be moderate as it is indicated by a DT_{50}-value of approximately 53 d.
Photodegradation was shown to proceed *via* the formation of a number of minor components and ultimate degradation to carbon dioxide (12% AR) as the major product.
Photodegradation processes on soil surfaces do not contribute significantly to the elimination of Fenoxaprop-ethyl from the soil environment. This is true in particular when being compared to the fast processes of microbial conversion as it is indicated by the results of simulation tests in aerobic soil (see Section 5.1.2.3).

Photo-oxidative degradation in air

Reference: Buerkle, L. (1999i): Estimation of the Reaction with Photochemically Produced Hydroxyl Radicals in the Atmosphere. Report No. OE99/056

Following the approach by Atkinson, the photochemical half-life of Fenoxaprop-P-ethyl in air was estimated with the software Atmospheric Oxidation Program (AOPWIN).
For the reaction of hydroxyl radicals formed in air with evaporated Fenoxaprop-P-ethyl, a low half-life of 13.4 hours (0.6 d) has been calculated.

[3] Mean value of two replicates

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

No data available

5.1.2.2 Screening tests

No data available

5.1.2.3 Simulation tests

Biodegradation in water/sediment tests

The behaviour of Fenoxaprop-P-ethyl has been investigated for the two positions of radiolabel [U-^{14}C-chlorophenyl] and [U-^{14}C-dioxyphenyl] in two separate studies each conducted with two water/sediment systems.

Study 1

Reference: Tarara G. (2000): Degradation in two sediment/water-systems at 20 degrees C under aerobic conditions (U-^{14}C-chlorophenyl) AE F046360(Fenoxaprop-P-ethyl **),. Report No CB98/113**

The behaviour of [U-^{14}C-chlorophenyl]-labelled Fenoxaprop-P-ethyl has been investigated in the two differing water/sediment systems sand (Rhine) and silt loam (Nidda). Systems were incubated for 199 d in maximum following German BBA Guidelines (Dec 1990).

Route of degradation:
No significant differences were observed for the metabolic profile between the two systems apart from different quantities formed of the individual metabolites. The fast initial primary degradation of Fenoxaprop-P-ethyl to Fenoxaprop-P AE F088406 as indicated by ester hydrolysis was followed by cleavage at either of the two ether functions in the molecule to form Benzoxazolone AE F054014 or the Phenol AE F040356 as minor metabolites.
Degradation by biotic processes was observed under the conditions of the test as indicated by formation of (^{14}C-) carbon dioxide (sand: 27.6% AR after 199 d; silt loam: 17.6% after 120 d). NER formation in system rhine increased till day 59 to a content of 75 % and decreased to 54.9 % at day 199 (end of study). In system nidda NER formation reached a maximum at day 199 (end of study) with 75.5 %.
The microbially induced nature of conversion in non-sterile samples has been demonstrated by investigations of sterilised samples. Any metabolic conversion including initial ester hydrolysis and further metabolic steps, NER and carbon dioxide formation were significant slowed-down when being compared to non-sterilised samples.

Rate of degradation:
Degradation of Fenoxaprop-P-ethyl was rapid to result in a degradation half-life of 0.1 d each in Rhine and Nidda total systems.

For the predominantly formed metabolite Fenoxaprop-P AE 088406 DT_{50}-values for the dissipation from water were 6.6 d ("Rhine") and 3.3 d ("Nidda"). DT_{50}-values for the degradation in total systems were 13 d ("Rhine") and 6.9 d ("Nidda"). The results are detailed in Table 183.

Table 183: Disappearance from water and degradation in total systems for Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P AE F088406 in two water/sediment systems

		Water			Total system		
		$DisT_{50}$ [d]	**$DisT_{90}$** [d]	**r^2**	**$DegT_{50}$** [d]	**$DegT_{90}$** [d]	**r^2**
„Rhine“	Fenoxaprop-P-ethyl	0.1	0.3	0.9831	0.1	0.4	0.9880
	Fenoxaprop-P AE F088406	9.6*	31.9	0.9897	13.0	43.3	0.9929
„Nidda“	Fenoxaprop-P-ethyl	0.1	0.3	0.9764	0.1	0.3	0.9788
	Fenoxaprop-P AE F088406	3.3	11.1	0.9590	6.9	22.8	0.9904

* Different from value in List of Endpoints, value taken from the report.

In summary Fenoxaprop-P-ethyl shows a fast primary degradation but the formation of CO2 was too low to indicate ultimative degradation to a level at least 70 % within 28 days.

Study 2
Reference: Fitzmaurice, M. (2004~~a~~): [^{14}C]-Fenoxaprop-P-ethyl: Degradation and retention in two sediment/water-systems. Code: AE F046360. Report No C046009

The behaviour of [U-^{14}C-dioxyphenyl]-labelled Fenoxaprop-P-ethyl has been investigated in the two differing water/sediment systems loamy sand ("pond") and clay ("river"). Systems were incubated for 118 d in maximum following Guideline OECD 308 (Apr 2002).

Route of degradation:
The study confirmed the metabolic profiles between the two systems to be similar with differences in quantities of individual metabolites formed.
The fast initial primary degradation of Fenoxaprop-P-ethyl to Fenoxaprop-P AE F088406 as indicated by ester hydrolysis was followed by cleavage at the heterocyclic ether bond in the molecule to form hydroxypropoxypropionic (HOPP) acid AE F096918 as another major metabolite[4]. Carbon dioxide formation in loamy sand "pond" was 45.9% AR after 118 d and 46.5 % AR in clay "river" after 90 d. NER formation increased in both systems to 33.5 % (loamy sand "pond") and 27.3 % (clay "river") till end of study (d 118).

Rate of degradation:
Degradation of Fenoxaprop-P-ethyl to Fenoxaprop-P AE 088406 was rapid to result in a degradation half-life of 0.16 d ("pond") and 0.29 d ("river") in total systems.
For the predominantly formed metabolite Fenoxaprop-P AE 088406 DT50-values for the dissipation from water were 34 d ("pond") and 35 d ("river"). DT50-values for the degradation in total systems were 40 d ("pond") and 39 d ("river") in total systems. No DT50 value has been derived for HOPP acid in the study report. The results are detailed in Table 184.

[4] Maximum occurrences: 22.9% (day 62, "pond"), 11.4 % (day 47, "river")

Table 184: Disappearance from water and degradation in total systems for Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P AE F088406 in two water/sediment systems

		Water			Total system		
		$DisT_{50}$ [d]	**$DisT_{90}$** [d]	**r^2**	**$DegT_{50}$** [d]	**$DegT_{90}$** [d]	**r^2**
„Pond“	Fenoxaprop-P-ethyl	-	-	-	0.16	0.54	0.984
	Fenoxaprop-P AE F088406	34	133	0.988	40	133	0.988
„River“	Fenoxaprop-P-ethyl	-	-	-	0.29	0.96	0.990
	Fenoxaprop-P AE F088406	35	116	0.981	39	129	0.980

Overall conclusions on biodegradation in water/sediment:

Primary degradation of Fenoxaprop-P-ethyl under conditions of two water/sediment tests was shown to proceed rapidly to form Fenoxaprop-P AE F088406 and hydroxypropoxypropionic (HOPP) acid AE F096918 as major metabolites (see Figure X).
Significant portions of carbon dioxide and NER formed in the course of the tests thus indicating ultimate degradation to be the major product of biotically induced conversion.

The results from water/sediment tests with regard to the dissipation from water and the degradation of Fenoxaprop-P-ethyl and Fenoxaprop-P AE F088406 are summarized in Table 185.

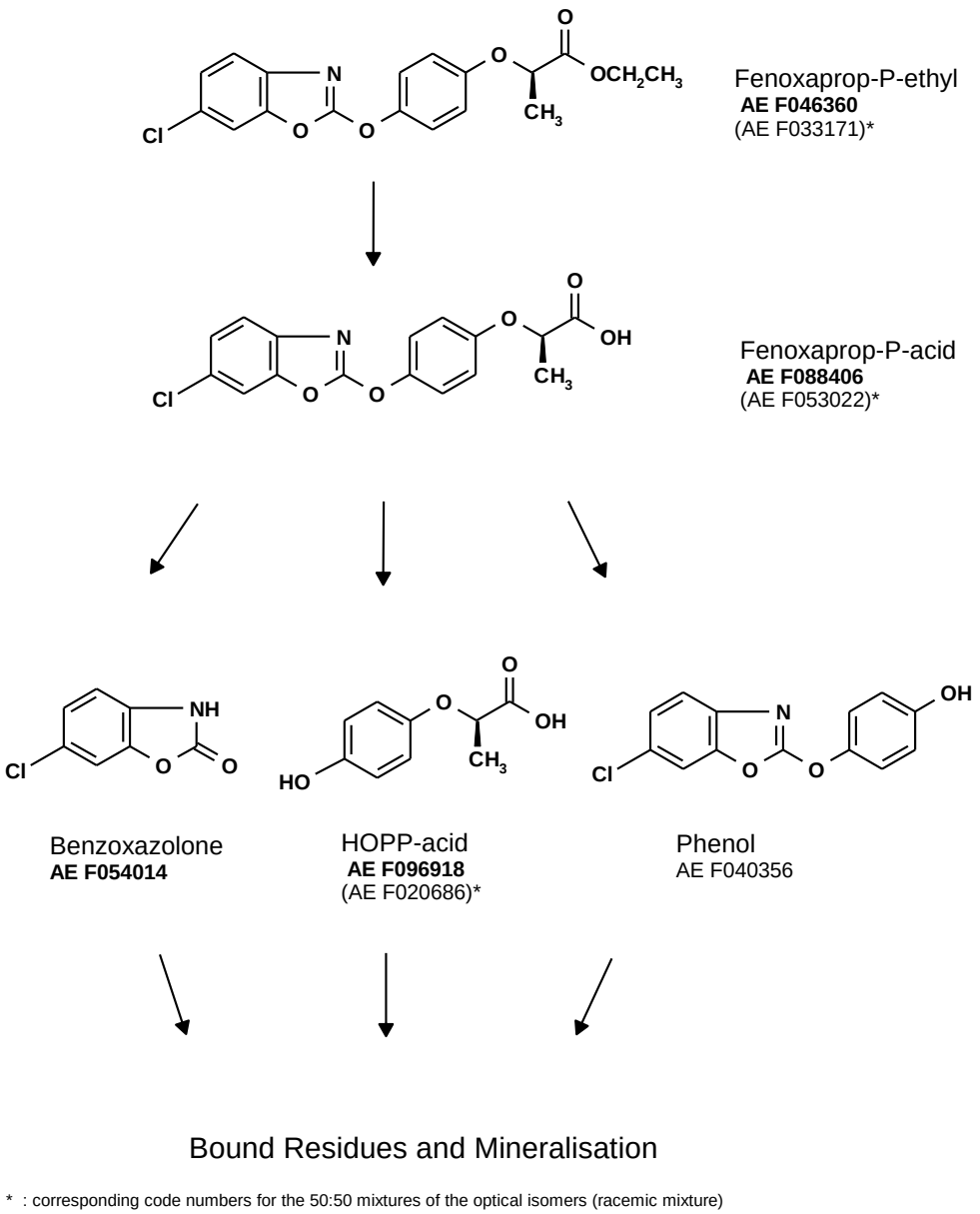
Table 185: Summary of dissipation from water and degradation in total water/sediment systems for Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P AE F088406

Compound	**System**	**Water**		**Total system**	
		$DisT_{50}$ [d]	**$DisT_{90}$** [d]	**$DegT_{50}$** [d]	**$DegT_{90}$** [d]
Fenoxaprop-P-ethyl	Rhine	0.1	0.3	0.1	0.4
	Nidda	0.1	0.3	0.1	0.3
	Pond	n.a.	n.a.	0.16	0.54
	Riwer	n.a.	n.a.	0.29	0.96
Geometric mean		**0.1**	**0.3**	**0.2**	**0.5**
Fenoxaprop-P AE F088406	Rhine	9.6	31.9	13.0	43.3
	Nidda	3.3	11.1	6.9	22.8
	Pond	34	113*	40	133
	Riwer	35	116	39	129
Geometric mean		**13.9**	**46.4**	**19.3**	**64.2**

* Different from value in DAR, value taken from the report.

Fenoxaprop-P-ethyl and Fenoxaprop-P AE F088406 were therefore shown to degrade with a geometric mean DT50-value of 0.2 d and 19.3 d in total water/sediment systems, respectively. The results indicate no long-term persistence of residues of Fenoxaprop-P-ethyl in the surface water or sediment environment.

Figure X: Proposed metabolic pathway of Fenoxaprop-P-ethyl in water/sediment:



* : corresponding code numbers for the 50:50 mixtures of the optical isomers (racemic mixture)

Biodegradation in soil

References:

1. Stumpf K.; Dambach P. (1988c): Aerobic soil metabolism (Hoe 046360 – chlorophenyl-^{14}C). Report No CB051/87
2. Buettner B.; Schweighoefer U.; Kuenzler K. (1992a): Aerobic Soil Metabolism Study at 11 and 21°C (Hoe 046360 – chlorophenyl-^{14}C). Report No CB91/017
3. Buerkle W.L.; Schuld G.; Grundschoettel P. (1986a): Aerobic Soil Metabolism Study (Hoe 033171 – dioxyphenyl-1-^{14}C). Report No CB058/85

Route of degradation:
The degradation of Fenoxaprop-P-ethyl in aerobic soil was shown to proceed *via* two major steps: rapid ester hydrolysis to form the herbicidally active metabolite Fenoxaprop-P AE F088406 is followed by cleavage at the central heterocyclic ether bond. The split of the molecule results basically in two major parts, the Benzoxazolone AE F054014 and hydroxyphenoxypropionic acid (HOPP-acid) AE F096918. While the latter compound could be observed under conditions of water/sediment testing its intermediate character is underlined by the fact that it was not observed to a significant extent in the degradation tests performed with aerobic soil.
Hydrolysis at the central heterocyclic ether bond results in complete loss of biological activity for metabolites Benzoxazolone AE F054014 and hydroxyphenoxypropionic acid (HOPP-acid) AE F096918. The cleavage of the ether bond has been shown to be induced either by biotic or chemical abiotic hydrolysis.

Rate of degradation:
The rate of biodegradation of Fenoxaprop-P-ethyl and its major metabolites Fenoxaprop-P AE F088406 and Benzoxazolone AE F054014 in aerobic soil has been estimated from results of three laboratory studies with six different soils and two positions of radiolabel conducted at 20-22°C (40% MWHC).
For Fenoxaprop-P-ethyl no reliable degradation rates have been calculated in the original studies as the shape of degradation curves suggested bi-phasic degradation characteristics. The same applies for graphical evaluations performed in the original reports. Degradation rates were therefore calculated on the basis of simple first order (SFO) kinetics by the RMS with the software "TableCurve" and normalised to reference conditions (20°C, moisture at field capacity pF2). The results are compiled for Fenoxaprop-P-ethyl and its major metabolites Fenoxaprop-P AE F088406 and Benzoxazolone AE F054014 in Table 186.

Table 186: Summary of normalised (20°C, pF 2 moisture) degradation rates of Fenoxaprop-P-ethyl, Fenoxaprop-P AE F088406 and Benzoxazolone AE F054014 in aerobic soil

		Fenoxaprop-P-ethyl (AE F046360)		Fenoxaprop-P (AE F088406)		Benzoxazolone (AE F054014)	
Soil	**Temp.**	**DT_{50}**	**DT_{90}**	**DT_{50}**	**DT_{90}**	**DT_{50}**	**DT_{90}**
SL V [a)]	20° C	0.3	1.0	3.7	12.3	5.8	19.3
LS 2.2 [a)]	20° C	0.3	1.0	12.8	42.5	4.8	15.9
SL S [a)]	20° C	0.6	2.0	2.9	5.6	7.0	23.2
SL 2 [a)]	20° C	0.4	1.3	1.7	5.6	10.1	33.5
SL V [b)]	21° C	0.5	1.7	26.7	88.6	12.1	40.2
SL 2 [c)]	22° C	0.6	2.0	5.9	19.2	-	-
SS 2 [c)]	22° C	0.4	1.3	14.9	49.5	-	-
Geometric mean:		0.43	1.42	6.6 [d)]	20.2 [d)]	7.5 [e)]	24.9 [e)]

Values of DT50 according to the List of Endpoints (EFSA Conclusion, 2007)
Values for DT90 were derived by multiplying DT50-value by a factor of 3.32 (estimation for simple first order kinetics)
[a)], [b)] Studies 1 and 2, conducted with label 1, *i.e.* ^{14}C-chlorophenyl-label
[c)] Study 3, conducted with label 2, *i.e.* ^{14}C-dioxyphenyl-label
[d)] Deviation from List of Endpoints after re-calculation
[e)] Value not given in List of Endpoints and therefore re-calculated

Results of laboratory tests on aerobic degradation showed well primary degradation in soil. Geometric mean DT_{50}-values (simple first order kinetics) were estimated to 0.43 d for Fenoxaprop-P-ethyl (n=7), 6.6 d for Fenoxaprop-P AE F088406 (n=7) and 7.5 d for Benzoxazolone AE F054014 (n=5).

Dependent on position of radiolabel, formation of CO2 was observed under the conditions of the test (^{14}C-chlorophenyl-label: 9.7 to 32.5% AR after 100 d; ^{14}C-dioxyphenyl-label: 45 to 55% after 64 d). The observation of non-extractable residues (NER) formed to reach 49 to 70% after 100 d (^{14}C-chlorophenyl-label) or 28 to 32% after 64 d (^{14}C-dioxyphenyl-label) during the tests.
In summary Fenoxaprop-P-ethyl shows a fast primary degradation followed by an ultimate degradation, but formation of CO_2 was too low to demonstrate an 70 % degradation in 28 days.

Field studies
None of the four field studies (two were conducted in the US, two in Canada) provided were found fully acceptable within the Annex I inclusion process by the RMS. The climatic conditions of the two US studies were not considered appropriate for the EU. For both Canadian studies climatic data were not complete while for one of the Canadian studies the presentation of the results was not appropriate. None of the data sets allowed for a reliable calculation of degradation rates from field studies.

5.1.3 Summary and discussion of degradation

Summary: Biotic degradation	Test guideline / design	GLP (y/n)	Reliability
Ready biodegradability No data submitted, substance considered not ready biodegradable.		--	--
Water/sediment system (simulation test) In water/sediment systems primary degradation of Fenoxaprop-P-ethyl was extensive to form metabolites Fenoxaprop-P AE F088406, Benzoxazolone AE F054014 and HOPP-acid AE F096918. A primary degradation is accompanied by the formation of Fenoxaprop-P AE F088406. Carbon dioxide formation was: Study 1: sand 27.6% AR after 199 d, silt loam 17.6% after 120 d; Study 2: "pond" 45.9% AR after 118 d, "river" 46.5% after 90 d). Biotically and chemically induced hydrolysis of Fenoxaprop-P-ethyl resulted in low DisT50-values of 0.1 d in water and 0.29 d in maximum for the DegT50 in total systems. The geometric mean DisT50 in water is 0.1 d and the corresponding DegT50 is 0.2 d in total systems. For the predominant metabolite Fenoxaprop-P AE 088406 DisT50-values were shown to range from 6.6 to 35 d in water and from 6.9 to 40 d for the DegT50 in total systems. The geometric mean of the DisT50 in water is 13.9 d and the corresponding DegT50 in total systems is 19.3 d. HOPP-acid AE F096918 has been identified as a second major, but transient metabolite. No DT50-value has been reported for HOPP-acid AE F096918. **Degradation in soil:** Results of biodegradation tests exhibited low persistence of Fenoxaprop-P-ethyl in soil. The fast and strongly biotically induced primary degradation in soil is accompanied by the formation of Fenoxaprop-P AE F088406 and the Benzoxazolone AE F054014 as major and transient metabolites. The transient character of residues formed including NER is underlined by carbon dioxide formation under test conditions (carbon dioxide: 14C-chlorophenyl-label: 9.7 to 32.5% AR after 100 d; 14C-dioxyphenyl-label: 45 to 55% after 64 d). From laboratory tests the rate of degradation in soil expressed by the geometric mean of normalised half-lives (SFO, 20°C, pF2 moisture) is 0.43 d for Fenoxaprop-P-ethyl and 6.6 d for Fenoxaprop-P AE F088406.		y y	y y

Summary: Abiotic degradation	Test guideline / design	GLP (y/n)	Reliability
Hydrolysis: Fenoxaprop-P-ethyl was shown to be sensitive towards abiotic hydrolysis under acidic and basic conditions. However,half-lives of more than 16 days have been determined at pH 5 and 7. The hydrolysis data are therefore not applied for the purpose of classification.		y	n

Photolysis In comparison, the contribution of direct or indirect photolytical processes to the overall elimination of Fenoxaprop-P-ethyl and its residues from the aquatic environment can be regarded as negligible.		y	n
Soil Photolysis Phototransformation of Fenoxaprop-ethyl on the surface of a sterilised soil was found to be moderate as it is indicated by a DT50-value of approximately 53 d.		y	n

Conclusion: The criteria for rapid degradation are not fulfilled because

Half lives of Fenoxaprop-P-ethyl in abiotic test are > 16 days,

$DT_{50\ WHOLE\ SYSTEM}$ in aerobic water-sediment system is < 16 d (geomean 0.2 d) indicating a fast primary degradation, but ultimative degradation to a level at least 70 % within 28 days could not be demonstrated as CO_2 formation was too low.

However the major metabolite Fenoxaprop-P in aerobic water-sediment system is relevant for classification and labelling (see aquatic toxicity Fenoxaprop-P), in addition please refer to table 194

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Reference:

1. Goerlitz, G.; Rutz, U. (1988a): Hoe 046360 Adsorption/Desorption in the System Soil/Water and Hoe 088406 Adsorption/Desorption in the System Soil/Water. Code: AE F046360. Report No CP070/87

2. Reynolds, J. (1992a): Adsorption and Desorption of ^{14}C-Fenoxaprop-P-Ethyl in Four Soils. Code: AE F046360. Report No RPT0099

3. Rupprecht, J. (1999c): The Adsorption/Desorption of ^{14}C-AE F088406 on Six Soils and One Sediment. Code: AE F088406. Report No BM98E501

Sorption properties of Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P AE F088406 to soil have been investigated in batch equilibrium tests in the laboratory.
Following evaluation in the EU review process the adsorption constants referenced to organic carbon content of soil (Koc) have been determined in eight (Fenoxaprop-P-ethyl) and five (Fenoxaprop-P AE F088406). On the basis of Freundlich isotherms $K_{d, ads}$- and $K_{oc, ads}$-values and the associated coefficient 1/n could be derived for the metabolites. This failed for Fenoxaprop-P-ethyl due to instability (*i.e.* rapid hydrolysis) under the conditions of the test. Sorption values as finally reported in the List of Endpoints were therefore based on single concentration determinations. The results are detailed in Tables 187, and 188.

Table 187: Adsorption behaviour of Fenoxaprop-P-ethyl in eight soils

Soil	OM (%)	pH	Kd, ads (ml/g)	Koc, ads (ml/g)	Kf, ads (ml/g)	Kf oc, ads (ml/g)	1/n
SL 2	1.06	5.4	104	16774	n.a.	n.a.	n.r.
SL S	1.51	6.3	57	6404	n.a.	n.a.	n.r.
SL V	2.17	5.9	82	6406	n.a.	n.a.	n.r.
LS 2.2	4.53	5.8	149	5602	n.a.	n.a.	n.r.
Clay	0.4	7.6	12.8	5419	n.a.	n.a.	n.r.
Silty clay loam	1.4	6.5	212	26207	n.a.	n.a.	n.r.
Sandy loam	4.4	6.4	443	17352	n.a.	n.a.	n.r.
Clay loam	4.56	6.8	176	6667	n.a.	n.a.	n.r.
Arithmetric mean			**154**	**11354**	**n.a.**	**n.a.**	**n.a.**

n.r.: not reliable; n.a.: not available from List of Endpoints

Table 188: Adsorption behaviour of Fenoxaprop-P AE F088406 in five soils

Soil	OC (%)	pH	Kd, ads (ml/g)	Koc, ads (ml/g)	Kf, ads (ml/g)	Kf oc, ads (ml/g)	1/n
Sandy loam	2.64	7.3	n.a.	n.a.	8.76	332	0.733
Sand	0.53	4.7	n.a.	n.a.	3.01	568	0.782
Silty clay loam	1.67	7.1	n.a.	n.a.	3.05	182	0.823
Sand	0.81	6.4	n.a.	n.a.	1.17	145	0.880
Clay loam	1.99	7.4	n.a.	n.a.	3.67	184	0.719
Arithmetric mean			**n.a.**	**n.a.**	**3.9**	**282**	**0.787**

n.a.: not available from List of Endpoints

For Fenoxaprop-P-ethyl it has been shown in two batch-equilibrium studies conducted in a total of eight soils that stability was not given due to rapid hydrolysis to Fenoxaprop-P AE F088406. Consequently the concentration of Fenoxaprop-P-acid AE F088406 was also determined in the experiments with adsorption and desorption values for Fenoxaprop-P-ethyl being corrected mathematically for degradation. For the Freundlich coefficient 1/n this resulted in unrealistically high values above 1 which were therefore considered as not reliable. Consequently, adsorption values K_d and K_{oc} were calculated on the basis of single concentration determinations. Values for $K_{OC, ads}$ ranged from 5 602 and 26 207 mL/g (arithm. mean: 11 354 mL/g), thus indicating strong adsorption to soil.
For environmental risk assessments a conservative $K_{OC, ads}$-value of 6 000 L/kg had been taken to express the immobility of Fenoxaprop-P-ethyl in soil.

For Fenoxaprop-P AE F088406 the adsorption to soil has been investigated in a batch-equilibrium study in a total of five soils to result in reliable values for $K_{d, ads}$, $K_{oc, ads}$ and the Freundlich coefficient 1/n. Adsorption as expressed by values of $K_{oc, ads}$ ranged from 145 to 568 mL/g (arithm. mean: 282 mL/g) to indicate well adsorption to soil. For the Freundlich coefficient 1/n values ranged from 0.719 to 0.880 (arithm. mean: 0.787) to indicate significant dependence of adsorption from concentration in soil.

5.2.2 Volatilisation

References:

1. Buerkle. (1999j): Estimation of the Reaction with Photochemically Produced Hydroxyl Radicals in the Atmosphere. Code: AE F046360. Report No OE99/056

Residues of Fenoxaprop-P-ethyl are nor expected to reach neither to persist in the atmosphere when considering the combination of short estimated photochemical half-life in air of 0.6 d (Atkinson approach) and the low potential for volatilisation as indicated by a vapour pressure of 5.3×10^{-7} Pa (20°C).
The same applies to residues of the relevant and herbicidally active metabolite Fenoxaprop-P AE F088406, again due to a short estimated photochemical half-life in air of 0.3 days. Due to its ability to form salts and thus to occur in its ionic form under the conditions of pH in the environment it can be estimated that the acid is even less volatile than Fenoxaprop-P-ethyl.

Fenoxaprop-P-Ethyl and Fenoxaprop-P AE F088406 thus exhibit low persistence in the atmosphere combined with a low vapour pressure to result in a very low potential for evaporation and long-range transport from treated areas. Conclusively an exposure to Fenoxaprop-P-Ethyl or Fenoxaprop-P AE F088406 in the atmosphere or in remote non-target areas resulting volatilisation and long-range transport can be excluded.

5.2.3 Distribution modelling

No data/information available.

5.3 Aquatic Bioaccumulation

Table 189: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient n-octanol/water OECD 117 HPLC method	Purified product [purity: 98.4% (w/w)] KOW = 38000 log KOW = 4.58 at 30 °C neutral medium [water/methanol (70/30 v/v) without buffer]		Schollmeier M., Eyrich U., Uhl A. (1992a) (Document A49082) Wolf R., Le Gren I. (2004) (Document C044472) Wolf R., (2004) (Document C045431)
Bioaccumulation and metabolism of 14C-Chlorophenyl AE F046360 in Bluegill Sunfish, *Lepomis macrochirus*, in a Flow-Through System. Test guideline: OECD 305; US EPA 165-4	BCF: Whole fish: 280 and 338 Non-edible portions: 548 and 619. 90 % level of steady state: after max. 1.4 d. Depuration after 14 days: ≥ 97 % for whole fish Depuration half-life (CT_{50}): 0.4 d.		Meyer B.N. & Young B.M. (1999a):

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

5.3.1.2 Measured bioaccumulation data

Reference: Meyer B.N. & Young B.M. (1999a): Bioaccumulation and metabolism of ^{14}C-Chlorophenyl AE F046360 in Bluegill Sunfish, *Lepomis macrochirus*, in a Flow-Through System. Report No. BM98E517

Test guideline: OECD 305; US EPA 165-4
GLP: Yes
Test item: unlabelled Fenoxaprop-P-ethyl, purity 99.5 %, batch no. 28283-133 spiked with U-^{14}C-chlorophenyl labelled Fenoxaprop-P-ethyl, radiochemical purity 97 %, batch no. Z 28052-0

Material and methods:
A bioaccumulation study of Fenoxaprop-P-ethyl in the bluegill sunfish was performed under flow-through conditions. The fish (144 individuals per treatment and control) were exposed

for up to 27 days to two nominal concentration levels of 0.001 mg/L and 0.01 mg/L, as well as to one solvent control (0.054 ml/L DMF). After the uptake period a 14-days depuration period with untreated dilution water followed. Fish and water samples were taken on day 0, 1, 3, 7, 9, 14, 21, 24 and 27 during the uptake phase. Additionally fish for analysis of metabolites were sampled on day 24 and 27. In the course of the depuration period fish samples were taken on day 1, 3, 7, 10 and 14, and water samples were taken on day 1.
During the study water quality parameters were: pH 7.4 – 8.1 , temperature 22.1 – 22.7°C, mean oxygen saturation 93 % (8.1 mg O_2/L) and water hardness 76 – 102 mg/L as $CaCO_3$.
Findings:
Concentration of Fenoxaprop-P-ethyl in water prior to the addition of fish was 82 % and 88 % in the low and high treatment level. After fish were added the percentage of parent rapidly dropped to 38 % and 50 %. The remaining radioactivity was composed of Fenoxaprop (AE F053022: 49 % and 45 %) and small amounts of AE F054014 (< 5 %). Fish tissue analyses showed the same pattern of metabolites.
The mean lipid content (wet weight basis) was estimated to be 7.2 % at study initiation. During the whole study the mean total lipid content was 9.0 ± 0.9% and 8.9 ± 1.1 % in the low and high treatment.

Table 190: Concentration of Fenoxaprop-P-ethyl equivalents (measured as total radioactivity with LSC) in fish tissue during 27 days exposure and 14 days depuration

mean measured water concentration	**tissue**	**(mg/kg)***	**BCF (measured)**	**% depuration**	
				3 days	**14 days**
0.00112 mg/L	edible	0.034	30	72	89
	whole fish	0.312	280	93	97
	non-edible	0.609	548	94	98
0.0115 mg/L	edible	0.405	36	82	90
	whole fish	3.828	338	96	99
	non-edible	7.010	619	96	98

* = total tissue concentrations

Table 191: Results of non-linear regression modelling based on a one-compartment model (whole fish)

parameter	**low treatment 0.001 mg/L nominal**	**high treatment 0.01 mg/L nominal**
uptake rate constant (k_u)	461.0 ± 87.6 L/kg d^{-1}	652.6 ± 201.9 L/kg d^{-1}
depuration rate constant (k_d)	1.61 ± 0.31 d^{-1}	1.90 ± 0.60 d^{-1}
depuration half-life ($t_{½}$)	0.43 d	0.36 d
time to 90% steady state (t_{90})	1.4 d	1.2 d
BCF	286x ± 9.2	343x ± 15.7
Correlation Coefficient	98.6%	98.9%

Conclusion: Fenoxaprop-P-ethyl rapidly accumulated in fish BCF values of 280 and 338 were found for the whole fish. In non-edible portions BCF values of 548 and 619 were measured. The 90 % level of steady state was quickly reached after max. 1.4 d. During the depuration period Fenoxaprop-P-ethyl was rapidly eliminated and after 3 days already ≥ 93 % of Fenoxaprop-P-ethyl equivalents had been excreted from whole fish. At test termination after 14 days the depuration was ≥ 97 % for whole fish. The depuration half-life (CT_{50}) was determined to be 0.4 d.

5.3.2 Summary and discussion of aquatic bioaccumulation

The log P_{OW} of fenoxaprop-P-ethyl is 4.58 and a bioaccumulation study with fish is triggered according to 91/414/EC. Fenoxaprop-P-ethyl with BCF values of 280 and 338 is characterised as low potential of bioaccumulation in fish according to the justification criteria of Annex I, Part 4 to the EC 1272/2008 (CLP), of which the trigger value is 500.

According to the 67/548EEC (DSD), a BCF in fish of ≥ 100 is indicative of the potential to bio concentrate for classification purpose. The bioaccumulation study showed that Fenoxaprop-P-ethyl rapidly accumulated in whole fish, the accumulated residues were excreted almost completely during the depuration period (≥ 97 % depuration after 14 d) with a depuration half-life (CT50) of 0.4 d. Therefore the potential of Fenoxaprop-P-ethyl to bioaccumulate in aquatic organisms is expected actually to be low. R53 needs to be warranted based on the determined BCF values and short and long-term aquatic toxicity tested

Summary
log KOW = 4.58 at 30 °C neutral medium
Fenoxaprop-P-ethyl rapidly accumulated in fish BCF values of 280 and 338 were found for the whole fish. In non-edible portions BCF values of 548 and 619 were measured.
Conclusion: **The measured BCF is in the range of 280 – 338 and is above the classification criteria of ≥ 100 (DSD) and below the classification criteria of ≥500 (CLP).**

5.4 Aquatic toxicity

Table 192: Summary of relevant information on aquatic toxicity

Method	Test organism	test condition	time	endpoint	test conc.	NOEC (mg ai/L)	EC_{50}/LC_{50} (mg ai/L)	Reference
Fenoxaprop-P-ethyl								
OECD 203, US EPA §72-1	*Oncorhynchus mykiss* Rainbow trout	flow through	96 hr	mortality	m	0.16	0.39	Stachura & Ruff 1999s
US EPA §72-1	*Oncorhynchus mykiss* Rainbow trout	static	96 hr	mortality	n	0.24	0.46	Fischer 1986b
OECD 203, US EPA §72-1	*Lepomis macrochirus* Bluegill sunfish	flow through	96 hr	mortality	m	0.088	0.19	Stachura & Ruff 1999r
OECD 204	*Oncorhynchus mykiss* Rainbow trout	flow through	21 d	mortality weight [1)]	n	0.1	-	Fischer 1989ap
US EPA §72-4	*Oncorhynchus mykiss* Rainbow trout (ELS)	flow through	91 d	mortality hatchability	n	0.036 ≥ 0.1	-	Stachura & Ruff 1999t
OECD 202, US EPA §72-2	*Daphnia magna* Waterflea	static renewal	48 hr	immobility	m	0.84	> 1.06	Stachura & Ruff 1998e
OECD 202	*Daphnia magna* Waterflea	static renewal	21 d	mortality reproduction	m	0.22	-	Fischer 1989ao
BBA Guideline, OECD 219	*Chironomus riparius* Midge	static	26 d	emergence development	in	0.2	-	Memmert 2002a
EPA 540/9-86-134	*Pseudokirchn. subcapitata* Green alga	static	72 hr 120 hr	biomass	m	- 0.05	0.54 0.37	Heusel 1991bs
OECD 201, US EPA §122-2	*Anabaena flos-aquae* Blue-green alga	static	72 hr	biomass growth rate	im	≥0.73	>0.73	Christ & Ruff 1999g
OECD 201, US EPA §123-2	*Navicular pelliculosa* Diatom (limnic)	static	72 hr 96 hr 72 hr 96 hr	biomass growth rate	m [1)]	1.7	2.38 4.26 4.26 > 6.31	Sowig, Weller & Gosch 1999ae
OECD 201, US EPA §122-2	*Skeletonema costatum* Diatom (marin)	static	72 hr 96 hr	biomass growth rate	im	0.38	>3.7	Young & Ruff 1999h
US EPA §122-2	*Lemna gibba* Duckweed	static renewal	7 d 14 d	biomass growth rate	im	≥ 2.76	> 2.76	Christ & Ruff 1997b
Fenoxaprop-p								
OECD 203, US EPA §72-1	*Oncorhynchus mykiss* Rainbow trout	static	96 hr	mortality	m	≥ 72.2	> 72.2	Heusel 1996j

Method	Test organism	test condition	time	endpoint	test conc.	NOEC (mg ai/L)	EC_{50}/LC_{50} (mg ai/L)	Reference
OECD 215	*Oncorhynchus mykiss* Rainbow trout	flow through	28 d	mortality growth	n	≥ 3.2	-	Sowig & Gosch 2003a
OECD 211, US EPA §72-4	*Daphnia magna* Waterflea	static	48 hr	immobility	n	56	126	Heusel 1993dy
OECD 211, US EPA §72-4	*Daphnia magna* Waterflea	static renewal	21 d	reproduction weight	n	1.0	-	Ebling et al. 2002a/ yes
EPA 540/9-86-134, 1986	*Pseudokirchn. subcapitata* Green alga	static	72 hr 120 hr	biomass	m	13.7	35.0 34.2	Heusel 1993dx

Test conc.: test concentration based on mean measured (m), initial measured (im) or nominal (n) concentration
[1)]toxcictiy values based on mean measured concentration of dissolved test substance (sum of AE F046360 + AE F053022)

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Reference: Stachura B.J. & Ruff D.F. (1999s): The 96 hour acute toxicity to the rainbow trout, *Oncorhynchus mykiss*, in a flow through system; Fenoxaprop-P-ethyl, technical 88.1% w/w; Code: AE F046360 00 1C97 0002. Report No. BM98W520

Test guideline: OECD 203; US-EPA E § 72-1
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 88.1 % w/w, sum of (D+) and (L-)-enantiomers: 95.8 % w/w, batch no.: 1+2/86

Material and methods:
A 96 hours test on the acute toxicity of Fenoxaprop-P-ethyl to juvenile rainbow trouts, was performed under flow through conditions at five nominal test concentrations, one control and one solvent control (DMF). The concentrations ranged from 0.13 mg/L to 1.0 mg/L. The fish were 30 mm (mean) in length and had an average weight of 0.343 g. Ten fish were exposed in duplicates to each test concentration under the following test conditions: 16/8-hour light/dark photoperiode, 13.1 – 13.7 °C, pH 7.1 – 7.5, 101 - 114 % O_2-saturation and conductivity 110 – 120 µS/cm.

Findings:
Mean measured concentrations were in the range of 58 – 85 % of nominal concentrations. The 96 hours LC_{50} was estimated to be 0.39 mg/L Fenoxaprop-P-ethyl (95 % CL 0.35 – 0.42 mg/L) based on mean measured concentration. Behavioural or sublethal effects like lethargy and irregular swimming were observed at test concentrations from 0.31 to 0.51 mg/L, therefore the 96 hours "no effect" concentration (NOEC) was determined to be 0.16 mg/L.

Conclusion: LC_{50} (96 h): 0.39 mg ai/L and NOEC: 0.16 mg ai/L, based on mean measured concentrations

Comment : Weight and length of test fish were lower than recommended by the OECD test guideline, but this is considered unlikely to have any influence on the results. Study considered acceptable.

Reference: Fischer, R. (1986b) The Effect of Hoe 046360 - substance, technical Identification code Hoe 046360 OH ZC96 0002 to *Salmo gairdneri* (Rainbow trout) in a Static Acute Toxicity Test (Sg347/a, method EPA). Report No. OEK86/092E

Test guideline: US-EPA E § 72-1
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 95.6 % w/w sum of (D+) and (L-)-enantiomers, batch no.: not stated

Material and methods:
A 96 hours test on the acute toxicity of Fenoxaprop-P-ethyl to rainbow trout, was performed under static conditions at seven nominal test concentrations, one control and one solvent control (acetone). The nominal test concentrations were 0.18, 0.24, 0.32, 0.42, 0.56, 0.75 and

1.0 mg/L, respectively. The fish were 6.7 cm (mean) in length and had an average weight of 4.1 g. Ten fish were exposed to each test concentration under following test conditions: 16/8-hour light/dark photoperiod, 14.3 – 15.6 °C, pH 7.4 – 7.9, 10.1 – 11.9 mg/L dissolved O_2 and total hardness 45.5 – 49.5 mg/l $CaCO_3$.

Findings:
Chemical analysis of test item concentrations in test media was carried out only in the 0.18, 0.42 and 1.0 mg/L test dilutions at 0, 48 and 96 hours. The measured concentrations were close the nominal concentrations in the in groups of 0.18 and 0.42 mg/L. The measured concentration in the highest test level was 0.55 mg/L which corresponds to the limit of solubility of the test item. The assessment is based on nominal concentrations, however the highest test concentration was not included into LC50 calculations.
The 96 hours LC_{50} was estimated to be 0.46 mg/L Fenoxaprop-P-ethyl (95 % CL 0.32 – 0.56 mg/L) based on nominal concentration. Behavioural or sublethal effects like swimming on the surface and slow reaction were observed at test concentrations from 0.32 – 0.42 mg/L, therefore the 96 hours "no effect" concentration (NOEC) was determined to be 0.24 mg/L.

Conclusion: LC_{50} (96 h): 0.46 mg ai/L and NOEC: 0.24 mg ai/L based on nominal concentrations

Reference: Stachura B.J. & Ruff D.F. (1999r): The 96-hours Acute Toxicity to the Bluegill Sunfish, *Lepomis macrochirus*, in a Flow Through System; Fenoxaprop-P-ethyl Technical 88.1% w/w; Code: AE F046360 00 1C97 0002. Report No. BM98W521

Test guideline: EU 92/69 C.1; OECD 203; US EPA § 72-1
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 81.1 % w/w, sum of (D+) and (L-)-enantiomers: 95.8 % w/w, batch no.: 1+2/86

Material and methods:
Bluegill sunfish (20 per treatment level) were exposed to nominal test concentrations of 0 (control) 0 (solvent control, DMF), 0.13, 0.22, 0.36, 0.6, and 1.0 mg/L, respectively, under flow through conditions for 96 hours. The fish were 2.5 cm (mean) in length and had an average weight of 0.348 g. Fish were exposed to each test concentration under following test conditions: 16/8-hour light/dark photoperiod, 21.9 – 22.2°C, pH 7.3 – 7.6, 96 – 102 % O_2 saturation and 150 – 170 µmhos/cm conductivity.
Findings:
The mean measured concentrations of Fenoxaprop-P-ethyl were 0.088, 0.192, 0.29, 0.551 and 0.886 mg/L, respectively (68 – 92 % of nominal concentrations). Mean measured concentrations of Fenoxaprop-P were determined as 0.011, 0.03, 0,023, not found and 0.021 mg/L.
The 96 hours LC_{50} was estimated to be 0.19 mg/L Fenoxaprop-P-ethyl (95 % CL 0.16 – 0.21 mg/L) based on mean measured concentrations. Behavioural or sublethal effects like lost of equilibrium, irregular swimming (surfacing and on bottom) and lethargy were observed at test concentrations of 0.192 mg/L, therefore the 96 hours "no effect" concentration (NOEC) was determined to be 0.088 mg/L and LOEC 0.192 mg/L.

Conclusion: LC_{50} (96 h): 0.19 mg ai/L and NOEC: 0.088 mg ai/L based on mean measured concentrations

Reference: Heusel, R. (1996j): Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) Fenoxaprop-P; substance, technical; Code: AE F088406 00 1C94 0001. Report No. CE96/122

Test guideline: OECD 203; EU C.1; US EPA §72-1
GLP: yes
Test item: Fenoxaprop-P, techn.: 95.4 % w/w sum of (D+) and (L-)-enantiomers, batch no.: not stated

Material and methods:
A 96 hours test on the acute toxicity of the metabolite Fenoxaprop-P (AE F 088406) to rainbow trout was performed under static conditions at five nominal test concentrations 10, 18, 32, 56, 100 mg/L and one control. The fish were 4.6 cm (mean) in length and had an average weight of 1.4 g. Ten fish were exposed to each test concentration under following test conditions: 16/8-hour light/dark photoperiod, 12.9 – 13.9°C, pH 7.7 – 8.3, 7.2 – 10.4 mg/L dissolved O_2 and a hardness (as Ca^{2+} + Mg^{2+}) of 1.61 mmol/L.

Findings:
Chemical analyses of test concentrations in test vessels were performed at the start and the end of the test. Mean recovery was 72.2 – 144.8 % of nominal concentration.
No mortalities and sublethal effects were observed during testing in any concentration.
Therefore the 96 hours LC_{50} and NOEC were ≥100 mg/L Fenoxaprop-P based on nominal concentration and ≥ 72.2 mg/L based on mean measured concentration.

Conclusion: LC_{50} (96 h) > 72.2 mg/L and NOEC ≥ 72.2 mg/L based on mean measured concentrations

In summary: Based on the lowest LC50 (96h) of 0.19 mg a.i./L, Acute Aquatic Hazard, Category 1 with M-factor 1 is assigned to Fenoxaprop-P-ethyl in accordance with the classiciation criteria of Annex I to CLP (EC1272/2008) and with R50 in accordance to DSD (67/548/EEC).

Acute fish toxicity of Fenoxaprop-P has no relevance for this dossier.

5.4.1.2 Long-term toxicity to fish

Reference: Fischer R. (1989ap): The Effect of Fenoxaprop-P-ethyl - substance, technical (Identification code: Hoe 046360 OH ZC97 0002) to *Salmo gairdneri* (Rainbow trout) in a 21-day Prolonged Toxicity Test (method OECD). Report No. CE98/034

Test guideline: OECD 204
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 89.9 % w/w, batch no.: not stated
Material and methods:
The prolonged toxicity of Fenoxaprop-P-ethyl to rainbow trout (*Oncorhynchus mykiss* formerly *Salmo gairdneri*) was assessed under flow through conditions over a 21 day exposure period. Five month old fish were exposed to six nominal concentrations: 0.005, 0.01, 0.05, 0.1 and 0.5 mg/L, one dilution water control and one solvent control (acetone). Ten trout per treatment and control were incubated under a 16/8-hour light/dark photoperiod and were fed daily during the study. Environmental test conditions were determined initially

and every 24 hours, mean values were 14.1 – 14.7°C, pH 7.8 – 8.0, oxygen 9.5 – 10.2 mg/L, conductivity 659 – 661 µmhos/cm and flow-rate 344 – 360 mL/min.
Daily mortality, behaviour and appearance of fish were checked in each test vessel. The length and weight of alive fish were measured at the start and end of testing.
Chemical analyses of Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P were conducted at the lowest, middle and highest tested concentration

Findings:
Mean measured concentrations (sum of AE F046360 and AE F053022) were in the range between 82.8 and 105.8 % of nominal concentrations. The quantity of the metabolite Fenoxaprop-P decreased dose-dependently from 26.9 % in the lowest concentration to 5.8 % in the highest concentration. The endpoints are based on nominal concentrations.
After 21 days no mortalities and sublethal effects due to the presence of test substance were observed at concentrations up to 0.1 mg/l, therefore the NOEC was determined to be 0.1 mg/L. At concentration of 0.05 mg/L one fish died due to a fungal infected tail fin, but this was not attributed to test substance. After 21 days at the concentration level of 0.5 mg/L the mortality was 80 % and the following sublethal effects were noted: slow reactions up to narcosis and no uptake of food. Also significant differences in weight and length compared to the control were noted at 0.5 mg/L. The 21 days EC_{50} (mortality) was calculated to be 0.27 mg/L (95% CL 0.16 – 0.62 mg/L).

Conclusion: 21 d EC_{50} (mortality): 0.27 mg/L, 21 d NOEC and LOEC (mortality, weight): 0.1 mg/L and 0.5 mg/L based on nominal concentrations

Reference: Stachura, B.J. & Ruff, D.F. (1999t): Effects on Early Life Stages of Rainbow Trout, *Oncorhynchus mykiss* U.S.EPA 72-4 Fenoxaprop-P-ethyl Technical 88.1%w/w; Code: AE F046360 00 1C97 0002. Report No. BM98W513

Test guideline: US EPA §72-4
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn. 88.1 % w/w, sum of (D+) and (L-)-enantiomers: 95.8 % w/w, batch no.: 1+2/86

Material and methods:
The chronic effects of Fenoxaprop-P-ethyl to early life stages of rainbow trout were assessed in flow through exposure systems. 4 x 15 embryos per treatment and control were exposed for up to 91 days to nominal concentrations 0 (dilution control), 0 (solvent control, acetone), 0.013, 0.022, 0.036, 0.06 and 0.1 mg/L. Embryos were incubated in total darkness, whereas after complete swim up the fry were exposed under a 16/8-hour light/dark photoperiod and was fed with nauplii and salmon starter three times per day.
Observations for mortality and abnormal appearance or behaviour were made daily until complete swim up. After swim up observations were performed only three times a week. At study termination weight and length were determined. The following endpoints were assessed: egg hatchability, fry survival and fry growth. The mean measured temperature of the test solutions was 10.1 ± 0.36, the pH-values were in the range of 6.8 – 7.5 and the oxygen saturation was 52 to 106 % during the study.
Chemical analyses of Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P were done at test initiation, weekly thereafter and at test termination.

Findings: Mean concentrations of Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P were in the range of 75 – 85 % and 17 – 28 % of nominal concentration. The sum of test substance

and metabolite amounted to 100 – 104 % of nominal concentrations. All evaluations based on nominal concentrations. Between control and solvent control no significant differences in hatch data and survival and length/weight data were found, therefore they were pooled for statistical analyses. At any treatment level hatchability was significantly affected when compared to controls. After 91 days survival of fish was significantly reduced at the nominal concentrations of 0.06 and 0.1 mg/L. No significant difference in length and weight data was observed at concentrations up to 0.036 mg/L. The growth data of 0.06 and 0.1 mg/L could not be included in statistical analyses due to mortalities at these treatment levels. Thus, on the basis of mortality the 91 d NOEC was determined to be 0.036 mg/L and the LOEC 0.06 mg/L. For hatchability the 91 d NOEC was ≥ 0.1 mg/L.

Conclusion: 91 d NOEC (mortality): 0.036 mg/L and LOEC (mortality): 0.06 mg/L based on nominal concentrations

Reference: Sowig P. & H. Gosch (2003a): Effects on survival and growth of juvenile rainbow trout (*Oncorhynchus mykiss*) in a 28 days flow-through study - Fenoxaprop-P, substance, technical (code: AE F088406 00 1C97 0001). Report No. CE02/058

Test guideline: OECD 215
GLP: yes
Test item: Fenoxaprop-P, techn. 97.4 % w/w, batch no.: not stated

Material and methods:
The effects of the metabolite Fenoxaprop-P on survival and growth of juvenile rainbow trout *Oncorhynchus mykiss* were studied in a 28 days in flow-through exposure system. 20 fry were exposed to nominal concentrations of 0 (control), 0.32, 0.56, 1.0, 1.8 and 3.2 mg/L. Mortality and sublethal effects (intoxication symptoms) were noted daily. Weight and length of fish were determined at beginning and for surviving fish at termination of testing. Environmental test conditions were monitored: 13.3 ± 0.2 °C, pH 7.3 – 7.9, 7.6 – 10.0 mg/L dissolved oxygen and 262 – 380 µS/cm conductivity.
Chemical analyses of Fenoxaprop-P in test water were performed on day -2, 0, 7, 13, 21 and 28.

Findings: All mean measured concentrations were above 80 % of nominal, thus the endpoints were based on nominal concentrations. No mortality and sublethal effects were observed at any time and treatment level during the study. The growth based on analysis of weight and length of fish was not affected by Fenoxaprop-P at any treatment level. Therefore the 28 d NOEC and LOEC based on effects on survival and growth was ≥ 3.2 mg/L and > 3.2 mg/L.

Conclusion: 28 d NOEC and LOEC (mortality, growth): ≥ 3.2 mg/l and > 3.2 mg/L based on nominal concentrations

In summary: "Technically, the OECD 210 Guideline (Fish Early Life Stage) is not a "chronic" test, but a sub-chronic test on sensitive life stages. It is widely accepted as a predictor of chronic toxicity and is used as such for purposes of classification in the harmonised system" (ECHA, Guidance on Classification and labelling, 2008). Considering of classification criteria of chronic aquatic toxicity according to the 2nd ATP to the EC1272/2008 (CLP), Fenoxaprop-P-ethyl needs to be classified as Chronic aquatic hazard, category 2, based on NOEC of 0.036 mg a.i./L for the fish earl life study and rapidly biodegradation property of the substance.

Long term fish toxicity of Fenoxaprop-P has no relevance for this dossier, because the recovery the measured concentration were 75-85% of nominal concentration, the NOCE value is justified based on the nominal concentration.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Reference: Stachura, B.J. & Ruff, D.F. (1998e): The 48 Hour Acute Toxicity to *Daphnia magna*, in a Static Renewal System Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 001 C97 0002. Report No. BM98W514

Test guideline: OECD 202, U.S. EPA § 72-2
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 88.1 % w/w, sum of (D+) and (L-)-enantiomers: 95.8 % w/w, batch no.: 1+2/86

Material and methods:
The acute toxicity of Fenoxaprop-P-ethyl to *Daphnia magna* (first instar < 24 h old) was studied over a 48 h exposure period under static renewal conditions (test solutions were prepared with synthetic hard water and were renewed at 24 hours). The daphnids were exposed to five nominal concentrations (0.52, 0.86, 1,4, 2.4, 4.0 mg/L), one control and one solvent control. All treatments were in duplicate with 10 daphnids per test vessel. The temperatures in the test solutions ranged from 19.8 – 20.1 °C, the pH in new and old test solutions ranged from 7.6 – 7.8 and the oxygen ranged from 93 – 97 % saturation during the study.

Findings:
Overall mean measured concentrations (fresh and 24 hours old solutions) were 0.32, 0.58, 0.84, 1.06, 0.97 mg/L (24 – 67 % of nominal concentrations). The maximum of solubility of Fenoxaprop-P-ethyl under test conditions was reported as 1.06 mg/L. In 2.4 and 4.0 mg/L treatments visible precipitation was noted.
No mortalities were observed in any treatment level. Sublethal effects like lethargy and effects by precipitation (trailed a flock like material, physically encumbered in precipitate) was observed at concentrations ≥ 2.4 mg/L. Therefore the NOEC was 0.84 mg/L and the LOEC 1.06 mg/L based on measured concentration. The 48 hour EC_{50} is greater than 1.06 mg/L (maximum solubility) and could not be determined under test conditions.

Conclusion: EC_{50} (48 h): > 1.06 mg/L (maximum solubility), NOEC and LOEC: 0.84 and 1.06 mg/L based on mean measured concentration

In summary: Based on the results of acute daphnia toxicity studies, no classification for Fenoxaprop-P-ethyl needs to be warranted.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Reference: Fischer, R. (1989ao): The Effect of Fenoxaprop-P-ethyl - substance, technical (Identification code: Hoe 046360 OH ZC97 0002) to *Daphnia magna* (Water flea) in a 21-day Reproduction Test (method OECD). Report No. CE89/033

Test guideline: OECD 202 (Part II), 1984
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn. 89.5 % w/w, batch no.: not stated

Material and methods:
The chronic effects of Fenoxaprop-P-ethyl on the survival and reproduction on *Daphnia magna* were determined. Four replicates of 10 daphnids (< 24 hours old) per test concentration were incubated under static renewal conditions for 21 days with daily feeding and observation. The nominal exposure concentrations were 0.01, 0.032, 0.1, 0.32 and 1.0 mg/L, additionally one water and one solvent (acetone) control were prepared. Test solutions were renewed every 2 – 3 days and samples of the freshly prepared and used test solutions were analysed for Fenoxaprop-P-ethyl and its metabolite Fenoxaprop-P. The mean temperature of freshly prepared test media was 19.4 °C (19.0 – 19.6 °C), dissolved oxygen was in the range of 9.6 – 10.2 mg/L and mean measured pH-values ranged from 7.6 – 7.9. Values for ”old” solutions were similar except for the oxygen content, which was lower, i.e. 6.5 (6.0 – 7.9) mg/L. Water hardness in fresh solutions was 211 – 231 mg/L $CaCO_3$.

Findings: In freshly prepared media measured concentrations of Fenoxaprop-P-ethyl were ≥ 80 %. In old solutions most of Fenoxaprop-P-ethyl was hydrolysed to Fenoxaprop-P: 15 – 36 % Fenoxaprop-P-ethyl and 39 – 62 % of its free acid.
Mean concentration of test substance measured in fresh and ”old” test solutions ranged from 53.6 to 78.8 % of nominal with an overall study mean of 64.4 % of nominal. The following mean measured values were reported: 0.008, 0.023, 0.0763, 0.22 and 0.88 mg/L. The results of the endpoints based on these measured values.
Until day 21 up to 0.22 mg/L parental mortality was not statistically different compared to controls. At 0.88 mg/L mortality of adults was higher compared to the solvent control, but the difference was not statistically significant. However, the number of live young per daphnid was significantly affected from day 12 until the end of testing at 0.88 mg/L, therefore, the 21 d NOEC was determined to be 0.22 mg/L.

Conclusion: 21 d NOEC (development rate): 0.22 mg/L, LOEC: 0.88 mg/L based on mean measured concentrations

Reference: Ebeling M., Nguyen D. & Gosch H. (2002a): Fenoxaprop-P *Daphnia magna* - Chronic Toxicity and Reproduction Test under semi-static conditions; code AE F088406 00 1C97 0001. Report No. CE02/057

Test guideline: OECD 211, 1998; US EPA § 72-4
GLP: yes
Test item: Fenoxaprop-P, techn. 97.4 % w/w, batch no.: not stated

Material and methods:
The effects of Fenoxaprop-P on survival, growth and reproduction were assessed under static renewal exposure conditions. The daphnids (3 x 5 daphnids and 10 daphnids individually per treatment level) were exposed for up to 21 days to nominal concentrations of 0 (untreated

control), 0.032, 0.1, 0.32, 1.0 and 3.2 mg/L. Effects on growth (length and weight) and reproduction were investigated in the individually exposed daphnids. Effects on survival were recorded in daphnids exposed in groups. Test solutions were renewed every 2 – 3 days and samples of freshly prepared and used test solutions were analysed for Fenoxaprop-P. Additionally chemical and physical parameters were measured and the following test conditions were reported as mean measured values: 19.6 °C (19.0 – 20.2 °C), 8.7 mg/L (7.8 – 9.1 mg/L) oxygen content and pH 7.8 (7.6 – 8.0).

Findings: The analytical data indicated that test concentrations in fresh and old solutions were in the range of 101.7 – 114.4 % of nominal concentrations during the study. Therefore the results are based on nominal concentrations.
Biological effects: Survival: during the 21 d exposure period no mortalities were observed in the control and at the treatment levels. Reproduction: In the control and all test concentrations the first release of neonate daphnids were recorded after 7 day. However, at day 21 the number of mean live young by parent alive was significantly reduced at highest concentration tested. Growth: The mean length of daphnids was not influenced by test substance up to 3.2 mg/L, whereas the mean dry weight was significantly affected at this concentration level. Therefore the 21 d NOEC and LOEC were determined to be 1.0 mg/L and 3.2 mg/L based on the most sensitive endpoints reproduction and weight.
Conclusion: 21 d NOEC and LOEC (reproduction, weight): 1.0 mg/L and 3.2 mg/L based on nominal concentrations
In summary: Based on the results of 21-d daphnia reproductive toxicity studies and rapidly degradation property of the substance, Chronic Aquatic Hazard Category 3 needs to warranted for Fenoxaprop-P-ethyl.

During the Fenoxaprop-P-ethyl was hydrolysed to Fenoxaprop-P, the NOEC value was evaluated based on mean concentration of test substance measured in fresh and ”old” test solutions. Due to low toxicity, chronic daphnia toxicity of Fenoxaprop-P has no relevance for this dossier.

5.4.3 Algae and aquatic plants

Reference: Heusel R. (1991bs): Effect to *Selenastrum capricornutum* (Green alga) in an Algal Assay Bottle Test (method EPA) Fenoxaprop-P-ethyl: substance, technical (Hoe 046360 00 ZC97 0002). Report No. E90/093

Test guideline: EPA 540/9-86-134
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 97.4 % w/w sum of (D+) and (L-)-enantiomers, batch no.: not stated

Material and methods:
The effects of Fenoxaprop-P-ethyl to the unicellular green alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in an algal assay bottle test were studied. The algal cultures (3000 cells/mL) were exposed to nine nominal concentrations: 0.056, 0.1, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, and 5.6 mg/L as well as to one dilution and one solvent control. The test samples were incubated for up to 120 hours under static conditions, at temperatures from 24.5 – 25 °C, pH 7.4 - 8 and continuous illumination. Cell densities were determined by cell counts (5 x 1 mm^2 x 0.1 mm in a counting chamber) under a microscope. The calculation of test substance inhibiting the growth (biomass: area under the curve) was done separately

for each treatment in comparison to the control. Chemical analyses of Fenoxaprop-P-ethyl for the nominal test concentrations of 0.056, 0.18, 1.0, 1.8 and 5.6 mg/L were conducted on test day 0, 3 and 5.

Findings:
The mean measured test concentrations over five days were in the range of 49 – 78 % of nominal. The endpoints are reported as nominal and mean measured concentrations. All mean measured concentrations are based on 49 % of nominal concentration (lowest value of measured concentrations).
The algal biomass (area under the curve) was significantly inhibited at nominal test concentrations ≥ 0.18 mg/L, thus the NOEC was 0.1 mg/L (nominal) and 0.05 mg/L (measured). The 72 hours and 120 hours E_bC_{50} were estimated to be 1.12 (95 % CL 1.0 – 1.8) mg/L and 0.76 (95 % CL 0.76 – 0.77) mg/L based on nominal concentration and 0.54 (95% CL 0.49 – 0.89) mg/L and 0.37 (95 % CL 0.37 – 0.38) mg/L based on measured concentrations.

Conclusion: 72 hour E_bC_{50}: 1.12 mg/L (nominal), 0.54 mg/L (mean measured) and NOEC: 0.1 mg/L (nominal), 0.05 mg/L (mean measured)

Reference: Christ M.T. & Ruff D.F. (1999g): Effect to *Anabaena flos-aquae* (Blue-Green Alga) in a Growth Inhibition Test Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 00 1C97 0002. Report No. BM98W518

Test guideline: OECD 201; US EPA §122-2
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 88.1 w/w, 95.8 % w/w sum of (D+) and (L-)-enantiomers, batch no.: 1+2/86

Material and methods:
The toxicity of Fenoxaprop-P-ethyl to *Anabaena flos-aquae* was assessed in a static system over a 96 hours exposure period. The algal cultures (1×10^4 cells/ml in AAP media) were exposed to a nominal concentration of 10 mg/L, control and solvent control.
The test samples were continuously illuminated, temperatures in the test solutions ranged from 124.5 – 24.9 °C, the pH was 6.9 – 7.3 and dissolved oxygen was in the range of 7.5 – 8.2 mg/L (89 – 98% saturation). Cell densities were determined by cell counts with a haemocytometer under microscope. Chemical analysis of Fenoxaprop-P-ethyl and its acid Fenoxaprop-P was performed in each test concentration at beginning and end of the study.

Findings:
At beginning of the study in the 10 mg/L treatment vessels precipitate was visible. The measured concentration of dissolved test substance was 0.7314 mg/L (maximum solubility under test conditions). At the end of the study the measured AE F046360 and AE F088406 concentrations were 0.3106 mg/L and 0.5094 mg/L, respectively. All toxicity values were expressed as the initial measured concentration.
The inhibition of biomass and growth rate in comparison to the pooled controls was 41 % and 35 % after 72 hours and 46 % (significantly different from pooled controls) and 17 % after 96 hours. The only statistically significant effect was the reduction of biomass after 96 hours. Thus, the 72 hours E_bC_{50} and E_rC_{50} were > 0.7314 mg/L.

Conclusion: 72 hours E_bC_{50} and E_rC_{50} > 0.73 mg/L, 72 hours NOEC ≥ 0.73 mg/L based on initial measured concentration

Reference: Sowig P., Weller O., Gosch H. (1999ae): Algal growth inhibition - *Navicula pelliculosa* Fenoxaprop-P-ethyl substance, technical Code: AE F046360 00 1C97 0002. Report No. CE98/107

Test guideline: OECD 201; US EPA § 123-2
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 88.1 w/w, 95.8 % w/w sum of (D+) and (L-)-enantiomers, batch no.: not stated

Material and methods:
A test on growth inhibition of *Navicular pelliculosa* was performed with Fenoxaprop-P-ethyl under static conditions.
The algal cultures (1 x 10^4 cells/ml in synthetic media) were exposed to five nominal concentrations: 1.0, 1.8, 3.2, 5.6, and 10 mg/L as well as to one dilution and one solvent control (acetone). The test samples were incubated for up to 96 hours under static conditions, at temperatures from 24.1 – 25.1 °C, pH 7.5 – 8.0, 7.5 – 8.2 mg/L oxygen content and continuous illumination. Cell densities were determined by cell counts (sample volume: 5 x 1 mm^2 x 0.1 mm in a counting chamber) under microscope. The calculation of test substance inhibiting the growth (biomass and growth rate) was done separately for each treatment in comparison to control using statistical software. Chemical analyses of Fenoxaprop-P-ethyl (extracted and dissolved) and the corresponding free acid were conducted for all treatment levels at the start and end of the testing.

Findings:
Measured concentrations of extracted Fenoxaprop-P-ethyl and the corresponding free acid in fresh and old solution were in the range of 61.1 – 95.9 % and 80.3 – 104.8 % of nominal, respectively. The mean measured values over the time of exposure ranged from 70.7 – 100.4 % of nominal. Concentration of dissolved test substance (sum of AE F046360 + AE F053022) were 0.72, 1.7, 2.53, 2.9 and 6.31 mg/L. Calculations of biological endpoints based on values of dissolved test substance (sum of AE F046360 + AE F053022).
No significant inhibition of biomass and growth rate were observed in concentration up to 1.8 mg/L, therefore the NOEC was 1.7 mg/L based on dissolved test substance. The 72 h E_bC_{50} and E_rC_{50} were calculated to be 2.38 mg/L (95% CL 1.7 – 2.53 mg/L) and 4.26 mg/L (95% CL 2.9 – 6.31 mg/L) and the 96 h E_bC_{50} and E_rC_{50} were 2.46 mg/L (95% CL 1.7 – 2.53 mg/L) and > 6.31 mg/L.

Conclusion: 72 h E_bC_{50}: 2.38 mg/L, E_rC_{50}: 4.26 mg/L, 96 h E_bC_{50}: 4.26 mg/L, E_rC_{50} > 6.31 mg/L, NOEC: 1.7 mg/L; based on mean measured concentration of dissolved test substance (sum of AE F046360 + AE F053022)

Reference: Young B.M. & Ruff D.F. (1999h): Effect to *Skeletonema costatum* (Marine Diatom) in a Growth Inhibition Test Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 00 1C97 0002. Report No. BM98W516

Test guideline: OECD 201; US EPA §122-2
GLP: yes
Test item: Fenoxaprop-P-ethyl, techn.: 88.1 w/w, 95.8 % w/w sum of (D+) and (L-)-enantiomers, batch no.: 1+2/86

Material and methods:
A test on growth inhibition of *Skeletonema costatum* was performed with Fenoxaprop-P-ethyl under static conditions. The algal cultures (1 x 10^4 cells/ml in MAA media) were exposed to five nominal concentrations: 0.19, 0.38, 0.75, 1.5 and 3 mg/L as well as to one dilution and one solvent control (acetone). The test samples were incubated for up to 96 hours under static conditions at temperatures from 20.4 – 21.8 °C, pH 7.9 – 9.1, 6.9 – 9.6 mg/L oxygen content and continuous illumination. The salinity was between 29 and 30 ‰ in the course of the study. The cell density was determined by cell counts with a haemocytometer under microscope. The inhibition of biomass and growth rate was calculated separately for each treatment in comparison to pooled controls. Chemical analyses of Fenoxaprop-P-ethyl and its acid Fenoxaprop-P (AE F088406) were conducted for all treatment levels at the start and the end of testing.

Findings:
Measured concentrations of Fenoxaprop-P-ethyl at test initiation were 0.212, 0.38, 0.823, 1.84 and 3.66 mg/L (100 – 123 % of nominal) and no AE F088406 was detected. At end of testing only the degradation product AE F088406 was found. Therefore all results are based on initial measured concentration.
No significant inhibition of biomass and growth rate was observed at concentrations up to 0.38 mg/L, therefore the NOEC was 0.38 mg/L. At highest concentration (3.7 mg/L) the inhibition of biomass and growth rate in comparison to the pooled controls was 42 % and 34 % after 72 hours and 12 % and 7 % after 96 hours. Thus, the E_bC_{50} and E_rC_{50} were > 3.7 mg/L.

Conclusion: 72 and 96 hours E_bC_{50} and E_rC_{50} > 3.7 mg/L, NOEC 0.38 mg/L

Comment: The change in pH of test media from start to end of testing is > 1 and was attributed to the rapid growth of diatoms, which consume CO_2 creating an alkaline environment. But this is considered unlikely to have any adverse influence on the results or quality of the investigation. Study considered acceptable.

Reference: Christ, M.T. & Ruff, D.F.(1997b): Toxicity to Duckweed (*Lemna gibba*), in a Static Renewal System; Fenoxaprop-P-ethyl Technical 88.1% w/w Code AE F046360 00 1C97 0002. Report No. BM97W502

Test guideline: USEPA § 122-2
GLP: yes
Test item: Fenoxaprop-P, techn.: 88.1% w/w, sum of (D+) and (L-)-enantiomers: 95.8 % w/w, batch no.: 1+2/86

Material and methods:
The toxicity of Fenoxaprop-P-ethyl to the duckweed *Lemna gibba* was assessed in a static renewal system (solution renewals on day 4, 7 and 11) over a 14 days exposure period. Three replicates of aquatic plants (15 fronds per replicate) in 20X-AAP media were exposed to five nominal concentrations: 0.40, 0.66, 1.1, 1.8 and 3 mg/L as well as to a dilution control and a solvent control (acetone). Environmental conditions throughout the study were monitored: 24.7 – 25.1 °C, pH 7.0 – 9.4, 71 – 101 % oxygen saturation, specific conductivity of 1500 – 1600 µmhos/cm and continuous illumination with an intensity of 4000 – 5600 lux.
Growth and abnormal appearance of fronds was observed on day 2, 4, 9, 11 and 14 and inhibition of frond growth (biomass and growth rate) was calculated relative to pooled control

data. Chemical analyses of Fenoxaprop-P-ethyl were conducted on day 0 and day 7 of each freshly prepared test solution and old samples were analysed on day 4, day 11, and day 14.

Findings:
Mean measured concentrations of fresh solutions were 0.54, 0.51, 1.19, 1.53, and 2.76 mg/L test item corresponding to 77 to 135% of the nominal concentrations. No Fenoxaprop-P-ethyl was found in any old treatment vessels.
On day 7 and 14 no significant inhibition of frond growth (biomass: AUC) and fronds growth rate was observed in any of the treatments compared to the pooled control data. Therefore the E_bC_{50} and E_rC_{50}> 2.76 mg/L, NOEC and LOEC ≥ 2.76 mg/L, based on initial measured concentration.

Conclusion: 7 d and 14 d E_bC_{50} and E_rC_{50}> 2.76 mg/L, NOEC ≥ 2.76 mg/L based on initial measured concentration

Reference: Heusel R. (1993dx): Effect to *Selenastrum capricornutum* (green algae) in an algal assay bottle test (method EPA) Fenoxaprop-P substance, technical (Hoe 088406 00 ZC93 0001). Report No. CE92/003

Test guideline: EPA 540/9-86-134, 1986
GLP: yes
Test item: Fenoxaprop-P (AE F088406), 95.6 % w/w, batch no: not stated

Material and methods:
The effects of the metabolite AE F088406 to the unicellular green alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in an algal assay bottle test were studied. The algal cultures (10^4 cells/mL) were exposed to nine nominal concentrations: 1.0, 1.8, 3.2, 5.6, 10, 18, 32, 56 and 100 mg/L as well as to one dilution and one solvent control (acetone). The test samples were incubated for up to 120 hours under static conditions, at temperatures from 25.0 –25.6 °C, pH 8.1 ± 0.7 and continuous illumination. Cell densities were determined by cell counts (5 x 1 mm^2 x 0.1mm in a counting chamber) under microscope. The calculation of inhibition of the growth (biomass: area under the curve) were done separately for each treatment in comparison to the control. Chemical analyses of AE F088406 for the nominal test concentrations of 1.0, 10 and 100 mg/L were conducted on test days 0, 2 and 5.

Findings: Based on chemical analyses the measured concentrations varied between 90.3 and 96.5% and 64.5 and 86.1% of nominal at initiation and termination of the study. The mean concentrations over 5 days ranged from 76.2 to 92.7 % nominal for all concentration levels. The endpoints are reported as nominal and mean measured concentrations. All mean measured concentrations are based on 76.2 % of nominal concentration (lowest value of measured concentrations).
The algal biomass was significantly inhibited at test concentrations ≥ 32 mg/L, thus the NOEC was 18 mg/L (nominal) and 13.7 mg/L (mean measured). The 72 hours and 120 hours E_bC_{50} was estimated to be 45.9 mg/L (95 % CL 32 – 56 mg/L) and 44.9 mg/L (95 % CL 32 - 56 mg/L) based on nominal concentration and 35 mg/L (95 % CL 24.4 – 42.7 mg/L) and 34.2 mg/L (95 % CL 24.4 – 42.7 mg/L) based on mean measured concentrations.

Conclusion: 72 hour E_bC_{50}: 45.9 mg/L (nominal), 35.0 mg/L (measured) and NOEC: 18 mg/L (nominal), 13.7 mg/L (measured)

In summary: Due to low water solubility (0.73 mg/L) and hydrolytic instability of test substance under the test conditions, result of algae toxicity studies varied with different species and test conditions. Indication of algae toxicity consisted of 72 h ErC50 of > 0.73 mg/L or 4.26 mg/L and EC50 of 0.54 mg/L or 2.38 mg/L, based on measured dissolved concentration of racemic mixture. NOEC values ranged from 0.05 mg/L (120 h) and 0.38 mg/L (marine species, 72 h). According to the "Guidance on C&L (ECHA, 2010), if the test data are reliable, classification shall be justified based on the lowest EC50 available. Hence, referring to the results of algae toxicity studies, the Acute Aquatic Hazard Category 1 with M-factor 1 and Chronic Aquatic Hazard Category 2 are assigned for -P-ethyl, techn.: 97.4 % w/w sum of (D+) and (L-)-enantiomers.

During the Fenoxaprop-P-ethyl was hydrolysed to Fenoxaprop-P, low toxicity (Ec50 >10 mg/L and NOEC > 1 mg/L), algae toxicity of Fenoxaprop-P has no relevance for this dossier.

5.4.4 Other aquatic organisms (including sediment)

Reference: Memmert, U. (2000a): Effects of Fenoxaprop-P-ethyl, substance technical; code: AE F046360 on the development of sediment-dwelling larvae of *Chironomus riparius* in a water-sediment system. Report No: Study project No. 732194

Test guideline: Draft BBA Guideline (1995); Draft OECD 219
GLP: yes
Test item: Fenoxaprop-P-ethyl, tech.: 96.2 % w/w, sum of (D+) and (L-)-enantiomers: 99.4 % w/w, batch no.: AALC00028; ^{14}C-Fenoxaprop-P-ethyl > 98 % (TLC), batch no.: Z 28084-0

Material and methods:
The toxicity of Fenoxaprop-P-ethyl (mixture of radiolabelled and unlabelled test item) to sediment dwelling larvae of *Chironomus riparius* was investigated in a 26 day static sediment toxicity test. For each treatment level (0.025, 0.050, 0.1, 0.2 and 0.4 mg/L), control and solvent control, three weeks before inserting test organism test vessels were filed with approximately 2 cm artificial sediment (artificial soil according to OECD 207, ref. 2) and 2000 mL reconstituted water (~ 15 cm layer). 25 first instar larvae were applied to each test vessel (four replicates per treatment level). One day after adding the larvae test substance was applied to the water column (simulating spray drift or overspray). During the study larvae were fed with fish food three times a week until day 19 when all larvae had emerged. Fully emerged male and female midges were counted daily from day 10 on after application. The test parameters emergence rate and development time/rate were calculated for each test vessel according to the test guideline.
Additionally test vessels for chemical analysis of Fenoxaprop-P-ethyl and its metabolites (two for the lowest, middle and highest concentration, one for solvent control) were prepared. Samples were taken on day 0, 7 and 26, and radioactivity was analysed in water, pore water and sediment.
For the test period the following water quality parameters were reported: Temperature 19.0 – 20.3°C), pH 6.6 – 7.6, and oxygen content 5.0 – 9.0 mg/L.

Findings: Analytical results: Measured initial concentrations in the water column of all treatment levels ranged from 89.3 – 163.6 % of nominal. At the two highest concentration levels (both above the water solubility limit of the test substance) a film of applied test item was noted on the water surface and had disappeared the next day (possibly due to degradation processes). At all test concentrations the radioactive residue in the water column had

decreased nearly constantly to about 20 – 40 % at test termination. The [14C]-concentration in the pore water was rather low (< 1.1 % applied) during the study in contrast to the sediment, where the [14C]-concentration had continuously increased during the test period. About half of the radioactivity in sediments was bound to sediment and was not extractable. Fenoxaprop-P-ethyl had degraded rapidly in the water-sediment system, after 7 days it could not be detected in any compartment. The main metabolite was Fenoxaprop-P, accounting for up to 73 – 86 % of the applied radioactivity on day 7. On day 26 the concentrations of this metabolite had decreased to approximately 23 – 49 % of initial radioactivity.
All reported biological results are based on nominal initial concentrations in the water column.
Biological results: After 26 days up to 0.2 mg/L nominal concentration the emergence rate (pooled males and females midges) was not significantly lower than in control. At 0.4 mg/L emergence rate was slightly lower than in the control, but statistically not significant. In the emergence rate between male and female midges No differences were observed. The development rate was significantly reduced at 0.4 mg/l. Therefore the 26 d NOEC, based on most sensitive endpoint development rate was estimated to be 0.2 mg/L. The LOEC, based on slightly reduced emergence rate and lower development rate, was 0.4 mg/L.

Conclusion: 26 d NOEC (development rate): 0.2 mg/L, LOEC: 0.4 mg/L based on nominal concentration.

Summary and discussion: Acute (short-term) aquatic toxicity:

Data element: Acute (short-term) aquatic toxicity of the active substance Fenoxaprop-P-ethyl Generally expressed in terms of LC50 or EC50 (mg/L)					
	L(E)C50 [mg/L]		Test guideline / design	GLP (y/n)	Reliability
Fish (96 hr LC50):					
Oncorhynchus mykiss Rainbow trout	0.39		OECD 203, US EPA §72-1	y	n
Oncorhynchus mykiss Rainbow trout	0.46		US EPA §72-1	y	n
Lepomis macrochirus Bluegill sunfish	**0.19**		OECD 203, US EPA §72-1	y	y
Crustacea (48 hr EC50):					
Daphnia magna	> 1.06		OECD 202, US EPA §72-	y	n
Algae and water plants: (ErC50)					
Pseudokirchn. subcapitata Green alga	0.54 0.37	biomass	EPA 540/9-86-134	y	n
Anabaena flos-aquae Blue-green alga	>0.73	biomass growth rate	OECD 201, US EPA §122-2	y	n
Lemna gibba Duckweed	> 2.76	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.					

Data element: Acute (short-term) aquatic toxicity of the degradation product Fenoxaprop-P Generally expressed in terms of LC50 or EC50 (mg/L)					
	L(E)C50 [mg/L]		Test guideline / design	GLP (y/n)	Reliability
Fish (96 hr LC50):					
Oncorhynchus mykiss Rainbow trout	> 72.2		OECD 203, US EPA §72-1	y	n
Algae and water plants: (ErC50)					
Pseudokirchn. subcapitata Green alga	35.0 **34.2**	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.					

Summary and discussion: Chronic (long-term) aquatic toxicity

Data element: Chronic (long-term) aquatic toxicity of the active substance Fenoxaprop-P-ethyl Generally expressed in terms of NOEC (mg/L)					
	NOEC [mg/L]		Test guideline / design	GLP (y/n)	Reliability
Fish (NOEC):					
Oncorhynchus mykiss Rainbow trout	0.1	mortality weight [1)]	OECD 204	y	n
Oncorhynchus mykiss Rainbow trout (ELS)	**0.036** ≥ 0.1	mortality hatchability	US EPA §72-4	y	y
Crustacea (21 d NOEC,):					
Daphnia magna	0.22	mortality reproduction	OECD 202, Part II 4	y	n
Algae and water plants: (NOEC)					
Pseudokirchn. subcapitata Green alga	- 0.05	biomass	OECD 201	y	n
Skeletonema costatum Diatom (marin)	0.38	biomass growth rate	OECD 221 (Draft October 2000)	y	n
Other aquatic organisms (26 d NOEC)					
Chironomus riparius Midge	0.2	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)]toxicitiy values based on mean measured concentration of dissolved test substance (sum of AE F046360 = Fenoxaprop-P-ethyl (D-enantiomer)+ AE F053022 = Fenoxaprop (racemic mixture))

Summary and discussion: Chronic (long-term) aquatic toxicity

Data element: Chronic (long-term) aquatic toxicity of the degradation product Fenoxaprop-P Generally expressed in terms of NOEC (mg/L)				
	NOEC [mg/L]	Test guideline / design	GLP (y/n)	Reliability
Fish (NOEC):				
Oncorhynchus mykiss Rainbow trout	≥ 3.2	OECD 215	y	n
Crustacea (21 d NOEC,):				
Daphnia magna Waterflea	**1.0**	OECD 211, US EPA §72-4	y	y
Algae and water plants: (NOEC)				
Pseudokirchn. subcapitata Green alga	13.7	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.				

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

As comparison of classification criteria on environment hazards according to the 2nd ATP to Regulation (EC) No 1272/2008 (CLP) and Directive 67/548/EEC (DSD) for Fenoxaprop-P-ethyl is summarised in Table 193.

Table 193: Summary for Fenoxaprop-P-ethyl

Endpoint	**Classifcation Criteria (criteria in bold)**		**Conclusion for Fenoxaprop-P-ethyl**
	CLP (2nd ATP)	**DSD**	
Degradation			
	No data are available for readily biodegradability. Ultimate degradation to a level of **70 % within 28 days** could not be shown in abiotic and biotic aquatic degradation studies. Available biotic degradation studies indicate a fast primary degradation, but due to relevance for classification and labelling of the main degradation product Fenoxaprop-P a non rapid degradation is proposed.		The classification as **R53** according to Directive 67/548/EEC is based on the fact that the active substance is not considered as ready biodegradable/rapid degradable.
Bioaccumulation			
Criteria LogKow	**Log K_{ow} is < 4** Fenoxaprop-P-ethyl Log K_{ow} = 4.58	**Log K_{ow} is < 3** Fenoxaprop-P-ethyl Log K_{ow} = 4.58	The measured BCF is in the range of 280 and 338 and is above the classification criteria of 100 (DSD) and below the classification criteria of 500 (CLP). Therefore depending on classification criteria Fenoxaprop-P-ethyl is considered to have **a bioaccumulation potential according to DSD** resulting in a classification as **R53** (Directive 67/548/EEC) **and a low bioaccumulation potential according to CLP.**
Criteria BCF	**BCF < 500** Fenoxaprop-P-ethyl BCF is in the range of 280 and 338	**BCF < 100** Fenoxaprop-P-ethyl BCF is in the range of 280 and 338	
Acute aquatic toxicity			
Criteria	**$LC/EC_{50} \leq 1$ mg/L**		Fenoxaprop-P-ethyl is very toxic to Bluegill sunfish *Lepomis macrochirus* with an EC50 of 0.19 mg/L and fulfills the criteria for the proposed classification as **R50** according to Directive 67/548/EEC and the criteria for the proposed classification as **H400** according to Regulation EC 1272/2008. **A M-factor of 1** is applicable based on $0.1 < L(E)C_{50} \leq 1$ mg/l.
	Lepomis macrochirus EC50 = 0.19 mg/L		
Chronic aquatic toxicity			
Criteria	**For non rapidly degradable substances: 0.01 <NOEC ≤0.1 mg/l**		Fenoxaprop-P-ethyl is chronic toxic to fish *Oncorhynchus mykiss* with a NOEC of 0.03628 mg/L.. Therefore

Endpoint	Classifcation Criteria (criteria in bold)			Conclusion for Fenoxaprop-P-ethyl
	CLP (2nd ATP)		**DSD**	
	Oncorhynchus mykiss	NOEC(91d) = 0.03628 mg/L		Fenoxaprop-P-ethyl fulfills the criteria for the proposed classification as **H410** according to Regulation EC 1272/2008. A M-factor of 1 is applicable based on 0.01 <NOEC ≤0.1 mg/l.

Table 194: Summary for the degradation product Fenoxaprop-P regarding relevance for classification and labelling

Endpoint	Classifcation Criteria (criteria in bold)		Conclusion for degradation product Fenoxaprop-P
	CLP (2nd ATP)	**DSD**	
Acute aquatic toxicity			
Criteria	**LC/EC_{50} ≤ 1 mg/L**	**LC/EC_{50} ≤ 100 mg/L**	The degradation product fenoxaprop-P is harmful to Green alga Pseudokirchn. subcapitata with an EC50 (only biomass data are available) of 34.2 mg/L and fulfills the criteria for the proposed classification as **R53** according to Directive 67/548/EEC . No classification is proposed according to Regulation EC 1272/2008.
	Pseudokirchn. subcapitata E_bC50 (only biomass data are available) = 34.2 mg/L.		
Chronic aquatic toxicity			
Criteria	**For rapidly/non rapidly degradable substances: 0.1 <NOEC ≤1 mg/l**		The degradation product Fenoxaprop-P is chronic toxic to daphnids (*Daphnia magna*) with a NOEC = 1 mg/L. Therefore depending on rapid or non rapid degradability Fenoxaprop-P fulfills the criteria for the proposed classification as **H412** (rapid degradable) **or H411** (non rapid degradable) according to Regulation EC 1272/2008.
	Daphnia magna NOEC(21d) = 1 mg/L		

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Conclusion of environmental classification according to Directive 67/548/EEC

Fenoxaprop-P-ethyl should be classified Dangerous for the Environment with the following risk and safety phrases:

N Dangerous for the Environment

R50 Very toxic to aquatic organisms

R53 May cause long term effects in the environment

Conclusion of environmental classification according to Regulation EC 286/2011 (2nd ATP to EC 1272/2008)

Based on the CLP Regulation, Fenoxaprop-P-ethyl should be classified as:

Classification categories	aquatic environmental hazard **acute category 1** aquatic environmental hazard **chronic category 1**	
GHS Pictogram		
Signal Word	Warning	
Hazard Statement	H400 H410	'Very toxic to aquatic life', 'Very toxic to aquatic life with long lasting effects'
M-factor (acute/chronic)	1	

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	0.1	mortality	OECD 204	y	n

Rainbow trout	(n)	weight [1)]	flow-through		
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%

6 OTHER INFORMATION

Bridging statement for read across between fenoxaprop-P-ethyl and fenoxaprop-ethyl

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.

Physchem properties, toxicological, environmental fate properties and environmental hazard assessments of this CLH report are based on studies and summaries of the Draft Assessment Report and its addenda

7 REFERENCES

7.1 Physico-chemical properties

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Asshauer J.	1986	Analytical Certificate Code: AE F053022 00 1B98 0001 Generated by: Hoechst AG GBC-Analytisches Laboratorium Document No: A33108 GLP / GEP: No Unpublished Confidential Information	Y	BCS
Bittner P., Rexer K.	1999cg	Determination of the density Fenoxaprop-P-ethyl substance, pure, Code: AE F046360 00 1B98 0002 Generated by: Hoechst Schering AgrEvo GmbH; Forschung Formulierung, Frankfurt Document No: C004890 GLP / GEP Yes Unpublished	Y	BCS
Buerkle L.W.	1999i	Estimation of the reaction with photochemically produced hydroxyl radicals in the atmosphere, Code: AE F046360 Generated by: Hoechst Schering AgrEvo GmbH; Entwicklung Umweltforschung, Frankfurt Document No: C003258 GLP / GEP No Unpublished	Y	BCS
Cichy M., Perez-Diaz C.	1999o	Analytical profiles of five production batches, Fenoxaprop-P-ethyl, technical grade, active ingredient, Code: AE F046360 Generated by: Hoechst Schering AgrEvo GmbH; Produktanalytik, Frankfurt Document No: C003613 GLP / GEP Yes Unpublished **Confidential Information**	Y	BCS
ECHA	2010	Guidance on the Application of the CLP Criteria	N	Published
Goerlitz G., Eyrich U.	1985a	Partition coefficient octanol/water Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A31446 GLP / GEP Yes Unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Goeritz G., Eyrich U	1987ad	Solubility in water Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A36178 GLP / GEP analog*) Unpublished	Y	BCS
Goerlitz G., Rutz U.	1989a	Solubility in organic solvents Code: Hoe 046360 Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A40979 GLP / GEP analog*) Unpublished	Y	BCS
Haase D., Rexer K.	2000j	Determination of the colour, Fenoxaprop-P-ethyl substance, technical, Code: AE F046360 00 1D96 0002 Generated by: Aventis CropScience GmbH, DEU; Formulierung Forschung & Entwicklung, Frankfurt Document No: C008079 GLP / GEP No Unpublished	Y	BCS
Haase D., Rexer K.	2000k	Determination of the odour, Fenoxaprop-P-ethyl substance, technical, Code: AE F046360 00 1D96 0002 Generated by: Aventis CropScience GmbH, DEU; Formulierung Forschung & Entwicklung, Frankfurt Document No: C008078 GLP / GEP No Unpublished	Y	BCS
Haase D., Rexer K.	2000l	Determination of the physical form Fenoxaprop-P-ethyl substance, technical, Code: AE F046360 00 1D96 0002 Generated by: Aventis CropScience GmbH, DEU; Formulierung Forschung & Entwicklung, Frankfurt Document No: C008077 GLP / GEP No Unpublished	Y	BCS
Heinrich, Rexer K.	1987c	Decomposition point of Hoe 046360 substance, technical Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A35719 GLP / GEP No Unpublished	Y	BCS
Heinrich, Rexer K.	1988k	Boiling point of Hoe 046360 substance, pure Generated by: Hoechst AG; GB C / Forschung Formulierung	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
		Document No: A38754 GLP / GEP No Unpublished		
Heinrich, Rexer K.	1988m	Odour of Hoe 046360 substance, pure Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A38752 GLP / GEP No Unpublished	Y	BCS
Heinrich, Rexer K.	1988n	Colour of Hoe 046360 substance, pure Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A38751 GLP / GEP No Unpublished	Y	BCS
Heinrich, Rexer K.	1988o	Physical form of Hoe 046360 substance, pure Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A38756 GLP / GEP Unpublished	Y	BCS
Hoffmann H.	2000aa	Explosive properties Fenoxaprop-P-ethyl substance, technical Code: AE F046360 00 1D96 0002 Generated by: Aventis Research & Technologies GmbH & Co KG, DEU; Analytical Technologies, Frankfurt Aventis CropScience GmbH, DEU; Forschung Formulierung & Entwicklung, Frankfurt Document No: C009472 GLP / GEP Yes Unpublished	Y	BCS
Hoffmann H.	2000ab	Auto-flammability (solids - determination of relative self-ignition temperature) Fenoxaprop-P-ethyl, substance, technical, Code: AE F046360 00 1D96 0002 Generated by: Aventis Research & Technologies GmbH & Co KG, DEU; Analytical Technologies, Frankfurt Aventis CropScience GmbH, DEU; Forschung Formulierung & Entwicklung, Frankfurt Document No: C009473 GLP / GEP Yes Unpublished	Y	BCS
Hoffmann H.	2000ac	Flammability (solids) Fenoxaprop-P-ethyl substance, technical, Code: AE F046360 00 1D96 0002 Generated by: Aventis Research & Technologies GmbH & Co KG, DEU; Analytical Technologies, Frankfurt	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
		Aventis CropScience GmbH, DEU; Forschung Formulierung & Entwicklung, Frankfurt Document No: C009471 GLP / GEP Yes Unpublished		
Hoffmann H.	2000z	Oxidizing properties Fenoxaprop-P-ethyl substance, technical,Code: AE F046360 00 1D96 0002 Generated by: Aventis Research & Technologies GmbH & Co KG, DEU; Analytical Technologies, Frankfurt Aventis CropScience GmbH, DEU; Forschung Formulierung & Entwicklung, Frankfurt Document No: C009474 GLP / GEP Yes Unpublished	Y	BCS
I. Le Gren	2003a	Fenoxaprop-P-ethyl. pka calculation using a modelling software. AE F046360. Generated by: Document No: C029715 GLP / GEP Yes Unpublished	Y	BCS
Kloeckner C., Weller O.	2000a	Spectral data (UV/VIS, IR, 1H-NMR, 13C-NMR, MS) and molar extinction coefficient, Fenoxaprop-P-ethyl Code: AE F046360 Generated by: Aventis CropScience GmbH, DEU; Produktanalytik, Frankfurt Document No: C008445 GLP / GEP Yes Unpublished	Y	BCS
Rexer K.	2001n	Determination of the surface tension Fenoxaprop-P-ethyl substance technical, Code: AE F046360 00 1D96 0001 Generated by: Aventis CropScience GmbH, DEU; Formulierung Forschung & Entwicklung, Frankfurt Document No: C011094 GLP / GEP No Unpublished	Y	BCS
Roechling, Rexer K.	1987d	Vapour pressure of Hoe 046360 substance, pure Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A42898 GLP / GEP No Unpublished	Y	BCS
Schollmeier M.	1992ao	Calculation of the Henry's constant Fenoxaprop-P-ethyl, Code: Hoe 046360 Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
		Document No: A48206 GLP / GEP Unpublished		
Schollmeier M., Eyrich U., Uhl A.	1992a	Determination of the partition coefficient n-octanol/water by HPLC (according to OECD Guideline #117) Hoe 046360, Code: Hoe 046360 00 ZB98 0001 Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A49082 GLP / GEP Yes Unpublished	Y	BCS
Schwab W.	1993c	Photodegradation in surface water, sterile buffer and distilled water (amendment to report CB91/035, A51353) of Fenoxaprop-P-ethyl, Hoe 046360-^{14}C Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A51426 GLP / GEP Yes Unpublished	Y	BCS
Schwab W.	1993e	Photodegradation in surface water, sterile buffer and distilled water of Fenoxaprop-P-ethyl, Hoe 046360-^{14}C Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A51353 GLP / GEP Yes Unpublished	Y	BCS
Smeykal H.	1999w	Melting point / melting range Fenoxaprop-P-ethyl, substance, pure, Code: AE F046360 00 1B99 0003 Generated by: Aventis Research & Technologies GmbH & Co KG, DEU; Analytical Technologies, Frankfurt Hoechst Schering AgrEvo GmbH; Forschung Formulierung, Frankfurt Document No: C004110 GLP / GEP Yes Unpublished	Y	BCS
Tognucci A.	1999a	Determination of the partition coefficient (n-octanol/water) of AE F054014 Generated by: RCC Ltd., Itingen, CHE; Environmental Chemistry & Pharmanalytics Division Hoechst Schering AgrEvo GmbH; Entwicklung Umweltforschung, Frankfurt Document No: C003620 GLP / GEP Yes Unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
van der Gaauw A.	2002a	(^{14}C)-Fenoxaprop-ethyl: Hydrolysis at five different pH values Code: AE F046360 Generated by: RCC Ltd., Itingen, CHE; Bayer CropScience GmbH, DEU; Document No: C028353 GLP / GEP Yes Unpublished	Y	BCS
Weilbaecher R., Goerlitz G.	1998a	Certificate of Analysis No. AZ 07576 Generated by: Hoechst Schering AgrEvo GmbH; Produktanalytik Document No: C001123 GLP / GEP No Unpublished	Y	BCS
Weller O.	1990d	Solubility in water (addendum to report CP 050/87) Code: Hoe 046360 Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A43650 GLP / GEP Yes Unpublished	Y	BCS
Wolf R.	2004	GLP-certificates Code: Fenoxaprop-p-ethyl, AE F046360 Generated by: Bayer CropScience AG, Monheim, DEU Document No: C045431 GLP / GEP: No Unpublished	Y	BCS
Wolf R., Le Gren I.	2004	Fenoxaprop-P-ethyl (AE F046360) Additional Information and clarification to section 1 (AnnexII and III), physical/chemical properties Statement. Code: AE F046360 / AE F046360 24 EW14 A7 Generated by: Bayer CropScience S.A., FRANCE Doc.No.:C044472 GLP / GEP No Unpublished	Y	BCS

7.2 Human health hazard assessment

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Annex II Data and Information					
Baeder C. et al.	Annex II, 5.6.2	1982a	An oral embryotoxicity study of Hoe 33171 0H AT204 in Wistar rats Hoechst, Report No. 613/82 Doc. No. A26170 GLP unpublished	Y	BCS
Baeder C. et al.	Annex II, 5.6.2	1982b	An oral embryotoxicity study of Hoe 33171 active ingredient (technical grade, Code: Hoe 33171 0H AT204) in Himalayan rabbits Hoechst, Report No. 667/82 Doc. No. A24756 GLP unpublished	Y	BCS
Baeder C. et al.	Annex II, 5.6.2	1983	Hoe 33171 – active ingredient technical (Code: Hoe 033171 0H ZC96 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration Hoechst, Report No. 83.0516 Doc. No. A29690 GLP unpublished	Y	BCS
Baeder C. et al.	Annex II, 5.6.2	1985a	Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Wistar rats following oral administration Hoechst, Report No. 85.1239 Doc. No. A33810 GLP unpublished	Y	BCS
Baeder C. et al.	Annex II, 5.6.2	1986a	Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration Hoechst, Report No. 86.0488 Doc. No. A33302 GLP unpublished	Y	BCS
Baeder C. et al.	Annex II, 5.6.2	1986b	Hoe 033171 – active ingredient technical (Code: Hoe 033171 0H ZD98 0001) Testing fo embryotoxicity and effects on postnatal development in Wistar rats following oral administration Hoechst, Report No. 86.0133 Doc. No. A35783 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Banduhn N.	Annex II, 5.4.2	1986	Mouse micronucleus test with Hoe 033171 substance technical grade RCC Project No. 066813 Doc. No. A34294 GLP unpublished	Y	BCS
Becker H. et al.	Annex II, 5.6.1	1986a	Multiple generation study on Hoe 033171 substance technical grade (Code: Hoe 033171 0H ZD97 0001) in rats, Report Part I RCC Project No. 034896 Doc. No. A32781 GLP unpublished	Y	BCS
Becker H. et al.	Annex II, 5.6.1	1986b	Multiple generation study on Hoe 033171 substance technical grade (Code: Hoe 033171 0H ZD97 0001) in rats, Report Part III (Pathology report F1 parents) RCC Project No. 034896, Part III Doc. No. A33840 GLP unpublished	Y	BCS
Brunk et al.	Annex II, 5.3.1	1980	Repeated-dose (30 days) oral toxicity study of Hoe 33171 0H AT 203 in Beagle dogs (Range-finding-test) Hoechst, Report No. 165/80 Doc. No. A25657 GLP unpublished	Y	BCS
Brunk et al.	Annex II, 5.3.2	1981a	Repeated-dose (3 month) oral toxicity study of Hoe 33171 0H AT 204 in dogs Hoechst, Report No. 674/81 Doc. No. A24131 GLP unpublished	Y	BCS
Brunk et al.	Annex II, 5.3.2	1984	Toxicological testing of Hoe 33171 – active ingredient technical by repeated oral administration to beagle dogs for one year Hoechst, Report No. 674/81 Doc. No. A29692 GLP unpublished	Y	BCS
Brunk et al.	Annex II, 5.5	1985	Toxicological testing of Hoe 33171 – active ingredient technical (Code: Hoe 033171 0H ZC94 0001) by repeated oral administration to beagle dogs for 2 years Hoechst, Report No. 85.0073 Doc. No. A31854 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Bürkle W.L. et al.	Annex II, 5.1	1985	Hoe 033171-(dioxyphenyl-1-^{14}C). Metabolism in rats orally administered at two doses, 2 and 10 mg/kg body weight Hoechst, Report No. (B) 3/85 Doc. No. A30377 GLP unpublished	Y	BCS
Cifone M.A.	Annex II, 5.4.1	1986	Evaluation of Hoe 046360 – substance technical in the rat primary hepatocyte unscheduled DNA synthesis assay Hazelton Biotechnologies Company, Project No. 20991 Doc. No. A34916 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2.1	1985a	Hoe 046360 – active ingredient technical. Testing for acute oral toxicity in the male and female NMRI mouse Hoechst, Report No. 85.1176 Doc. No. A37268 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2.2	1985b	Hoe 046360 – active ingredient technical. Testing for acute dermal toxicity in the male and female Wistar rat Hoechst, Report No. 85.1175 Doc. No. A36023 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2	1985c	Hoe 046360 – active ingredient technical. Testing for acute intraperitoneal toxicity in the male and female Wistar rat Hoechst, Report No. 85.1197 Doc. No. A37244 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2.4	1985d	Hoe 046360 – active ingredient technical. Testing for primary dermal irritation in the rabbit Hoechst, Report No. 85.1125 Doc. No. A36061 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2.5	1985e	Hoe 046360 – active ingredient technical. Testing for primary eye irritation in the rabbit Hoechst, Report No. 85.1215 Doc. No. A36022 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Diehl K.-H., Leist K.-H.	Annex II, 5.2.6	1986a	Hoe 046360 – active ingredient technical. Testing for sensitizing properties in the Pirbright-White guinea pig in a maximisation test Hoechst, Report No. 86.0003 Doc. No. A37243 GLP unpublished	Y	BCS
Diehl K.-H., Leist K.-H.	Annex II, 5.2.6	1986b	Hoe 046360 – active ingredient technical. Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Hoechst, Report No. 86.0466 Doc. No. A36040 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.3.2	1981	Repeated-dose (3 months) oral toxicity study of the active substance Hoe 33171 administered in the feed to rats Hoechst, Report No. 695/81 Doc. No. A35788 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1983a	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0 H AS 201). Chronic feeding study in rats (Interim killing after 6 months) Hoechst, Report No. 24/83 Doc. No. A30803 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1983b	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0 H AS 201). Chronic feeding study in rats (Interim killing after 12 months) Hoechst, Report No. 83.0613 Doc. No. A29693 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1983c	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0H AS 201). Chronic feeding study in mice (interim killing after 12 months) Hoechst, Report No. 83.0654 Doc. No. A29695 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Donaubauer et al.	Annex II, 5.5	1984a	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0 H AS 201). Chronic feeding study (24 months) in rats Hoechst, Report No. 84.0632 Doc. No. A30807 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1984b	Supplement to Report No. 83.0654. Hoe 33171 – active ingredient technical. Chronic feeding study in mice (interim killing after 12 months). Determination of hepatic enzyme levels Hoechst, Report No. 84.0782 Doc. No. A29696 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1985a	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0 H AS 201). Combined chronic toxicity and carcinogenicity study in rats (24 and 28 months feeding studies). Summary and evaluation of results Hoechst, Report No. 85.0688 Doc. No. A31880 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1985b	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0 H AS 201). Combined chronic toxicity and carcinogenicity study in rats. Part II: Carcinogenicity study (28-month feeding study) Hoechst, Report No. 85.0682 Doc. No. A31878 GLP unpublished	Y	BCS
Donaubauer et al.	Annex II, 5.5	1985c	Hoe 33171 – active ingredient technical. (Code: Hoe 33171 0H AS 201). Carcinogenicity study in mice (24-month feeding study) Hoechst, Report No. 85.0046 Doc. No. A30816 GLP unpublished	Y	BCS
Ebert E. et al.	Annex II, 5.3.3	1988	Hoe 046360 - active ingredient technical. Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rats Hoechst, Report No. 88.1774 Doc. No. A40800 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Eckert H.G. Kellner H.-M.	Annex II, 5.1	1987	Hoe 046360-^{14}C. Kinetics in the rat after single oral administration of 10 mg/kg body weight Hoechst, Report No. 01-L42-0514-87 Doc. No. A37448 GLP unpublished	Y	BCS
Edwards C.N.	Annex II, 5.4.1	1986a	Forward mutation in schizosaccharomyces pombe P1. Test substance: Hoe 046360 Substance technical (Code: Hoe 046360 0H ZC96 0002) LSR-RTC, Report No. 157011-M-01986 Doc. No. A34056 GLP unpublished	Y	BCS
Edwards C.N.	Annex II, 5.4.1	1986b	Mitotic gene conversion in S. cerevisiae D4. Test substance: Hoe 046360 substance technical LSR-RTC, Report No. 157010-M-01886 Doc. No. A34058 GLP unpublished	Y	BCS
Ehling G., Leist K.-H.	Annex II, 5.2.1	1992	Fenoxaprop-P-ethyl; Substance, Technical. Testing for acute oral toxicity in the male and female Wistar rat Hoechst, Report No. 92.0049 Doc. No. A47470 GLP unpublished	Y	BCS
Ehling G.	Annex II, 5.3.2	1993a	Hoe 33171, Substance technical. Subchronic oral toxicity (13 week range finding (feeding) study) in the NMRI mice Hoechst, Report No. 93.0157 Doc. No. A50244 GLP unpublished	Y	BCS
Hack R., Leist K.-H.	Annex II, 5.2.6	1992	Fenoxaprop-P-ethyl; Substance, technical. Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Hoechst, Report No. 91.1199 Doc. No. A47403 GLP unpublished	Y	BCS
Hofmann T. et al.	Annex II, 5.3.3	1989	Hoe 046360 substance technical. Testing for subchronic inhalation toxicity (28 applications within 40 days) in male and female Wistar rats Hoechst, Report No. 89.0584 Doc. No. A40799 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Hofmann T., Jung R.	Annex II, 5.2.3	1991	Fenoxaprop-P-ethyl; Substance, Technical. Testing for acute aerosol inhalation toxicity in the male and female SPF Wistar rat, 4-hour LC_{50} Hoechst, Report No. 91.1089 Doc. No. A46998 GLP unpublished	Y	BCS
Hollander, Leist	Annex II, 5.2.3	1982	Aerosol inhalation of HOE 33171 active ingredient in male and female SPF-Wistar rats. A four-hour LC_{50} Hoechst, Report No. 352/82 Doc. No. A24752 GLP unpublished	Y	BCS
Hollander, Weigand	Annex II, 5.2.2	1978	HOE 33171 0H AT202 Op.No.1618I. Acute percutaneous toxicity to the female SPF-Wistar-rat Hoechst, Report No. 443/78 Doc. No. A24673 GLP unpublished	Y	BCS
Hollander, Weigand	Annex II, 5.2.1	1979a	Acute oral toxicity of HOE 33171 0H AT203 to the male rat Hoechst, Report No. 576/79 Doc. No. A24696 GLP unpublished	Y	BCS
Hollander, Weigand	Annex II, 5.2.1	1979b	Acute oral toxicity of HOE 33171 0H AT203 to the female rat Hoechst, Report No. 577/79 Doc. No. A24698 GLP unpublished	Y	BCS
Hollander, Weigand	Annex II, 5.2.2	1979c	Acute percutaneous toxicity of HOE 33171 0H AT203 to the female rat Hoechst, Report No. 578/79 Doc. No. A24702 GLP unpublished	Y	BCS
Hollander, Weigand	Annex II, 5.2.4 and 5.2.5	1979d	HOE 33171 0H AT203. Irritance to the rabbit skin and eye mucosa Hoechst, Report No. 406/79 Doc. No. A24688 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
James P. et al.	Annex II, 5.6.2	1983	A study of the effect of the active ingredient Hoe 033171 technical on pregnancy of the mouse (Code: Hoe 033171 0H ZC96 0002) Huntingdon Research Centre, Report No. HST 221/222-R/83666 Doc. No. A30282 GLP unpublished	Y	BCS
Jung et al.	Annex II, 5.4.1	1982	Study of the mutagenic potential of the compound Hoe 33171 0H AS201 in strains of Salmonella typhimurium (Ames Test) and Escherichia coli Hoechst Report No. 432/82 Doc. No. A24677 GLP unpublished	Y	BCS
Jung, Weigand	Annex II, 5.2.6	1982	Test for sensitizing properties of HOE 33171 0H AS201 in the guinea pig according to Buehler Hoechst, Report No. 573/82 Doc. No. A30110 GLP unpublished	Y	BCS
Jung, Weigand	Annex II, 5.4.2	1986	Hoe 046360, substance technical. Micronucleus test in male and female NMRI mice after oral administration Hoechst Report No. 86.0921 Doc. No. A34297 GLP unpublished	Y	BCS
Kaleja R.	Annex II, 5.9	1997	Medical Data. Medical surveillance of manufacturing plant personnel. Proposed first aid measures Hoechst AG, Department of Occupational Medicine, Report No. TOX 97/0005 Doc. No. A58432 GLP: not applicable unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1982	Hoe 33171-^{14}C. Study of kinetics and residue determinations following oral and intravenous application in rats Hoechst, Report No. 01-L42-0364-82 Doc. No. A24284 GLP not specified unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1984a	Hoe 033171-(dioxyphenyl-1-^{14}C). Investigations into the excretion, and determination of residues after oral administration of 2 mg/kg body weight to rats Hoechst, Report No. 01-L42-0436-84 Doc. No. A32611 GLP unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1984b	Hoe 033171-(chlorophenyl-U-14-C). Study of kinetics and residue concentrations following oral application of 10 mg/kg body weight in rats Hoechst, Report No. 01-L42-0439-84E Doc. No. A30454 GLP unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1984c	Hoe 033171-(dioxyphenyl-1-^{14}C). Investigations into the kinetics and determination of residues after oral administration of 10 mg/kg body weight to rats Hoechst, Report No. 01-L42-0440-84 Doc. No. A32612 GLP unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1984d	Hoe 033171-(chlorophenyl-U-14-C), study of kinetics and residue concentrations following repeated oral applications of 2 mg/kg/day in rats Hoechst, Report No. 01-L42-442-84E Doc. No. A30456 GLP unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1987a	Hoe 046360-^{14}C. Kinetics in the rat after single oral and intravenous administration of 2 mg/kg body weight Hoechst, Report No. 01-L42-0519-87 Doc. No. A37450 GLP unpublished	Y	BCS
Kellner H.-M., Eckert H.G.	Annex II, 5.1	1987b	Hoe 046360-^{14}C. Kinetics in the rat after repeated (14+1) oral doses of 2 mg/kg body weight Hoechst, Report No. 01-L42-0521-87 Doc. No. A37449 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Leist et al.	Annex II, 5.3.1	1980a	Range-finding-test with Hoe 33171 0H AT203 in a 32-day study with SPF-Wistar-rats Hoechst, Report No. 164/80 Doc. No. A26171 GLP unpublished	Y	BCS
Leist et al.	Annex II, 5.3.1	1980b	Toxicity test of Hoe 33171 0H AT203 in a 32-day study with SPF-mice Hoechst, Report No. 336/80 Doc. No. A26168 GLP unpublished	Y	BCS
Leist et al.	Annex II, 5.3.1	1981	Toxicity test of Hoe 33171 0H AT204 in a 30-day study with SPF-mice Hoechst, Report No. 356/81 Doc. No. A26169 GLP unpublished	Y	BCS
Leist K.H., Ebert E.	Annex II, 5.3	1989	Comparison of the toxicological profile of Hoe 046360 and Hoe 033171 (substances technical) Hoechst, Report No. 89.0416 Doc. No. A40415 GLP not applicable unpublished	Y	BCS
Leist K.-H., Ehling G.	Annex II, 5.7	1993	Statement on neurotoxic potential of Hoe 046360, substance technical Hoechst, Pharma Development Central Toxicology Doc. No. A50069 GLP: not applicable unpublished	Y	BCS
Mayer, Weigand	Annex II, 5.2.1	1979a	HOE 33171 0H AT203. Acute oral toxicity to the male mouse Hoechst, Report No. 423/79 Doc. No. A24692 GLP unpublished	Y	BCS
Mayer, Weigand	Annex II, 5.2.1	1979b	HOE 33171 0H AT203. Acute oral toxicity to the female mouse Hoechst, Report No. 424/79 Doc. No. A24694 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Mayer, Weigand	Annex II, 5.2	1979c	HOE 33171 0H AT203. Acute intraperitoneal toxicity to the male rat Hoechst, Report No. 421/79 Doc. No. A24681 GLP unpublished	Y	BCS
Mayer, Weigand	Annex II, 5.2	1979d	HOE 33171 0H AT203. Acute intraperitoneal toxicity to the female rat Hoechst, Report No. 422/79 Doc. No. A24690 GLP unpublished	Y	BCS
Mellano D., Mondino A.	Annex II, 5.4.1	1982a	Study of the mutagenic activity “in vitro” of the compound Hoe 33171 0H AS 201 with Schizosaccharomyces pombe RBM Experiment No. M 417 Doc. No. A24239 GLP unpublished	Y	BCS
Mellano D., Mondino A.	Annex II, 5.4.1	1982b	Study of the capacity of the test article Hoe 33171 0H AS 201 to induce chromosome aberrations in human lymphocytes cultured in vitro RBM Experiment No. M 419 Doc. No. A26227 GLP unpublished	Y	BCS
Mellano D., Mondino A.	Annex II, 5.4.1	1982c	Study of the mutagenic activity of the compound Hoe 33171 0H AS 201 with Saccharomyces cerevisiae – gene conversion – DNA repair test RBM Experiment No. M 416 Doc. No. A24238 GLP unpublished	Y	BCS
Mellano D., Mondino A.	Annex II, 5.4.1	1982d	Study of the capacity of the test article Hoe 33171 0H AS 201 to induce “unscheduled DNA synthesis” in cultured HeLa cells RBM Experiment No. M 418 Doc. No. A24582 GLP unpublished	Y	BCS
Mosesso P.	Annex II, 5.4.1	1987	Chromosome aberrations in human lymphocytes cultured in vitro. Test substance: Hoe 046360 – Substance technical LSR-RTC, Report No. 157012-M-02086 Doc. No. A35218 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Müller W. et al.	Annex II, 5.4.1	1994	Hoe 046360; substance technical (Code: Hoe 046360 00 ZC97 0002). Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli Hoechst, Report No. 94.0627 Doc. No. A53077 GLP unpublished	Y	BCS
Müller W.	Annex II, 5.4.1	1995	Hoe 046360, substance technical. Detection in the unscheduled DNA synthesis test in mammalian cells in vitro Hoechst Report No. 95.0206 Doc. No. A54045 GLP unpublished	Y	BCS
Osterburg I. et al.	Annex II, 5.6.2	1984	Hoe 033171, technical grade (Code: Hoe 033171 0H ZC96 0002), oral embryotoxicity study in the Cynomolgus monkey Hazleton Laboratories Deutschland, Report No. 245-169/6 Doc. No. A29702 GLP unpublished	Y	BCS
Pensler M. et al.	Annex II, 5.6.2	1987a	Hoe 046360 – active ingredient technical (Code: Hoe 046360 0H ZC96 0002) Testing for embryotoxicity and effects on post-natal development in Wistar rats after oral administration Hoechst, Report No. 87.0309 Doc. No. A35687 GLP unpublished	Y	BCS
Sachsse K. et al.	Annex II, 5.3.1	1987a	Hoe 046360 Technical. Repeated-dose oral toxicity 28-day feeding study in dogs Research and Consulting Company AG, Project No. 060658 Doc. No. A36558 GLP unpublished	Y	BCS
Sachsse K. et al.	Annex II, 5.3.2	1987b	Hoe 046360 Technical. Sub-chronic oral toxicity 13-week feeding study in Beagle dogs Research and Consulting Company AG, Project No. 060682 Doc. No. A36617 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Sachsse K. et al.	Annex II, 5.8.2	1987c	Hoe 046360 Technical. 28-day dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver Research and Consulting Company AG, Project No. 060658 Doc. No. A36957 GLP unpublished	Y	BCS
Sachsse K. et al.	Annex II, 5.8.2	1987d	Hoe 046360 Technical. 13-week dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver Research and Consulting Company AG, Project No. 060682 Doc. No. A36959 GLP unpublished	Y	BCS
Schmid H. et al.	Annex II, 5.8.2	1996	13-week oral toxicity (feeding) study with Hoe 046360 + Hoe 107892 (2:1) in the rat. Influence of the coadministration of Hoe 107892 on the toxicological profile of Hoe 046360 Research and Consulting Company AG, Project No. 610121 Doc. No. A57200 GLP unpublished	Y	BCS
Schütz et al.	Annex II, 5.5	1984	Supplement to Report No. 83.0613. Hoe 33171 – active ingredient technical. Chronic feeding study in rats (interim killing after 12 months). Determination of hepatic enzyme levels Hoechst, Report No. 84.0639 Doc. No. A29694 GLP unpublished	Y	BCS
Schütz et al.	Annex II, 5.5	1985	Supplement to Report No. 84.0632 of 29 September 1984. Hoe 33171 – active ingredient technical. Chronic feeding study (24 months) in rats. Determination of residues in organs and tissues Hoechst, Report No. 85.0205 Doc. No. A30804 GLP unpublished	Y	BCS
Schwalbe-Fehl M.	Annex II, 5.1	1988	Hoe 033171 and Hoe 046360. Comparison and evaluation of the metabolism and pharmacokinetics in rats Hoechst, Report No. (B)258/88 Doc. No. A38647 GLP not applicable unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Seeberg A.H.	Annex II, 5.4.1	1986	Gene mutation in Chinese hamster V79 cells. Test substance: Hoe 046360 Substance technical. Final report. LSR-RTC, Report No. 157013-M-02186 Doc. No. A34057 GLP unpublished	Y	BCS
Suter P. et al.	Annex II, 5.3.1	1987a	Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in rats Research and Consulting Company AG, Project No. 060636 Doc. No. A36568 GLP unpublished	Y	BCS
Suter P. et al.	Annex II, 5.3.1	1987b	Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in mice Research and Consulting Company AG, Project No. 060647 Doc. No. A36557 GLP unpublished	Y	BCS
Suter P., Luetkemeier H.	Annex II, 5.3.2	1987a	Hoe 046360 Technical. Sub-chronic oral toxicity 13-week feeding study in mice Research and Consulting Company AG, Project No. 060660 Doc. No. A36567 GLP unpublished	Y	BCS
Suter P., Luetkemeier H.	Annex II, 5.8.2	1987b	Hoe 046360 Technical. 28-day dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver Research and Consulting Company AG, Project No. 060636 Doc. No. A36955 GLP unpublished	Y	BCS
Suter P., Luetkemeier H.	Annex II, 5.8.2	1987c	Hoe 046360 Technical. 28-day dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver Research and Consulting Company AG, Project No. 060647 Doc. No. A36958 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Suter P., Luetkemeier H.	Annex II, 5.8.2	1987d	Hoe 046360 Technical. 13-week dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver Research and Consulting Company AG, Project No. 060660 Doc. No. A36960 GLP unpublished	Y	BCS
Tennekes H. et al.	Annex II, 5.3.2	1987	Hoe 046360 Technical. Sub-chronic oral toxicity: 13-week feeding study in rats Research and Consulting Company AG, Project No. 060671 Doc. No. A36566 GLP unpublished	Y	BCS
Tennekes H., Luetkemeier H.	Annex II, 5.8.2	1987	Hoe 046360 Technical. 13-week dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver Research and Consulting Company AG, Project No. 060671 Doc. No. A36954 GLP unpublished	Y	BCS
Till C.P.	Annex II, 5.1	1993	Hoe 046360-^{14}C. Metabolism in rats following single oral administration of test substance at a dose level of 10 mg kg^{-1} body weight in the presence of coadministered Hoe 107892 Hoechst UK, Report No. CT1D241192 Doc. No. A49483 GLP unpublished	Y	BCS
Troschau G.	Annex II, 5.5	1996	Fenoxaprop-ethyl – substance technical (Code Hoe 033171 00 ZD96 0005) Carcinogenicity study in mice Hoechst, Report No. 96.0880 Doc. No. A57500 GLP unpublished	Y	BCS
Wink O. et al.	Annex II, 5.1	1987	Hoe 046360-^{14}C. Metabolism in male and female rats after a single oral administration of 10 mg/kg body weight Hoechst, Report No. CM022/86 Doc. No. A37324 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Annex III Data and Information					
Dick I.	Annex III, 7.3	2000	(^{14}C)-Fenoxaprop-P-ethyl. Comparative in vitro dermal penetration study in human and rat skin applied as an oil in water suspension Huntingdon Life Sciences Report No. TOX/00/249-7 Doc. No. C007848 GLP unpublished	Y	BCS
Dreher D.M.	Annex III, 7.1.6	2002	AE F046360 24 EW14 A7: Skin sensitization in the guinea pig (Buehler method) SPL Project No. 282/623 Doc. No. C021468 GLP unpublished	Y	BCS
Ehling G.	Annex III, 7.1.1	1993b	Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L; Testing for acute oral toxicity in the male and female Wistar rat Hoechst, Report No. 93.0496 Doc. No. A51244 GLP unpublished	Y	BCS
Ehling G.	Annex III, 7.1.2	1993c	Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L; Testing for acute dermal toxicity in the male and female Wistar rat Hoechst, Report No. 93.0410 Doc. No. A51088 GLP unpublished	Y	BCS
Ganzelmeier H. et al.	Annex III, 7.2.2	1997	Abdrift und Bodenbelastungen beim Ausbringen von Pflanzenschutzmitteln Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft Berlin-Dahlem, Heft 328		
Hack R.	Annex III, 7.1.4	1993a	Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L; Testing for primary dermal irritation in the rabbit Hoechst, Report No. 93.0404 Doc. No. A51087 GLP unpublished	Y	BCS
Hack R.	Annex III, 7.1.5	1993b	Testing for primary eye irritation in the rabbit Hoechst, Report No. 93.0193 Doc. No. A50455 GLP unpublished	Y	BCS

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Hack R.	Annex III, 7.1.6	1993c	Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L; Testing for sensitising properties in the Pirbright-White guinea pig according to the technique of BUEHLER Hoechst, Report No. 93.0577 Doc. No. A51451 GLP unpublished	Y	BCS
Hofmann T.	Annex III, 7.1.3	1993	Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L; Testing for acute aerosol inhalation toxicity in the male and female SPF Wistar rat. 4-hour LC_{50} Hoechst, Report No. 93.0430 Doc. No. A51050 GLP unpublished	Y	BCS
Lloyd G.A., Bell G.J.	Annex III, 7.2.2	1983	Hydraulic nozzles: comparative spray drift study Ministery of Agriculture, Fisheries & Food, GBR, Operator Protection Group, Harpenden Laboratory		
Möllerfeld J.	Annex III, 7.3	1992	Dermal penetration of ^{14}C HOE 046360 in the rat Battelle Europe Study No. BF-ME-08-90-01-DPR-1 Doc. No. A48898 GLP unpublished	Y	BCS
Needham D.	Annex III, 7.3	2002	(^{14}C)-Fenoxaprop-P-ethyl: in vivo dermal absorption in the rat using an oil in water emulsion formulation encoded: AE F046360 24 EW14 A7xx Covance Report No. 1490/021-D1145 Doc. No. C025112 GLP unpublished	Y	BCS
Simonnard A.	Annex III, 7	1988	Repeated dose dermal toxicity study (21 applications within 29 days) in rats with a 14-day withdrawal period CIT Study No. 3836 Doc. No. A42695 GLP unpublished	Y	BCS

7.3 Environmental hazard assessment

7.3.1 Degradation and Aquatic Bioaccumulation

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Buerkle, W. L.; Schuld, G.; Grundschoettel, P.; Schwab, W.	1986	Hoe 033171-dioxyphenyl-1-14C - Aerobic soil metabolism study - only for EPA registration Generated by: Hoechst AG, Frankfurt am Main, Germany Report No: CB058/85 Edition Number: M-287600-01-1 GLP / GEP: yes Unpublished	Y	BCS
Buettner, B.; Schweighoefer, U.; Kuenzler, K	1992	Aerobic soil metabolism study at 11 and 21 C Hoe 046360-chlorophenyl-U-14C Generated by: Hoechst AG, Frankfurt am Main, Germany Report No: CB91/017 Edition Number: M-135697-01-1 GLP / GEP: yes Unpublished	Y	BCS
Fitzmaurice	2004	[14C]-Fenoxaprop-p-ethyl: Degradation and retention in two water/sediment systems. Code AE F046360 Generated by:Battelle ArgiFood Ltd, Battelle House, Ongar, UK Report No. C046009 GLP / GEP: no unpublished	Y	BCS
Goerlitz, G.; Rutz, U	1988	Adsorption in the system soil/water Code: Hoe 088406 Generated by: Hoechst AG, Frankfurt am Main, Germany Report No CP070/87 Edition Number: M-120443-01-1 GLP / GEP: yes Unpublished	Y	BCS
Hardy, I. A. J. & M. Patel	2004	Fenoxaprop-p-ethyl: Kinetic modelling analysis of data from a water sediment study. Generated by:Battelle ArgiFood Ltd, Battelle House, Ongar, UK Report No. CX/04/072 GLP / GEP: no unpublished	Y	BCS
Kley, C.	2002b	Kinetic Evaluation of the Aerobic Aquatic Metabolism of chlorophenyl-U-^{14}C-labelled Fenoxaprop-P-ethyl in Two Water/Sediment Systems Using TOPFIT 2.0 Generated by: Bayer CropScience GmbH; Metabolism and E-Fate, Frankfurt Report No: OE02/116 GLP / GEP: not applicable Unpublished	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Meyer B.N. & Young B.M.	1999a	Bioaccumulation and metabolism of ^{14}C-Chlorophenyl AE F046360 in Bluegill Sunfish, *Lepomis macrochirus*, in a Flow-Through System Generated by: AgrEvo USA Company; AgrEvo Research Center; Environmental Chemistry Department; 703 NOR-AM Road; PO Box 538; Pikeville, NC 27863 Report No: BM98E517 GLP / GEP: yes unpublished	Y	BCS
Reynolds, J. L	1992	Adsorption and desorption in four soils of 14C-Fenoxaprop-P-ethyl XenoBiotics Laboratories, Inc., Plainsboro, NJ, USA Report No RPT0099 Edition Number: M-137847-02-1 GLP / GEP: yes Unpublished	Y	BCS
Rupprecht, J. K.	1999	The adsorption/desorption of (14C)-AE F088406 on six soils and one sediment Generated by: AgrEvo USA Company, Environmental Chemistry, Pikeville, NC, USA Report No BM98E501Edition Number: M-181475-01-1 GLP / GEP: yes Unpublished	Y	BCS
Sarafin, R.; Jordan, H. J.	1989	Photodegradation on soil Hoe 033171-14C (fenoxaprop-ethyl) Generated by: Hoechst AG, Frankfurt am Main, Germany Report No: CB 071/88 Edition No M-122796-01-1 GLP / GEP: yes unpublished	Y	BCS
Schollmeier M., Eyrich U., Uhl A.	1992a	Determination of the partition coefficient n-octanol/water by HPLC (according to OECD Guideline #117) Hoe 046360, Code: Hoe 046360 00 ZB98 0001 Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A49082 GLP / GEP Yes Unpublished	Y	BCS
Schollmeier M.; Eyrich U	1993	Determination of the abiotic hydrolysis as a function of pH according to OECD Guideline No. 111 and EEC Guideline C.7. Hoe 088406 (Fenoxaprop-P) Generated by: Hoechst AG, Produktentwicklung GB-C, Oekologie I, Frankfurt, Germany Report No: CP93/009 GLP / GEP: yes Unpublished	Y	BCS
Schwab, W.	1993c	Hoe 046360-^{14}C: Photodegradation of Fenoxaprop-P-ethyl in surface water, sterile buffer and distilled water Generated by: Hoechst AG; GB-C, Produkt-entwicklung Oekologie I, Frankfurt; Germany Report No: CB91/035 GLP / GEP: yes Unpublished	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Stumpf, K.; Dambach, P.	1988	Aerobic soil metabolism Hoe 046360 - chlorophenyl-14C Generated by: Hoechst AG, Frankfurt am Main, Germany Report No: CB051/87 Edition Number: M-120879-01-1 GLP / GEP: yes Unpublished	Y	BCS
Tarara G.	2000	Degradation in two sediment/water-systems at 20 degrees C under aerobic conditions (U-14C-chlorophenyl) AE F046360 Generated by: Hoechst Schering AgrEvo GmbH; Entwicklung Umweltforschung, Frankfurt Report No: CB98/113 GLP / GEP: yes Unpublished	Y	BCS
van der Gaauw, A.	2002	[^{14}C]-Fenoxaprop-p-ethyl: Hydrolysis at five different pH values. Generated by: RCC Ltd., Itingen, CHE; Environmental Chemistry & Pharmanalytics Division, Bayer CropScience GmbH, DEU; Metabolism and E-Fate, Frankfurt Report No: 815670 GLP / GEP: yes Unpublished	Y	BCS

7.3.1 Aquatic Toxicity

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Christ M.T. & Ruff D.F.	1997b	Toxicity to Duckweed (*Lemna gibba*), in a Static Renewal System; Fenoxaprop-P-ethyl Technical 88.1% w/w Code AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company; Research Center; Ecotoxicology Department; 703 NOR-AM Road; PO Box 538; Pikeville, NC 27863 Report No: BM97W502 GLP / GEP: yes Unpublished	Y	BCS
Christ M.T. & Ruff D.F.	1999g	Effect to Anabaena flos-aquae (Blue-Green Alga) in a Growth Inhibition Test Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company AgrEvo Research Center Ecotoxicology Department 703 NOR-AM Road PO Box 538 Pikeville, NC 27863 Report No: BM98W518 GLP / GEP: yes Unpublished	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Ebeling M., Nguyen D., Gosch H.	2002a	Fenoxaprop-P *Daphnia magna* - Chronic Toxicity and Reproduction Test under semi-static conditions; code AE F088406 00 1C97 0001 Generated by: Bayer CropScience GmbH; Ecotoxicology, D-65926 Frankfurt Report No: CE02/057 GLP / GEP: yes unpublished	Y	BCS
Fischer R.	1989ap	The Effect of Fenoxaprop-P-ethyl - substance, technical (Identification code: Hoe 046360 OH ZC97 0002) to *Salmo gairdneri* (Rainbow trout) in a 21-day Prolonged Toxicity Test (method OECD) Generated by: Oekologisches Laboratorium, Pflanzenschutz Forschung Biologie, Hoechst AG, D-6230 Frankfurt, Germany Report No: CE89/034 GLP / GEP: yes Unpublished	Y	BCS
Fischer, R.	1986b	The Effect of Hoe 046360 - substance, technical Identification code . Hoe 046360 OH ZC96 0002 to *Salmo gairdneri* (Rainbow trout) in a Static Acute Toxicity Test (Sg347/a, method EPA) Generated by: Oekologisches Laboratorium, Pflanzenschutz Forschung Biologie, Hoechst AG, D-6230 Frankfurt am Main 80, Fed. Rep. of Germany Report No: OEK86/092E GLP / GEP: yes Unpublished	Y	BCS
Fischer, R.	1989ao	The Effect of Fenoxaprop-P-ethyl - substance, technical (Identification code: Hoe 046360 OH ZC97 0002) to *Daphnia magna* (Water flea) in a 21-day Reproduction Test (method OECD) Generated by: Oekologisches Laboratorium, Pflanzenschutz Forschung Biologie, Hoechst AG, D-6230 Frankfurt am Main 80, Fed. Rep. of Germany Report No: CE89/033 GLP / GEP: yes Unpublished	Y	BCS
Heusel R.	1993dy	Effect to *Daphnia magna* (water flea) in a Static-Acute Toxicity Test (method OECD) Fenoxaprop-P substance, technical (Hoe 088406 00 ZC93 0001) Generated by: Hoechst AG; GB C / Product Development Ecology, D-6230 Frankfurt Report No: Project No. CE92/002 GLP / GEP: yes Unpublished	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Heusel R.	1993dx	Effect to *Selenastrum capricornutum* (green algae) in an algal assay bottle test (method EPA) Fenoxaprop-P substance, technical (Hoe 088406 00 ZC93 0001) Generated by: Hoechst AG; Ecobiology, D-65926 Frankfurt, Germany Report No: CE92/003 GLP / GEP: yes Unpublished	Y	BCS
Heusel R.	1996j	Acute toxicity to rainbow trout (Oncorhynchus mykiss) Fenoxaprop-P, substance, technical Code: AE F088406 00 1C94 0001 Generated by: Hoechst Schering AgrEvo GmbH; Environmental Biology Frankfurt Report No: CE96/122 GLP / GEP: yes Unpublished	Y	BCS
Heusel, R	1991bs	Effect to Selenastrum capricornutum (Green alga) in an Algal Assay Bottle Test (method EPA) Fenoxaprop-P-ethyl: substance, technical (Hoe 046360 00 ZC97 0002) Generated by: Hoechst Company; Ecological Laboratory, D-6230 Frankfurt, Germany Report No: CE90/093 GLP / GEP: yes Unpublished	Y	BCS
Memmert, U.	2000a	Effects of Fenoxaprop-P-ethyl, substance technical; code: AE F046360 on the development of sediment-dwelling larvae of *Chironomus riparius* in a water-sediment system. Generated by: RCC Ltd., Environmental Chemistry & Pharmanalytics Division, CH-4452 Itingen, Switzerland Report No: Study project No. 732194 GLP / GEP: yes Unpublished	Y	BCS
Sowig P. & Gosch H.,	2003a	Effects on survival and growth of juvenile rainbow trout (*Oncorhynchus mykiss*) in a 28 days flow-through study Fenoxaprop-P, substance, technical (code: AE F088406 00 1C97 0001) Generated by: Bayer CropScience GmbH, Ecotoxicology; D-65926 Frankfurt, Germany Report No: CE02/058 GLP / GEP: yes unpublished	Y	BCS
Sowig P., Weller O., Gosch H.,	1999ae	Algal growth inhibition - Navicula pelliculosa Fenoxaprop-P-ethyl substance, technical Code: AE F046360 00 1C97 0002 Generated by: Hoechst Schering AgrEvo GmbH; Ecobiology, D-65926 Frankfurt Report No: CE98/107 GLP / GEP: yes Unpublished	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Stachura B.J. & Ruff D.F.	1998e	The 48 Hour Acute Toxicity to *Daphnia magna*, in a Static Renewal System Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 001 C97 0002 Generated by: AgrEvo USA Company Research Center Ecotoxicology Department 703 NOR-AM Road PO Box 538 Pikeville, NC 27863 Report No: BM98W514 GLP / GEP: yes Unpublished	Y	BCS
Stachura B.J. & Ruff D.F.	1999s	The 96 hour acute toxicity to the rainbow trout, *Oncorhynchus mykiss*, in a flow through system; Fenoxaprop-P-ethyl, technical 88.1% w/w; Code: AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company; Research Centre; Ecotoxicology Department; 703 NOR-AM Road; PO Box 538; Pikeville, NC 27863 Report No: BM98W520 GLP / GEP: yes Unpublished	Y	BCS
Stachura, B.J., Ruff, D.F.	1999r	The 96-hours Acute Toxicity to the Bluegill Sunfish, *Lepomis macrochirus*, in a Flow Through System; Fenoxaprop-P-ethyl Technical 88.1% w/w; Code: AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company; Research Centre; Ecotoxicology Department; 703 NOR-AM Road; PO Box 538; Pikeville, NC 27863 Report No: BM98W521 GLP / GEP: yes Unpublished	Y	BCS
Stachura, B.J., Ruff, D.F.	1999t	Effects on Early Life Stages of Rainbow Trout, *Oncorhynchus mykiss* U.S.EPA 72-4 Fenoxaprop-P-ethyl Technical 88.1%w/w; Code: AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company; Research Center; Ecotoxicology Department; 703 NOR-AM Road; PO Box 538; Pikeville, NC 27863 Report No: BM98W513 GLP / GEP: yes Unpublished	Y	BCS
Young B.M. & Ruff D.F.	1999h	Effect to *Skeletonema costatum* (Marine Diatom) in a Growth Inhibition Test Fenoxaprop-P-ethyl Technical 88.1% w/w Code: AE F046360 00 1C97 0002 Generated by: AgrEvo USA Company AgrEvo Research Center Ecotoxicology Department 703 NOR-AM Road PO Box 538 Pikeville, NC 27863 Report No: BM98W516 GLP / GEP: yes Unpublished	Y	BCS

8 ANNEXES