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Fenoxaprop-P-ethyl

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Co-Rapporteur Member State: FINLAND

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INTRODUCTION

Fenoxaprop-P-ethyl was included in Annex I of Council Directive 91/414/EEC as a new active substance (Commission Directive 2008/66/EC of 30 June 2008). The approval is now in place under Regulation (EC) 1107/2009 (repealing Commission Directive 91/414/EEC) as specified in Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011.

In the Review Report for the active substance Fenoxaprop-P-ethyl (SANCO/3777/08-rev.1, 14 December 2007) for the first approval, there were no substantial data gaps left open for the section of mammalian toxicity.

Dossier submission
For the renewal of the approval of fenoxaprop-P-ethyl, the notifiers Bayer and Cheminova submitted a complete dossier by the deadline of 30 June, 2016. The dossier was submitted to support the application for renewal of the regulatory approval of the active substance fenoxaprop-P-ethyl under Commission Implementing Regulation (EU) 844/2012 of 18 September 2012, and reviewed the toxicological studies, including additional data and risk assessments, for fenoxaprop-P-ethyl. The dossier summarised new information and data which was considered relevant for the renewal of the approval of fenoxaprop-P-ethyl under Regulation (EC) 1107/2009, and which reflects changes in the requirements under Commission Regulation (EU) No 283/2013, and the associated Annex. Where additional and/or new data on fenoxaprop-P-ethyl have been provided, justifications have been included. Also justifications have been given if new data were required but none had been provided. Originally submitted tests and studies considered within the previous EU review process of fenoxaprop-P-ethyl that were still considered relevant to support the application for renewal were referenced. In this case detailed summaries had generally not been provided. The dossier referred to the Commission Implementing Regulation (EU) No. 540/2011 for fenoxaprop-P-ethyl and to the EFSA conclusion (EFSA Scientific Report (2007) 121, 1-76), and in particular the endpoints provided in Appendix I thereof.

Present dRAR
The present dRAR includes the originally evaluated study summaries from the DAR (RMS Austria), for which additional information was included occasionally when considered helpful for the scientific discussion.

The new information and data submitted for the renewal of fenoxaprop-P-ethyl are highlighted in light blue in the present dRAR. Also, additional information to previously submitted studies is highlighted in light blue.

The originally derived and agreed reference values for fenoxaprop-P-ethyl (EFSA Scientific Report (2007) 121, 1-76) were followed in the present evaluation in the dRAR: ADI (0.01 mg/kg bw/d), ARfD (0.1 mg/kg bw/d) and AOEL (0.014 mg/kg bw/d).

The RMS also paid special attention to the new criteria for classification and labelling according to Regulation (EC) 1272/2008, which can be found in the “conclusions” at the end of each relevant study.
Fenoxaprop-P-ethyl was classified as STOT RE 2 (H373 (kidneys)) and Skin Sens. 1 (H317) and was included in ATP07 (Regulation (EC) 1221/2015) of Regulation (EC) 1272/2008.

Details of the literature search undertaken can be found in Chapter B.6.10, References Relied on. One relevant scientifically peer-reviewed open literature reference has been identified for fenoxaprop-P-ethyl and accepted as supplementary information, which was about poisoning cases with a plant protection product including fenoxaprop-P-ethyl. No peer-reviewed data has been identified for its metabolites.

B.6. TOXICOLOGY AND METABOLISM DATA

B.6.1. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION IN MAMMALS

B.6.1.1. Absorption, distribution, metabolism and excretion by oral and intravenous route

No new data were submitted to address ADME end-points. Reference is made to data submitted in support of the approval of fenoxaprop-P-ethyl. As two of these studies were performed by additional intravenous administration of fenoxaprop-P-ethyl and fenoxaprop-ethyl, the results were not separated.

Absorption

The absorption of fenoxaprop-P-ethyl in male and female rats was rapid 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. In a study with a single dose of 2 mg/kg bw, maximum blood levels of 3.88 ±0.66 and 4.38 ±0.14µg equivalents fenoxaprop-P-ethyl/g in males and females respectively were determined after a single dose of 10 mg/kg bw, maximum blood levels of 19.86 ±1.62 and 23.27 ±4.02 /µg equivalents fenoxaprop-P-ethyl/g in males and females, respectively. The blood level curve was biphasic with half-lives of 9-11 hours for the initial phase and 68-75 hours for the terminal phase. The highest concentrations at the end (7 d after treatment) of a repeated-dose study with a 14-day administration and a radioactive dose on day 15 in males and females respectively were measured in the kidneys (0.19 and 0.24 /µg equivalents/g) and in the blood (0.18 and 0.16 /µg equivalents/g). The minimum rate of absorption (urinary excretion including cage washes and residues in tissues/organs (excluding faeces)) 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 overall concentrations from the tissues analysed 7 days after treatment were rather low with 0.7 to 2 % of the total applied dose after single and also after repeated dosing. The highest concentrations were found in the kidneys, blood, fatty tissues (subcutaneous, retroperitoneal) and the liver. In a study with single administration of 10 mg/kg bw, liver, kidneys and blood had the highest radioactivity concentrations with ranges of 0.4 to 1.5 mg a.i. equivalents/kg. Intravenous administration of 2 mg/kg bw showed similar results.

Elimination

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 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 substances were administered via intravenous injection, higher amounts of radioactivity were excreted renally (50-59 %) as 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 compound was found in the urine after oral administration of 10 mg/kg bw. The major metabolite in the urine of males was the mercapturic acid derivative of 6-chloro-2,3-dihydrobenzoxazol-2-one. In the urine of females, also the mercapturic acid derivative of 6-chloro-2,3-dihydro-benzoxazol-2-one and the free acid from the parent compound 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. Another major metabolite in the faeces was the free acid, 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.

Comparative *in vitro* metabolism

In the renewal dossier *in vitro* interspecies comparative metabolism data should be provided, according to the data requirement in Regulation (EU) No. 283/2013, even if internationally validated methods and criteria for the interpretation of the results are missing ("Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology", EFSA Supporting publication 2016:EN-1074). For this purpose, a new comparative metabolism study has been provided and fenoxaprop-P-ethyl was tested with S9 fractions from mouse, rat, rabbit, dog and human liver.

According to the study results, fenoxaprop-P-ethyl degraded rapidly mostly to the major metabolite M11 (Hoe 054014) in all species. M11 is the sulfate ester of 6-chloro-4-hydroxy-2(3H)-benzoxazolone, where a 13-week oral toxicity study in the rat is available (see section B.6.1.2). Ten of these metabolites (M1, M2, M3, M7, M9, M10, M12, M13, M14, and M16) appeared in all species only in trace levels (below 1 % of the total radioactivity). Further 5 metabolites (M4, M5, M6, M8, M14) occurred in mouse, rat and humans also at levels below 1 % but occasionally appeared in rabbit and/or dog at levels up to 4 % at maximum. No unique human metabolite was identified.

Comparison of the absorption, distribution, metabolism and excretion behaviour of fenoxaprop-P-ethyl and fenoxaprop-ethyl:

A comparison of the metabolism of fenoxaprop-P-ethyl and fenoxaprop-ethyl is given by Schwalbe-Fehl, M.; 1988; M-120271-01-1.

The metabolism and pharmacokinetic behaviour of both compounds was investigated in male and female rats after oral administration of the radiolabelled test substances at two dose levels, i.e. 2 mg/kg bw and 10 mg/kg bw. Fenoxaprop-P-ethyl and fenoxaprop-ethyl were both excreted rapidly. In general, approx. 75% or more of the administered radioactivity were recovered in the excreta of the 0-48 hours sampling interval. Excretion via urine and faeces was in the same order of magnitude. No significant differences in the organ and tissue concentrations could be observed between fenoxaprop-P-ethyl and fenoxaprop-ethyl. Comparison of the metabolism of fenoxaprop-P-ethyl and fenoxaprop-ethyl in rats showed that the pathway of metabolism is identical for both compounds. Therefore, based on the similar absorption, distribution, metabolism and excretion behaviour of both compounds, confirmed by the similar toxicological profile of both, the bridging of toxicity data from the long-term studies and the 2-generation study with fenoxaprop-ethyl to fenoxaprop-P-ethyl is justified.

Summary of ADME studies and study results with fenoxaprop-P-ethyl

Study, reference	Dose level	Results
Kinetics in the rat after single oral and intravenous administration of 2 mg/kg bw Hoe046360-^{14}C [redacted]; *1987a* A37450, CA 5.1.1/01	2 mg/kg bw	Oral: rapid absorption, peak at 6 h; Excretion 53% via faeces in ♂, 57% via urine in ♀, none through exhalation; Distribution highest in kidneys, blood (both ♀>♂) and fatty tissue (♂>♀) Intravenous: Excretion via kidneys; Highest distribution in blood, kidneys (both ♀>♂) and retroperitoneal fat (♂)
Kinetics in the rat after single oral administration of 10 mg/kg bw Hoe 046360-^{14}C [redacted]; *1987* A37448, CA 5.1.1/04	10 mg/kg bw	Absorption: Peak at 8 h after treatment, comparable in both sexes Excretion: mainly via faeces in ♂ (52%), via urine in ♀ (59%) Distribution: highest concentrations in kidneys and in blood 7 d after treatment (♀>♂), high concentrations in liver, lungs, retroperitoneal fat and plasma
Kinetics in the rat after repeated (14 + 1) oral doses of 2 mg/kg bw Hoe 046360-^{14}C [redacted]; *1987b* A37449, CA 5.1.1/07	2 mg/kg bw	Excretion predominantly via urine (♀>♂) Distribution: highest concentration in kidneys and blood (♂>♀) ; >0.1 µg/g in liver and retroperitoneal fat
Metabolism in male and female rats after a single oral administration of 10 mg/kg bw Hoe 046360-^{14}C [redacted]..; *1987* A37324, CA 5.1.1/09	10 mg/kg bw	Excretion: >80% (first 2 days), at sacrifice around 94% excreted; in ♀ mostly via urine (52.2%), in ♂ mostly via faeces (50%) Distribution: highest concentration in kidneys (♀>♂), blood and liver (♂>♀) Metabolites: in urine mostly mercapturic acid Hoe 069225 (♂ 27.3%, ♀ 15.5%), free carboxylic acid Hoe 088406 only in ♀ (17.9 %); in faeces mostly Hoe 088406 (♂13.5, ♀9.7) and unchanged parent compound Hoe 046360 (♂ 11.2, ♀ 8.9) detected; in blood, kidneys and liver mainly the benzoxazol moiety Hoe 054014.
Metabolism in rats following single oral administration of tests substance at a dose level of 10 mg/kg bw, in the presence of co-administered Hoe 107892 [redacted] *1993* A49483, CA 5.1.1/11	10 + 10 mg/kg bw (substance + safener)	with safener: renal excretion 35 % and 44 %, faecal excretion 54 % and 41 % in ♂ and ♀, resp., 4% radioactivity at the end of study for both sexes without safener: renal excretion 35 % and 51 %, faecal excretion 54 % and 38 % in ♂ and ♀, resp.; 4 % and 5 % radioactivity at the end of study for ♂ and ♀, resp. Metabolites: 4 (♂) and 6 (♀) major metabolites; free acid Hoe 088406 in urine of ♀, in faeces (2 metabolites) mostly free acid Hoe 088406

Summary of ADME studies and results with fenoxaprop-ethyl

Study, reference	Dose level	Results

Study, reference	Dose level	Results
Kinetics and residue determinations following oral and intravenous applications in rats [redacted]; *1982* A24284, CA 5.1.1/02	2 mg/kg bw	Oral: rapid absorption already at 15 min after treatment, peak at 8 h; Excretion mostly via urine in ♀ (33.9%), in ♂ similar values for renal and faecal elimination (23.1% and 21.3%) ; Distribution highest in kidneys (♀>♂) and blood, high concentrations also in liver, retroperitoneal fat (♂) and subcutaneous fat (♀); Concentrations in respiratory air under detection limit of 0.01 % Intravenous: Peak already after 5 min; Excretion similar to that of oral route
Excretion and residues after oral administration of 2 mg/kg bw to rats Hoe 033171 (dioxyphenyl-1-^{14}C) [redacted]; *1984a* A32611, CA 5.1.1/03	2 mg/kg bw	Excretion: more renal (67 %) than faecal (26.3 %) Distribution: highest in subcutaneous and retroperitoneal fat, ovaries 0.019 µg/g and carcass 0.022 µg/g; kidneys, liver and plasma <0.01 µg/g
Kinetics and residue concentrations following oral application of 10 mg/kg bw in rats Hoe 033171 (chlorphenyl-U-^{14}C) [redacted] *1984b* A30454, CA 5.1.1/5	10 mg/kg bw	Excretion: higher via faeces (50%) than via urine (44%) in ♂, higher via urine (60%) than via faeces (35%) in ♀ Distribution: highest concentrations in retroperitoneal fat in ♂ and in blood in ♀ 7 d after treatment; high in subcutaneous fat, kidneys, liver, gonads (♀), heart and lungs
Kinetics and residues after oral administration of 10 mg/kg bw to rats Hoe 033171 (dioxyphenyl-1-^{14}C) [redacted] *1984c* A32612, CA 5.1.1/6	10 mg/kg bw	Excretion: mainly via urine (65%) than faeces (31%) Distribution: highest in retroperitoneal fat and subcutaneous fat, high in carcass and in ovaries
Kinetics and residue concentrations following repeated oral applications of 2 mg/kg/day in rats Hoe 033171 (chlorophenyl-U-^{14}C) [redacted] *1984d* A30456, CA 5.1.1/8	2 mg/kg bw	Excretion: mainly via urine (66% in ♀ > 50% in ♂) than faeces (40% in ♂ > 31% in ♀) Distribution: highest in kidneys (♀ 0.30 µg/g) and blood (♂ 0.24 µg/g)
Metabolism in rats orally administered at two doses, 2 and 10 mg/kg bw Hoe 033171-dioxyphenyl-1-^{14}C [redacted] *1985* A30377, CA 5.1.1/10	2 mg/kg bw and 10 mg/kg bw	Excretion: highest amount within 1 d after treatment (high dose: 73 % ♂, 65 % ♀, low-dose: 80%); higher renal excretion in ♀ (55%, in low-dose 71 %) than in ♂ (48%), faecal higher in ♂ (53%) than in ♀ (33%, in low-dose 38%) Metabolites: in urine predominantly HPP-acid Hoe 020686 in ♂ (47.5%), in ♀ both HPP-acid (27.5%, low-dose: 49.6%) and free acid Hoe 053022 (27.0%, low-dose 21.3%); in faeces 7-20 % unchanged substance Hoe 033171, 11-17.5 % free acid, up to 1 % hydrolysed HPP-acid

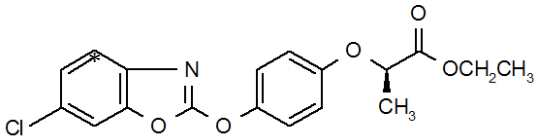
B.6.1.1.1. Studies in the rat with Fenoxaprop-P-ethyl

B.6.1.1.1.1. Kinetics - single low dose administration

Reference:	**Kinetics in the rat after single oral and intravenous administration of 2 mg/kg body weight Hoe 046360-14C**
Author(s), year:	[redacted];1987a
Report/Doc. number:	01-L42-0519-87 / A37450
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex received a single dose of 2 mg/kg bw Fenoxaprop-P-ethyl by oral gavage (2 groups) or by intravenous injection (1 group). One additional group consisting of one male and one female was used for exhalation tests (oral gavage). Fenoxaprop-P-ethyl was labelled with carbon-14 on the chlorophenyl ring and showed a radiochemical purity of 99 %. The test substance was dissolved in sesame oil for oral administration and in polyethylene glycol 400 for i.v. injection.

Test material: Hoe 046360 0H ZE99 0001, batch No.: 16030



AE F046360

*[chlorophenyl-U-14C]-florasulam
Specific activity: 903.7 MBq/g

Test animals: SPF Wistar Rat, strain WISKf (SPF71), Hoechst AG
6-8 weeks and mean body weights of 200 ±16 g ♂ and 191 ±15 g ♀.
Number of animals: 5 rats per sex per group, additionally one per sex for exhalation tests
Dosing scheme: See Table 6.1.1-1

Pharmacokinetic investigations: Blood samples were taken from the tip of the tail at the following time intervals: 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120, 144 and 168 hours.
Excretion / tissue distribution investigations: Following dosing, the rats were kept in metabolism cages and urine, cage washes and faeces were collected for 7 days. Collection intervals for urine were: 0-2, 2-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, gonads, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood, plasma and diaphragm.
Expired CO_2 group: The air was removed continuously over a 0 – 48 hour period after dosing and was passed through an exhalimeter where it was investigated for volatile radioactivity.

Table 6.1.1-1 Dosing scheme, Kinetics in the rat after single oral and i.v. administration of Fenoxaprop-P-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Blood kinetics	2	oral	5 males 5 females	single
Excretion / tissues distribution	2	oral	5 males 5 females	single
Expired CO_2	2	oral	1 male 1 female	single
Excretion / tissues distribution	2	intravenous	5 males 5 females	single

Results:
The recovery rates following oral administration were approximately 97 % for males and 96 % for females. After i.v. application, recovery rates were about 93 % for males and 90 % for females.

Pharmacokinetic investigations (blood levels), single oral dose of 2 mg/kg bw: Absorption took place rapidly. There were already mean concentrations ranging from 0.4 to 0.6 µg equivalents / g by the time of the first blood sampling 0.25 h after treatment. Between 2 and 8 h after treatment, the concentrations remained at a fairly constant level, reaching a maximum 6 h after treatment. This was higher in females (4.38 ± 0.14 µg equivalents/g) than in males (3.88 ± 0.66 µg equivalents/g). The lowering of concentration was biphasic. In the males, half-lives of 10.4 ± 1.4 h were detected for the initial phase and 67.8 ± 1.7 h for the terminal phase. In females, the half-lives were 8.9 ± 0.4 h for the initial phase and 67.9 ± 10.4 h for the terminal phase.

Table 6.1.1-2 Blood levels after a single oral administration of 2 mg/kg bw Fenoxaprop-P-ethyl to rats (µg equiv. / g)

Time (hours)	Blood levels (µg equivalents / g)		Time (hours)	Blood levels (µg equivalents / g)	
	Males	Females		Males	Females
0.25	0.5935	0.4022	24	1.738	1.623
0.5	1.192	0.7896	48	0.8035	0.7835
1	1.915	1.439	72	0.5000	0.5181
2	3.112	2.977	96	0.3679	0.3903
4	3.786	4.089	120	0.2699	0.3089
6	**3.881**	**4.384**	144	0.2180	0.2599
8	3.837	4.360	168	0.1914	0.1985

Maximum values in **bold**

Excretion, single oral dose of 2 mg/kg bw: The route of excretion varied slightly according to sex. Excretion in the males took place to a greater extent via faeces, whereas the renally excreted portion was higher in the females. Excretion via faeces was 53 % and 37 % for males and females, respectively. The renal portion (including cage wash) accounted for 43 % and 57 %, respectively. Elimination was biphasic for faeces and urine. Half-lives of faecal excretion were 12 h for males and 9 h for females for the rapid phase and 83 h (with marked variations, ± 39 h) for males and 39 h for females for the terminal phase. For urine **bold** values designate maximum excretion, half-lives were 10 h and 9 h for the initial phase and 51 h and 44 h for the terminal phase for males and females, respectively.

Excretion, single intravenous dose of 2 mg/kg bw: Most of the radioactivity was excreted via the kidneys, regardless of sex, with a mean of 51 % in males and 60 % in females including cage washes. The corresponding portion of radioactivity excreted via faeces was 41 % in males and 29 % in females. As after oral treatment, elimination was biphasic for excretion via urine and faeces, with half-lives between 10 and 13 h for the initial phase, and between 54 and 74 h for the terminal phase, regardless of sex.

Table 6.1.1-3 Mean % of the administered radioactivity, Excretion after a single oral and i.v. administration of 2 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Collection interval (h)	Oral		Intravenous	
		Males	Females	Males	Females
Urine	0 – 2	0.0810	0.4059	1.856	2.338
	2 – 4	0.2521	0.7804	0.5869	0.6180
	4 – 8	3.955	5.402	6.299	6.478
	8 – 24	**23.18**	**33.14**	**25.13**	**27.36**
	24 – 48	10.10	11.57	10.80	14.62
	48 – 72	2.636	2.839	3.116	3.875
	72 – 96	1.001	0.9427	1.178	1.220
	96 – 120	0.4884	0.5658	0.5154	0.7576
	120 – 144	0.3494	0.4136	0.4155	1.147
	144 – 168	0.2660	0.2703	0.3234	0.6106
	Total (0 – 168)	**42.31**	**56.33**	**50.22**	**59.02**
Faeces	0 – 8	-	-	0.6287	0.5700
	0 – 24, #8 – 24	**31.31**	**20.10**	**19.67#**	**12.90#**
	24 – 48	15.65	12.94	14.78	10.23
	48 – 72	4.097	2.866	3.898	3.041
	72 – 96	1.160	0.5987	0.8129	0.7646
	96 – 120	0.2639	0.2437	0.2995	0.2932
	120 – 144	0.3259	0.1379	0.2006	0.6652
	144 – 168	0.2530	0.2406	0.1728	0.4320
	Total (0 – 168)	**53.06**	**37.14**	**40.46**	**28.90**
Cage wash	0 – 24	0.2687	0.3460	0.3175	0.3983
	24 – 48	0.1766	0.1590	0.1572	0.4558
	48 – 168	0.0083	0.0299	0.0343	0.0500
	Total (0 – 168)	**0.4536**	**0.5349**	**0.5090**	**0.9040**
∑ excreta	after 168 hours	**95.82**	**94.00**	**91.18**	**88.82**
Tissues / Carcass	after 168 hours	**1.664**	**1.561**	**1.800**	**1.630**
Total recovery	after 168 hours	**97.49**	**95.57**	**92.98**	**90.25**

Maximum values in **bold**

Table 6.1.1-4 Half-lives (h) for the elimination of radioactivity in blood and excreta after a single oral or i.v. dose of 2 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Elimination phase	Oral administration		i.v. administration	
		Males	Females	Males	Females
Blood	Phase I	10.39 ± 1.42	8.89 ± 0.43	n.d.	n.d.
	Phase II	67.76 ± 1.67	67.90 ± 10.44	n.d.	n.d.
Urine	Phase I	10.12 ± 1.09	8.58 ± 1.06	11.28 ± 0.82	10.49 ± 1.63
	Phase II	50.61 ± 5.02	44.21 ± 10.67	73.85 ± 12.44	53.98 ± 16.23
Faeces	Phase I	12.29 ± 1.33	9.29 ± 1.33	10.04 ± 0.87	12.75 ± 3.10
	Phase II	82.76 ± 38.62[1)]	39.27 ± 5.27	62.48 ± 11.16	61.73 ± 10.05[2)]

n.d. = not determined, [1)] n=3, [2)] n=2

Distribution, single oral dose of 2 mg/kg bw: At termination on day 7 after treatment, measurable concentrations were present in all of the examined organs and tissues, except the brain of most of the females. The highest values were found in the kidneys, the fatty tissue and the blood. The concentrations were generally higher in females than in males and corresponded to approximately 1.7 % and 1.6 % of the administered dose in the males and females, respectively.

Distribution, single i.v. dose of 2 mg/kg bw: Similar to oral administration, measurable concentrations were present in all of the examined organs and tissues at termination of the study. The highest values were found in blood (males) and kidneys (females). As after oral administration, the concentrations were generally slightly higher in females than in males. The measured concentrations amounted to approximately 1.8 % of the administered dose in the males and 1.6 % in the females.

Table 6.1.1-5 Tissue distribution after a single oral and i.v. administration of 2 mg/kg bw Fenoxaprop-P-ethyl to rats, µg equiv. / g

Tissue	Oral (µg equivalents / g)		i.v. (µg equivalents / g)	
	Males	Females	Males	Females
Spleen	0.0351	0.0410	0.0440	0.0657
Kidneys	**0.1440**	**0.2886**	**0.2027**	**0.4522**
Gonads	0.0183	0.0696	0.0223	0.0757
Liver	0.0848	0.0688	0.1051	0.1152
Heart	0.0504	0.0570	0.0528	0.0786
Lungs	0.0608	0.0629	0.0858	0.1216
Skeletal muscle	0.0159	0.0151	0.0228	0.0252
Subcutaneous fat	0.1028	0.0879	0.1097	0.0950
Retroperitoneal fat	**0.1681**	**0.1215**	**0.2373**	0.0773
Brain	0.0042	0.0051	0.0091	0.0094
Bones	0.0199	0.0192	0.0224	0.0215
Blood	**0.1457**	**0.1798**	**0.2460**	**0.3250**
Plasma	0.0721	0.0869	0.1105	**0.1798**
Diaphragm	0.0352	0.0361	0.0514	0.0535

highest values in **bold**

Respiratory air, single oral dose of 2 mg/kg bw: No volatile radioactivity was found in the extracted air during the 48 h investigation period.

Conclusion:
After oral dosing, measurable radioactivity was already present in the blood at the first sampling time 15 minutes after treatment. Peak concentrations were reached in males and females 6 h after dosing. Excretion after oral treatment was mainly via faeces in males (faeces: 53 %, urine: 43 %) and mainly via urine in females (faeces: 37 %, urine: 57 %), while after intravenous treatment excretion was mainly via urine in both sexes (50 – 59 %). It may be assumed that elimination was largely complete by the end of the study 7 days after treatment. Although measurable radioactivity was still present in urine and faeces, it amounted to appreciably less than 1 % of the administered dose. The residual radioactivity was generally low and yielded on average 1.7 % of the administered dose. It was mainly concentrated in the kidney, the fatty tissue and the blood, where the radioactivity level at the end of the study was twice as high as in the plasma, indicating binding to transport proteins. The levels of radioactivity in tissues were generally rather higher in females than in males. No measurable radioactivity could be found in the respiratory air after oral dosing. Based on the amount of radioactivity excreted via urine (plus cage wash and tissues/carcass), the absorption rate is considered to be higher than 44 % for males and 58 % for females after single oral administration of 2 mg ^{14}C-chlorophenyl-Fenoxaprop-P-ethyl per kg bw.

B.6.1.1.1.2. Kinetics - single high dose administration

Reference:	**Kinetics in the rat after single oral administration of 10 mg/kg body weight Hoe 046360-14C**
Author(s), year:	[redacted] 1987
Report/Doc. number:	01-L42-0514-87 / A37448
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex received a single dose of 10 mg/kg bw Fenoxaprop-P-ethyl dissolved in sesame oil by oral gavage (2 groups). Radioactively labelled Fenoxaprop-P-ethyl was mixed with non-radioactive test substance in a ratio of 1:2. ^{14}C-chlorophenyl-Fenoxaprop-P-ethyl (Code: Hoe 046360 0H ZE99 0001) had a radiochemical purity > 99%, while the unlabelled test substance (Code: Hoe 046360 0H ZC96 0002) had a purity of 95.6 % (according to certificate of analysis No. 02912).

Test material: [chlorophenyl-U-14C]-fenoxaprop-p-ethyl and fenoxaprop-p-ethyl (1:2)
Specific Activity: 357.0 and 347.9 MBq/g (batch 16030 h and i, resp.), used for excretion and distribution

226.3 and 357.0 MBq/g (batch 16030 f and h, resp.), used for blood level kinetics

Test animals: SPF Wistar rat, WISKf (SPF71) strain, [redacted]
7-8 weeks and mean body weights of 212 ± 14 g ♂ and 195 ± 9 g ♀.
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.1-6

Table 6.1.1-6 Dosing scheme, Kinetics in the rat after single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Blood kinetics	10	oral	5 males 5 females	single
Excretion / tissues distribution	10	oral	5 males 5 females	single

Pharmacokinetic investigations: Blood samples were taken from the tip of the tail at the following time intervals: 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120, 144 and 168 hours.
Excretion / tissue distribution investigations: Following dosing, the rats were individually placed in metabolism cages and urine, cage washes and faeces were collected for 7 days. Collection intervals for urine were: 0-2, 2-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, gonads, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood, plasma and diaphragm.

Results:
The quantities excreted via urine and faeces, together with the residual radioactivity in the organs and tissues at the end of the study, yielded a total balance of 98.76 ± 0.83 % in males and 99.45 ± 0.96 % in females.

Pharmacokinetic investigations (blood levels), single oral dose of 10 mg/kg bw: The maximum blood levels were measured about 7 h after treatment. They were comparable in both males and females: 19.86 ± 1.62 and 23.7 ± 4.02 µg equivalents / g, respectively. Reduction of radioactivity in the blood was biphasic and very similar in both sexes. Calculation of the biological half-lives yielded 11.0 ± 1.4 h (males) and 10.3 ± 1.1 (females) for the rapid phase, and 75.1 ± 15.4 h (males) and 72.9 ± 2.3 h (females) for the terminal phase.

Table 6.1.1-7 Blood levels after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl to rats (µg equivalents / g)

Time (hours)	Blood levels (µg equivalents / g)		Time (hours)	Blood levels (µg equivalents / g)	
	Males	Females		Males	Females
0.25	1.409	1.381	24	10.15	12.10
0.5	2.979	2.933	48	4.251	4.606
1	7.944	5.475	72	3.461	3.036
2	12.02	10.04	96	1.806	1.985
4	17.63	17.51	120	1.468	1.660
6	19.26	21.48	144	1.179	1.287
8	**19.85**	**21.92**	168	0.9764	1.193

Maximum values in **bold**

Excretion, single oral dose of 10 mg/kg bw: The portion of orally administered radioactivity excreted via faeces was higher in males (52 %) than in females (38 %). Correspondingly, the renal portion (including cage washings) was higher in females (59 %) than in males (45 %). As in the blood, elimination was biphasic. The biological half-lives for urine and faeces were on average between 7 and 11 h for the rapid phase and between 30 and 66 h for the terminal phase, regardless of sex or route of excretion.

Table 6.1.1-8 Mean % of the administered radioactivity, Excretion after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Collection interval (h)	Oral	
		Males	Females

Sample	Collection interval (h)	Oral	
		Males	Females
Urine	0 – 2	0.4911	0.2831
	2 – 4	0.7616	1.060
	4 – 8	4.425	5.941
	8 – 24	**22.14**	**31.61**
	24 – 48	10.88	14.83
	48 – 72	3.099	2.264
	72 – 96	1.086	0.7094
	96 – 120	0.5104	0.5220
	120 – 144	0.3695	0.4244
	144 – 168	0.3011	0.3012
	Total (0 – 168)	**44.06**	**57.95**
Faeces	0 – 8	1.129	**21.93 (0-24 h)**
	8 – 24	**31.73**	
	24 – 48	14.80	13.33
	48 – 72	3.207	2.057
	72 – 96	0.9476	0.4933
	96 – 120	0.2393	0.3025
	120 – 144	0.1664	0.1148
	144 – 168	0.1160	0.2425
	Total (0 – 168)	**52.33**	**38.47**
Cage wash	0 – 24	0.7844	1.103
	24 – 48	0.1214	0.3042
	48 – 168	0.0100	0.0237
	Total (0 – 168)	**0.9158**	**1.431**
∑ excreta	after 168 hours	**97.31**	**97.85**
Tissues / Carcass	after 168 hours	**1.458**	**1.599**
Total recovery	after 168 hours	**98.76**	**99.45**

Maximum values in **bold**

Table 6.1.1-9 Half-lives ($t_{1/2}$, h) for the elimination of radioactivity in blood and excreta after a single oral dose of 10 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration	
		Males	Females
Blood	Phase I	11.0 ± 1.4	10.3 ± 1.1
	Phase II	75.1 ± 15.4	72.9 ± 2.3
Urine	Phase I	11.0 ± 0.8	8.7 ± 1.0
	Phase II	65.5 ± 12.6	62.7 ± 13.9
Faeces	Phase I	10.7 ± 0.9	7.4 ± 2.6
	Phase II	46.8 ± 10.7	30.3 ± 4.9

Distribution, single oral dose of 10 mg/kg bw: At termination of the study 7 days after treatment, measurable radioactivity was present in all of the examined organs and tissues and in the blood and plasma. These concentrations were generally higher in the females than in the males. The highest values were found in the kidneys and in the blood, followed by the retroperitoneal fatty tissue, the liver and the lungs. The concentrations found in the examined tissues amounted to approximately 1.5 % of the administered radioactivity in the males and 1.6 % in the females.

Table 6.1.1-10 Tissue distribution after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl to rats, µg equiv. / g

Tissue / organ	Oral (µg equivalents / g)		Tissue / organ	Oral (µg equivalents / g)	
	Males	Females		Males	Females
Spleen	0.2327	0.2417	Subcutaneous fat	0.2734	0.3373
Kidneys	**0.8406**	**1.281**	Retroperitoneal fat	0.5737	0.3988
Gonads	0.0821	0.2446	Brain	0.0224	0.0252
Liver	0.4519	0.3247	Bones	0.0844	0.0853
Heart	0.2013	0.2867	**Blood**	**0.7986**	**0.9663**
Lungs	0.3539	0.4192	Plasma	0.3745	0.4535

Tissue / organ	Oral (µg equivalents / g)		Tissue / organ	Oral (µg equivalents / g)	
	Males	Females		Males	Females
Skeletal muscle	0.0666	0.0742	Diaphragm	0.1684	0.2191

highest values in **bold**

Conclusion:
In this study, Fenoxaprop-P-ethyl was rapidly absorbed leading to maximum blood levels 6-8 hours after treatment. Excretion after oral treatment was mainly via faeces in males (faeces: 52 %, urine: 44 %) and mainly via urine in females (faeces: 38 %, urine: 58 %). Lowering of the concentrations in blood, urine and faeces took place biphasically. The highest concentrations in organs and tissues 7 days after treatment were found in the kidneys and in the blood. The total amount of radioactivity in organs and tissues was 1.5 % in males and 1.6 % in females. The minimum absorbed quantity of radioactivity (urine excretion including cage wash and residues in tissues / organs) was 47% for males and 61 % for females.

B.6.1.1.1.3. Kinetics - repeated low dose administration

Reference:	**Hoe 046360-14C. Kinetics in the rat after repeated (14 + 1) oral doses of 2 mg/kg body weight**
Author(s), year:	[redacted] 1987b
Report/Doc. number:	01-L42-0521-87 / A37449
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex received repeated dose treatment with 2 mg/kg bw Fenoxaprop-P-ethyl dissolved in sesame oil by oral gavage. Non-labelled test substance dissolved in sesame oil was administered by oral gavage on 14 successive days followed by a single dose of radioactively labelled Fenoxaprop-P-ethyl (^{14}C-chlorophenyl) on the 15th day of the study. The unlabelled test substance (Code: Hoe 046360 0H ZC96 0002) had a purity of 95.6 % while ^{14}C-chlorophenyl-Fenoxaprop-P-ethyl (Code: Hoe 046360 0H ZE99 0001) had a radiochemical purity > 99%.

Test material: fenoxaprop-p-ethyl and [chlorophenyl-U-14C]-fenoxaprop-p-ethyl
Specific Activity: 903.7 MBq/g

Test animals: SPF Wistar rat, WISKf (SPF71) strain, [redacted]
7-8 weeks and mean body weights of 247 ± 15 g ♂ and 204 ± 10 g ♀.
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.1-6

Table 6.1.1-11 Dosing scheme, Kinetics in the rat after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-P-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Blood kinetics	2	oral	5 males 5 females	Daily 14+1

Excretion / tissue distribution investigations: The test animals were individually placed in metabolism cages and urine, cage washes and faeces were collected for 7 days after the last dosing. Collection intervals for urine were: 0-2, 2-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, gonads, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood, plasma and diaphragm.

Results:
The quantities excreted via urine and faeces, together with the residual radioactivity in the organs and tissues at the end of the study, yielded a total balance of 96.27 ± 1.29 % in males and 99.07 ± 1.42 % in females.

Excretion, repeated oral dose of 2 mg/kg bw: The radioactivity administered on day 15 was excreted predominantly via urine. Higher rate of radioactivity was excreted via urine in the females (65 %) than in the males (54 %), including cage washings. Correspondingly, the amounts excreted via faeces were higher for males (41 %) than for females (33 %). Elimination was biphasic. The biological half-lives calculated for renal and faecal excretion were on average between 8 and 11 h for the rapid phase and between 41 and 55 h for the terminal phase, regardless of sex or route of excretion.

Table 6.1.1-12 Mean % of the administered radioactivity, Excretion after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Collection interval (h)	Oral	
		Males	Females
Urine	0 – 2	0.7276	1.041
	2 – 4	0.7259	0.6243
	4 – 8	5.879	9.073
	8 – 24	**26.28**	**38.36**
	24 – 48	13.17	11.21
	48 – 72	3.512	2.176
	72 – 96	1.377	0.7566
	96 – 120	0.6004	0.4367
	120 – 144	0.3575	0.3534
	144 – 168	0.3049	0.3121
	Total (0 – 168)	**52.93**	**64.34**
Faeces	0 – 8	**21.48 (0-24 h)**	0.7980
	8 – 24		**19.05**
	24 – 48	12.24	9.369
	48 – 72	3.794	2.132
	72 – 96	2.211	0.4758
	96 – 120	0.6281	0.2707
	120 – 144	0.1721	0.1845
	144 – 168	0.1116	0.4600
	Total (0 – 168)	**40.63**	**32.74**
Cage wash	0 – 24	0.8665	0.4706
	24 – 48	0.2850	0.1597
	48 – 168	0.0187	0.0170
	Total (0 – 168)	**1.170**	**0.6474**
∑ excreta	after 168 hours	**94.74**	**97.72**
Tissues / Carcass	after 168 hours	**1.526**	**1.343**
Total recovery	after 168 hours	**96.27**	**99.07**

Maximum values in **bold**

Table 6.1.1-13 Half-lives ($t_{1/2}$, h) for the elimination of radioactivity in excreta after repeated doses of 2 mg/kg bw Fenoxaprop-P-ethyl to rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration	
		Males	Females
Urine	Phase I	11.2 ± 0.3	8.0 ± 0.9
	Phase II	51.2 ± 10.6	54.8 ± 8.5
Faeces	Phase I	10.9 ± 0.4	9.4 ± 2.0
	Phase II	41.7 ± 6.0	48.6 ± 26.5

Distribution, repeated oral dose of 2 mg/kg bw: Measurable radioactivity was present in all examined tissues and organs 7 days after the last treatment. The highest concentrations were found in the kidneys regardless of sex with mean values of 0.19 µg equivalents / g in the males and 0.24 µg equivalents / g in the females. Comparable concentrations were measured in the blood (0.18 µg/g in males, 0.16 µg/g in females). Concentrations higher than 0.1 µg/g were found only in the liver and the retroperitoneal fatty tissue among the males. In all other examined organs, concentrations were lower than 0.1 µg/g. The concentrations found in the examined tissues and organs amounted to approximately 1.5 % of the administered radioactivity in the males and 1.3 % in the females.

Table 6.1.1-14 Tissue distribution after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-P-ethyl to rats, µg equiv. / g

Tissue /	(µg equivalents / g)	Tissue /	(µg equivalents / g)

organ	Males	Females	organ	Males	Females
Spleen	0.0332	0.0258	Subcutaneous fat	0.0556	0.0605
Kidneys	**0.1855**	**0.2355**	Retroperitoneal fat	0.1062	0.0895
Gonads	0.0224	0.0554	Brain	0.0057	0.0038
Liver	0.1001	0.0654	Bones	0.0180	0.0116
Heart	0.0449	0.0485	**Blood**	**0.1820**	**0.1598**
Lungs	0.0697	0.0540	Plasma	0.0997	0.0934
Skeletal muscle	0.0146	0.0127	Diaphragm	0.0393	0.0369

highest values in **bold**

Conclusion:
Excretion was rapid and took place to a greater extent via urine than via faeces in both sexes. The renal portion among females (65 %) was 11 % higher than among males (54 %). Elimination can be assumed to have been more or less completely terminated by the end of the study 7 days after treatment. The total amount of radioactivity in organs and tissues found at the end of the study was 1.5 % in males and 1.3 % in females. The minimum absorbed quantity of radioactively labelled test substance (urinary excretion plus cage washes plus residues in tissues/organs) was considered to be approximately 56 % for males and 66 % for females.

B.6.1.1.1.4. Metabolism - single high dose administration

Reference:	**Hoe 046360-14C. Metabolism in Male and Female Rats after a Single Oral Administration of 10 mg/kg body weight.**
Author(s), year:	[redacted]..; 1987
Report/Doc. number:	CM022/86 / A37324
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	- Individual body weights of animals not stated - SD values for mean body weight of animals not stated, however a range was given - No pilot studies conducted and only one dose used.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 25 rats per sex received a single dose of 10 mg/kg bw Fenoxaprop-P-ethyl dissolved in sesame oil by oral gavage. 1 male and 1 female rat served as controls. The administered test substance was a blend of about 40 % labelled Fenoxaprop-P-ethyl (chlorophenyl-U-^{14}-C, Code: Hoe 046360 0H ZE99 0001, radiochemical purity > 99 %) and about 60 % unlabelled Fenoxaprop-P-ethyl (Code: Hoe 046360 0H ZC96 0002).

Test material: 40% fenoxaprop-p-ethyl and 60% [chlorophenyl-U-14C]-fenoxaprop-p-ethyl
Specific Activity: 373.8 MBq/g

Test animals: SPF Wistar rat, WISKf (SPF71) strain, [redacted]
8-10 weeks and mean bw of 219 g ♂ (210-225 g) and 191 g ♀ (185-195 g).
Number of animals: 25 rats per sex
Dosing scheme: See Table 6.1.1-15

Table 6.1.1-15 Dosing scheme, Metabolism and kinetics in the rat after single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Tissue distribution / Metabolism	10	oral	25 males 25 females	Single
	0 (control)	oral	1 male 1 female	-

Excretion / tissue distribution investigations: Following dosing, the rats were kept in metabolism cages (groups of 2 rats / cage) and urine, cage washes and faeces were collected for 7 days. Samples were pooled from all animals of one sex. Collection intervals for urine, cage washes and faeces were: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment, again pooled from all animals of one sex: liver, kidneys, lungs, spleen, gonads, heart, brain, skeletal muscle, diaphragm, blood, subcutaneous fat and retroperitoneal fat.
Laboratory investigations: The following parameters were measured or calculated:

- radioactivity concentrations in urine, faeces and tissue samples
- metabolite pattern in urine (0-24, 24-48 and 48-72 h after application) and faeces samples (0-24 and 24-48 h after application)
- identification and characterization of the main metabolites in urine, faeces, liver, kidneys and blood
- extent of racemization of Hoe 046360 and its free carboxylic acid Hoe 088406 (the free acid is the only metabolite which contains both the ^{14}C-labelling and the optical active centre in the molecule)

Results:
Excretion, single oral dose of 10 mg/kg bw: In the pooled analysis (all animals from one sex) of radioactivity in urine and faeces a high percentage of elimination was found. More than 80 % of the administered dose (males: 80.8 %, females: 81.6 %) was found in the excreta during the first two days. At the day of sacrifice (7 days post administration) the mean value of the totally excreted radioactivity was 94.2 % (males: 94.0 %, females: 94.4 %) of the administered dose. The female rats excreted higher percentages (52.2 %) of the administered dose via urine than the males (44 %). Consequently, the percentage of radioactivity found in faeces was higher in males (50 %) than in females (42.2 %).

Table 6.1.1-16 Mean % of the administered radioactivity, Excretion after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl to rats; pooled analysis of all animals from one sex

Sample	Collection interval (h)	Oral	
		Males	Females
Urine	**0 – 24**	**24.4**	**28.4**
	24 – 48	11.9	15.9
	48 – 72	4.2	3.6
	72 – 96	1.5	1.6
	96 – 120	0.6	0.6
	120 – 144	0.4	0.4
	144 – 168	0.2	0.3
	Total (0 – 168)	**43.2**	**50.8**
Faeces	**0 – 24**	**28.9**	**19.4**
	24 – 48	14.8	16.5
	48 – 72	4.4	4.3
	72 – 96	1.0	0.9
	96 – 120	0.5	0.5
	120 – 144	0.2	0.2
	144 – 168	0.2	0.4
	Total (0 – 168)	**50.0**	**42.2**
Cage wash	0 – 24	0.6	1.0
	24 – 48	0.2	0.4
	Total (0 – 168)	**0. 8**	**1.4**
∑ excreta	after 168 hours	**94.0**	**94.4**
Tissues / Carcass	after 168 hours	**0.761**	**0.767**
Total recovery	after 168 hours	**94.76**	**95.17**

Maximum values in **bold**

Distribution, single oral dose of 10 mg/kg bw: Organs and tissues from all animals of one sex were pooled for analysis of radioactivity concentrations. A total amount of 0.761 % (males) and 0.767 % (females) of the administered dose was present in the organs and tissues 7 days after the dosing. The analysis showed that organs mainly involved in metabolism had the highest concentrations (kidneys > blood >> liver).

Table 6.1.1-17 Tissue distribution after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl to rats, pooled analysis of all animals from one sex, µg equiv. / g

Tissue / organ	Oral (µg equivalents / g)		Tissue / organ	Oral (µg equivalents / g)	
	Males	Females		Males	Females
Spleen	0.274	0.257	Skeletal muscle	0.106	0.086
Kidneys	**1.128**	**1.463**	Subcutaneous fat	0.251	0.396
Gonads	0.133	0.329	Retroperitoneal fat	0.551	0.658
Liver	0.616	0.414	Brain	0.031	0.028
Heart	0.491	0.323	**Blood**	**1.227**	**1.152**
Lungs	0.498	0.519	Diaphragm	0.278	0.198

highest values in **bold**

Metabolites in the urine: In both sexes, no unchanged Hoe 046360 was eliminated via urine, indicating rapid and extensive metabolisation of the active ingredient by the rats. The major form of renal excretion was clearly identified as the mercapturic acid Hoe 069225. This metabolite represented 61.8 % of the radioactivity in the urine of male rats (27.3 % of applied dose) and 29.6 % of the radioactivity in the urine of female rats (15.5 % of applied dose). The different quantities of Hoe 069225 reflect a sex-related qualitative difference in the metabolic profile of the urine. The free carboxylic acid (Hoe 088406) was excreted by female rats only (17.9 % of applied radioactivity), but not by the male rats. Furthermore, the metabolite Hoe 067978 was observed in the urine of female rats only (1.7 % of applied dose). The metabolites Hoe 054014 (males: 1.6 %; females: 2.7 % of applied dose) and Hoe 080919 (males: 3.7 %; females: 3.0 % of applied dose) were clearly identified in both sexes. Besides the mercapturic acid conjugates of Hoe 069225, glucuronic acid conjugates of Hoe 069225 and sulphate ester conjugates of Hoe 067978 were found in the urine of both sexes.

Metabolites in the faeces: In the 0-24 h faeces of both sexes, approximately 10 % of the applied dose were excreted in the form of unchanged Hoe 046360 and an average of 12 % was excreted as the free acid Hoe 088406. Furthermore, the metabolites Hoe 067978 (males: 8.1 %, females: 6.6 % of the applied dose), Hoe 054014 (males: 2.2 %, females: 1.9 %), Hoe 069225 (males: 0.4 %, females: 0.6 %), and Hoe 080918 (males: 2.1 %, females: 1.8 %) were identified. The metabolite Hoe 064124 exceeded the limit of detection in faeces of female rats only (0.3 % of applied dose). Hydrolysis experiments were carried out to obtain information on the nature of the radioactivity in the non-extractable residues (males: 11.1 %, females: 11.8 % of the applied dose). On average, 28 % of the non-extractable radioactivity was solubilized after reflux with HCl whereas 72 % still remained in the solid matrix. More than 60 % of the corresponding radioactivity consisted of Hoe 054014 and Hoe 064124. Furthermore, 8 unknown radioactive compounds were separated but none of them exceeded the value of 1.5 % of the administered dose.

Metabolites in the blood: 64 % (males) and 70 % (females) of the radioactivity in the blood still remained in the solid matrix as bound residues. The bulk of solubilized radioactivity represented the metabolite Hoe 054014.

Metabolites in the liver: 76 % (males) and 67 % (females) of the total radioactivity in the liver still remained bound in the organ after extraction experiments. The major metabolite was Hoe 054014.

Metabolites in the kidney: The bound residues in the kidneys after extractions were 48 % in the males and 58 % in the females. Again, the major metabolite was Hoe 054014.

Enantiomeric purity of the excreted active ingredient and its free acid: Investigation of the enantiomer ratio in the intact parent compound isolated from the 0-24 h faeces samples showed that no change had taken place compared to the applied active ingredient. Also, no change in the enantiomer ratio was observed in the free acid isolated from female 0-24 h urine and from the 0-24 h and 24-48 h faeces samples of both sexes.

Table 6.1.1-18 % of the administered dose, Metabolites in excreta of rats after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl

Metabolites	Metabolites in excreta of rats (% of the administered dose)		
	males	females	Total excreta

	urine	faeces	urine	faeces	males	females
Hoe 046360 parent compound	-	11.2	-	8.9	11.2	8.9
Hoe 088406 free acid	-	**13.5**	**17.9**	**9.7**	13.5	**27.6**
Hoe 054014 (6-chloro-2,3-dihydro-benzoxazol-2-one)	1.6	2.2	2.7	1.9	3.8	4.6
Hoe 064124 (5-hydroxylation of chlo-rophenyl ring)	-	-	-	0.3	-	0.3
Hoe 067978 (4-hydroxylation of chlo-rophenyl ring)	-	8.1	1.7	6.6	8.1	8.3
Hoe 067978 (sulphate ester conjugate)	3.9	-	3.9	-	3.9	3.9
Hoe 069225 (mercapturic acid)	**27.3**	0.4	15.5	0.6	**27.7**	16.1
Hoe 069225 glucuronic acid conju-gate	5.7	-	3.4	-	5.7	3.4
Hoe 080918 (6-chloro-2,3-dihydro-benzoxazol-2-thione)	3.7	2.1	3.0	1.8	5.8	4.8
Sum of known metabolites	**42.2**	**37.5**	**48.1**	**29.8**	**79.7**	**77.9**
Sum of unknown metabolites	2.0	1.4	4.2	0.6	3.4	4.8
Non-extractable residues	-	11.1	-	11.8	11.1	11.8

Maximum values in **bold**

Table 6.1.1-19 % of the administered dose, Metabolites in the blood, liver and kidneys of rats after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl

Metabolites	**Metabolites in selected organs (% of the administered dose)**					
	Blood		**Liver**		**Kidneys**	
	males	**females**	**males**	**females**	**males**	**females**
Hoe 046360 parent compound	-	-	-	-	-	-
Hoe 088406 free acid	0.5	1	-	-	5	-
Hoe 054014 (6-chloro-2,3-dihydro-benzoxazol-2-one)	20.5	15	10	13	21	14
Sum of known metabolites	**21**	**16**	**10**	**13**	**26**	**14**
Sum of unknown metabolites	15	14	14	20	26	28
Non-extractable residues	64	70	76	67	48	58
Total incorporated (% of dose)	0.254	0.305	0.250	0.165	0.088	0.110

Conclusion:

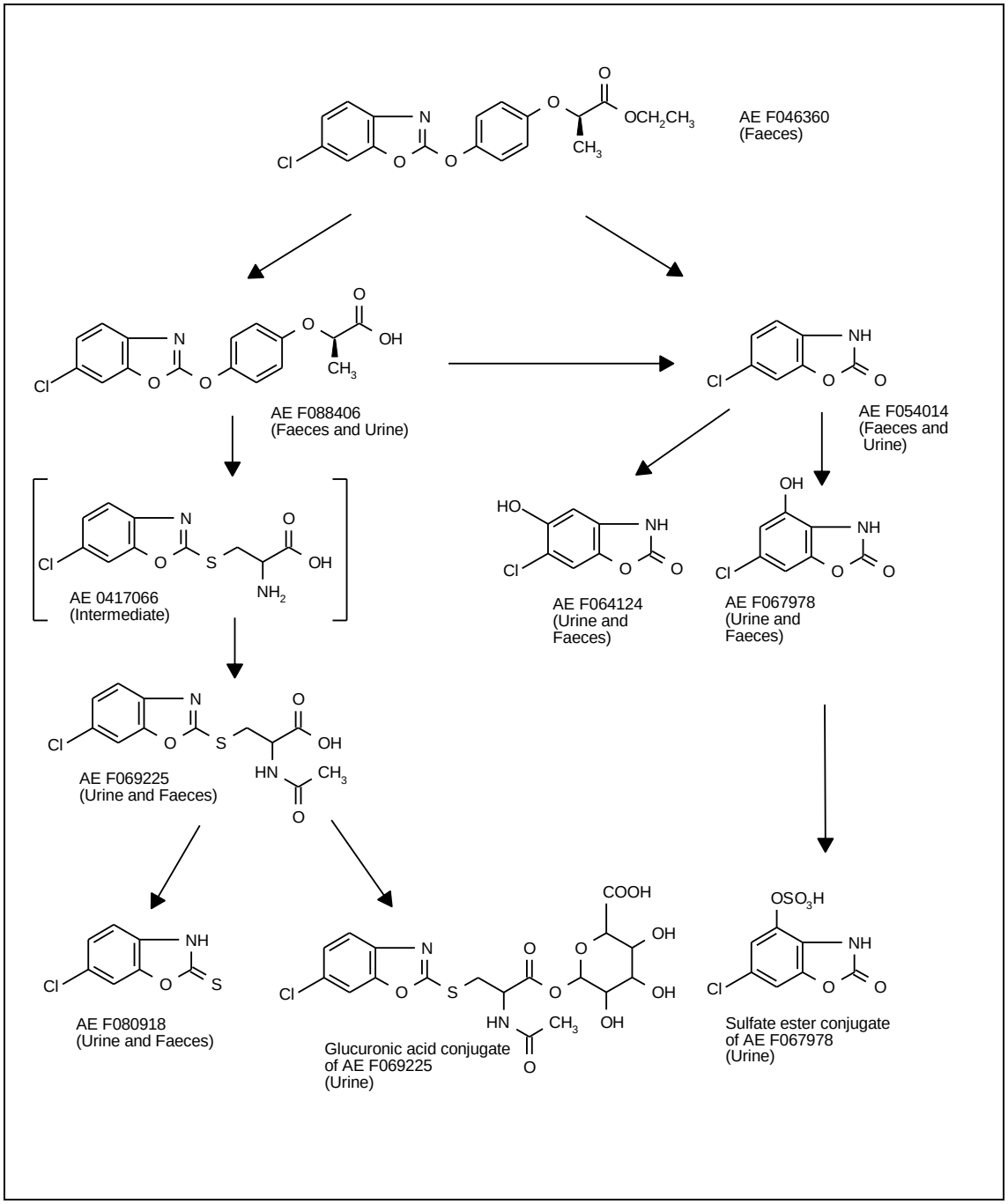
After oral administration of 10 mg Hoe 046360 /kg bw, excretion proceeded very rapidly and was practically completed within the first 4 days after administration of the test substance. Slight sex dependent differences were observed in the excretion route. Female rats excreted approximately 8 % more radioactivity via urine than male rats did. At least 44 % (males: 44 %, females: 52 %) was absorbed from the intestines and completely metabolized after absorption, since no unchanged parent compound was detected in the urine. On average, 10 % of the applied dose was present in faeces in the form of the intact Hoe 046360.

Significant differences were observed with respect to the free carboxylic acid Hoe 088406 which was observed only in the urine of female rats but not in the urine of male rats. From this result it may be concluded that female rats do not have the capacity to metabolize all the absorbed material to metabolites beyond the free acid.

The most important metabolites in urine and faeces besides the free acid Hoe 088406 were: Hoe 069225 (mercapturic acid conjugate), Hoe 054014, Hoe 080918, Hoe 067978, Hoe 064124, and glucuronic acid and sulphate conjugates of Hoe 067978. More than 77 % of the administered radioactivity consisted of the above mentioned metabolites. The sum of unknown but extracted metabolites was less than 5 % of the applied dose. The non-extractable radioactivity in the faeces was below 12 % of the applied dose. On average 28 % of this fraction was solubilized by hydrochloric acid and consisted mainly of Hoe 054014 and Hoe 064124. It was demonstrated that the radioactive residues in blood, liver and kidneys contained the same metabolite structures, especially Hoe 054014, as found in the excreta. Based on the identified metabolites, a metabolic pathway was proposed (Figure 6.1.1-1).

Chiral separation investigations showed clearly that no inversion of the configuration of the optical centre, either in the excreted Hoe 046360, or in the free acid Hoe 088406, occurred after administration to rats.

Figure 6.1.1-1 Proposed metabolic pathway of Fenoxaprop-P-ethyl in rats



B.6.1.1.2. Studies in the rat with Fenoxaprop-ethyl

B.6.1.1.2.1. Kinetics - oral and intravenous administration

Reference:	**Hoe 33171-14C. Study of kinetics and residue determinations following oral and intravenous application in rats.**
Author(s), year:	[redacted]; 1982
Report/Doc. number:	01-L42-0364-82 / A24284
Guideline(s):	Not specified
Deviations from OECD 417 (2010):	- Age of animals not stated. - No pilot studies conducted and only one dose used.
GLP:	Not specified
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex received a single dose of 2 mg/kg bw Fenoxaprop-ethyl by oral gavage (2 groups) or by intravenous injection (2 groups). The exact amount applied was determined radiometrically after the application by comparison with standards and is stated in the table headings. One additional group consisting of one male and one female was used for exhalation tests and received 40 mg/kg bw by oral gavage. Fenoxaprop-ethyl (Code: Hoe 33171 0HAT 302, Batch No.: 9024 II) was labelled with carbon-14 on the chlorophenyl ring and showed a radiochemical purity of >98 %. The test substance was suspended in starch paste for oral administration and dissolved in polyethylene glycol 400 for i.v. injection.

Test material: [chlorophenyl-U-14C]-fenoxaprop-ethyl and unlabelled fenoxaprop-ethyl (ratio 1:9)
Specific Activity: 26.34 MBq/g

Test animals: SPF Wistar rat, [redacted]
mean body weight of 196.7 ±17.4 g (♂) and 179.5 ±9.2 g (♀).
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.1-20

Table 6.1.1-20 Dosing scheme, Kinetics in the rat after single oral and i.v. administration of Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Blood kinetics	2	oral	5 males 5 females	single
Blood kinetics	2	intravenous	5 males 5 females	single
Excretion / tissue distribution	2	oral	5 males 5 females	single
Excretion	2	intravenous	5 males 5 females	single
Respiratory air	40	oral	1 male 1 female	single

Pharmacokinetic investigations: Blood samples were taken from the retrobulbar venous plexus at the following times: 0.25, 0.5, 1, 2, 3, 4, 6, 8, 24, 32, 48, 72, 96, 120, 144 and 168 hours. For i.v. application groups, an additional blood sample was taken 0.083 h after application.
Excretion / tissue distribution investigations: During the trial the animals were kept in individual metabolism cages from which faeces and urine were collected separately. Collection intervals for urine were: 0-4, 4-8, 8-24, 24-48, 48-72 h, and 3-4, 4-5, 5-6 and 6-7 days. Cage washings were performed after 1, 2 and 7 days. Faeces were collected after 0-1, 1-2, 2-3, 3-4, 4-5, 5-6 and 6-7 days. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, gonads, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood and rest of the body.
Expired CO_2 group: The air was removed continuously over a 0 – 24 hour period after dosing and was passed through an exhalimeter where it was investigated for volatile radioactivity.

Results:
The recovery rates following oral administration were 101.3 ± 0.3 % for males and 98.8 ± 7.7 % for females. For i.v. application, complete recovery rates could not be determined as no tissue distribution investigations were performed.

Pharmacokinetic investigations (blood levels), single oral dose: At the time of the first sampling 0.25 h after treatment there were already mean concentrations ranging from 0.5 to 0.6 µg equivalents/ml found in the blood. A maximum concentration was measured 8 h after treatment in both sexes, with a mean of 3.73 ± 0.35 µg equivalents/ml in males and 4.53 ± 1.14 µg equivalents/ml in females. Half-lives were calculated for the 2-phase decline. In males, the first phase was 14.6 ± 3.7 h and the second phase was 73.4 ± 10.0 h. In females, the half-lives were 6.4 ± 1.5 h and 75.0 ± 8.9 h, respectively.

Pharmacokinetic investigations (blood levels), single intravenous dose: The first blood level determinations were made 5 min. after i.v. injection. The values of 4.22 ± 0.89 µg equivalents/ml (males) and 5.12 ± 1.19 µg equivalents/ml (females) were the highest values measured. The decline in concentration proceeded in three phases. In the fastest phase (phase I), which was predominant during about the first hour post application, the half-lives amounted to 1.3 ± 0.4 h (males) and 0.72 ± 0.5 h (females). For phase II (2-48 h post application), 11.2 ± 1.1 h (males) and 7.8 ± 1.2 h (females) were calculated. For phase III which lasted from 48 h onwards, the half-lives were 97.5 ± 17.2 h (males) and 72.8 ± 10.4 h (females).

Table 6.1.1-21 Blood levels after single oral administration of 2.52 and 2.27 mg/kg bw and single intravenous administration of 2.06 and 2.39 mg/kg bw Fenoxaprop-ethyl to male and female rats, respectively (µg equiv. / ml)

Time (hours)	Oral (µg equivalents / ml)		i.v. (µg equivalents / ml)	
	Males	Females	Males	Females
0.083	n.d.	n.d.	**4.223**	**5.123**
0.25	0.5801	0.598	3.991	4.934
0.5	1.419	1.076	3.593	4.585
1	1.934	1.800	3.458	4.301
2	3.021	2.725	3.048	4.148
3	3.290	3.209	2.941	3.926
4	3.288	3.498	2.795	3.819
6	3.679	4.127	2.586	3.734
8	**3.730**	**4.526**	2.380	3.551
24	2.798	1.988	1.363	1.411
32	1.968	1.426	1.022	n.d.
48	1.334	0.893	0.6298	0.6543
72	0.8469	0.684	0.4229	0.4684
96	0.6591	0.518	0.3314	0.3656
120	0.4781	0.423	0.3456	0.2963
144	0.4047	0.339	0.2568	0.2510
168	0.3262	0.276	0.2047	0.1814

n.d. = not determined
highest values in **bold**

Excretion, single oral and intravenous dose: Regardless of the application route, more radioactivity was eliminated in the urine than in the faeces. The proportion eliminated renally was greater for the females than for the males. The elimination in the urine and faeces proceeded in two phases, but the half-lives of both phases could not be determined in every case. The half-lives in the urine and faeces for the more rapid phase were similar for both application routes and lay between 8 and 12 h. For the slower phase, the half-lives following oral administration were found to be about 45 h (males) and 37 h (females) for urine and about 34 h (males) and 43 h (females) for faeces. Data for the slow elimination phase after i.v. application are incomplete.

Table 6.1.1-22 Mean % of the administered radioactivity, Excretion after a single oral dose (♂: 2.52 mg/kg bw, ♀: 2.27 mg/kg bw) and a single i.v. administration (♂: 2.34 mg/kg bw, ♀: 2.29 mg/kg bw) of Fenoxaprop-ethyl to rats

Sample	Collection interval (h)	Oral		Intravenous	
		Males	Females	Males	Females
Urine	0 – 4	4.12	3.16	1.89	7.44
	4 – 8	5.64	10.74	4.16	3.23
	8 – 24	**23.09**	**33.92**	**13.41**	**31.04**
	24 – 48	11.97	13.49	8.62	9.29
	48 – 72	3.50	3.24	3.03	4.20
	72 – 96	1.35	1.50	1.99	1.56
	96 – 120	0.84	0.73	1.76	1.35
	120 – 144	0.58	0.45	2.41	0.89
	144 – 168	0.43	0.31	1.23	0.75
	Total (0 – 168)	**51.5**	**67.5**	**38.5**	**59.8**
Faeces	**0 – 24**	**21.25**	**13.22**	11.45	**11.69**
	24 – 48	16.10	8.58	**12.08**	7.66
	48 – 72	4.62	2.36	3.02	1.90
	72 – 96	1.17	0.48	1.40	0.47
	96 – 120	0.44	0.39	1.12	0.62
	120 – 144	0.23	0.17	2.25	0.57
	144 – 168	0.16	0.13	1.80	0.72
	Total (0 – 168)	**44.0**	**25.3**	**33.1**	**23.5**
Cage wash	0 – 24	1.25	2.49	1.42	1.91
	24 – 48	1.14	1.05	0.77	1.00
	48 – 168	0.12	0.19	0.19	0.13
	Total (0 – 168)	**2.51**	**3.73**	**2.38**	**3.04**
∑ excreta	after 168 hours	**98.0**	**96.6**	**74.0**	**86.3**
Tissues / Carcass	after 168 hours	**3.31**	**2.23**	**n.d.**	**n.d.**
Total recovery	after 168 hours	**101.3**	**98.8**	**n.d.**	**n.d.**

n.d. = not determined
Maximum values in **bold**

Table 6.1.1-23 Half-lives (h) for the elimination of radioactivity in blood and excreta after a single oral or i.v. dose of Fenoxaprop-ethyl to rats

Sample	Elimination phase	Oral administration		i.v. administration	
		Males	Females	Males	Females
Blood	Phase I	14.6 ± 3.7	6.4 ± 1.5[1)]	1.3 ± 0.4	0.72 ± 0.5[2)]
	Phase II	73.4 ± 10.0	75.0 ± 8.9	11.2 ± 1.1	7.8 ± 1.2
	Phase III	-	-	97.5 ± 17.2	72.8 ± 10.4
Urine	Phase I	10.2 ± 1.1	7.9 ± 0.3[1)]	9.4 ± 2.8[2)]	9.8 ± 0.5[1)]
	Phase II	44.7 ± 9.4	36.5 ± 7.8	37.7 ± 5.4[2)]	70.1 ± 30.2
Faeces	Phase I	9.5 ± 2.5	11.4 ± 1.7	-	11.8 ± 1.0[1)]
	Phase II	33.7 ± 4.0	42.7 ± 23.2	40.0 ± 16.3[1)]	-

n.d. = not determined, [1)] n=4, [2)] n=3

Distribution, single oral dose: The highest amounts of radioactivity were found in the kidneys with 0.22 ± 0.04 µg equivalents/g in males and 0.38 ± 0.11 µg equivalents/g in females. The liver showed concentrations of 0.13 ± 0.02 µg/g (males) and 0.10 ± 0.03 µg/g (females). In the male rats the retroperitoneal fat contained 0.23 ± 0.16 µg/g and the subcutaneous fat 0.17 µg/g while the concentrations in the fat of the females were about 0.05 µg/g. The blood levels in both sexes at the time of sacrifice were around 0.3 µg/g. In the remaining organs and tissues examined the concentrations were below 0.1 µg/g. The whole amount found in organs and tissues at the end of the study was approximately 3 % for males and 2 % for females.

Table 6.1.1-24 Tissue distribution after a single oral administration of 2.52 (males) and 2.27 (females) mg/kg bw Fenoxaprop-ethyl to rats, µg equiv. / g

Tissue / organ	Oral (µg equivalents / g)		Tissue / organ	Oral (µg equivalents / g)	
	Males	Females		Males	Females
Spleen	0.0481	0.057	Subcutaneous fat	0.1682	0.058
Kidneys	**0.2166**	**0.376**	**Retroperitoneal fat**	**0.2296**	0.045
Gonads	0.0331	0.0513	Brain	0.0070	0.008
Liver	0.1333	0.097	Bones	0.0284	0.0242
Heart	0.0902	0.049	**Blood**	**0.3117**	**0.317**
Lungs	0.0848	0.099	Carcass	0.0954	0.039
Skeletal Muscle	0.0245	0.019			

highest values in **bold**

Respiratory air, single oral dose of 2 mg/kg bw/d: For one male and one female rat, the radioactivity eliminated in the respiratory air was monitored continuously for 24 h following oral administration of 40 mg/kg bw. No values exceeding the detection limit of 0.01 % of the applied radioactivity were measured.

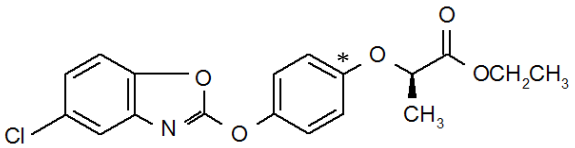
Conclusion:
Following oral administration of 2 mg ^{14}C-chlorophenyl-Fenoxaprop-ethyl per kg bw, the mean maximum blood levels were measured 8 h post application in both sexes. The maximum blood levels after i.v. dosing were detected 5 minutes post injection. Regardless of the application route or sex, more test substance was eliminated in the urine. For oral administration, renal excretion amounted to 54.0 % in males and 71.3 % in females. In faeces, 44.0 % (males) and 25.3 % (females) of the radioactivity were found. 7 days after treatment, elimination was largely complete after oral administration. Residues in tissues amounted to a total of 2 – 3 % after oral dosing. The highest concentrations were found in kidneys (0.2 – 0.38 µg/g). With the exception of fat, liver and blood concentrations, all other tissue values were found to be smaller than 0.1 µg/g. No measurable radioactivity could be detected in the respiratory air after oral dosing. The absorption rate is assumed to be larger than 57 % (males) and 73 % (females) after single oral administration of 2 mg/kg bw, based on urinary excretion plus cage wash and tissues/carcass.

B.6.1.1.2.2. Excretion and residue determination - low dose administration

Reference:	**Hoe 33171-(dioxyphenyl-1-14C). Investigations into the excretion, and determination of residues after oral administration of 2 mg/kg body weight to rats.**
Author(s), year:	[redacted]; 1984a
Report/Doc. number:	01-L41-0436-84 / A32611
Guideline(s):	EPA Guideline 85-1 (1982)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	yes
Acceptability:	Yes

Material and Methods:
A group of 5 female rats received a single dose of 2 mg/kg bw Fenoxaprop-ethyl dissolved in sesame by oral gavage. The experimental animals were about 16 – 18 weeks old and had body weights between 190 and 200 g. Fenoxaprop-ethyl was labelled with carbon-14 in the 1-position of the dioxyphenyl ring and had a radiochemical purity of 96 %.

Test material: Hoe 033171 0H ZE 99 0002



*[dioxyphenyl-U-14C]-fenoxaprop-ethyl
diluted with unlabelled fenoxaprop-ethyl (ratio 1:9)
Specific activity: 26.34 MBq/g

Test animals: SPF Wistar rat, [redacted]
16-18 weeks and mean body weight of 195 ±3.5 g

Number of animals: 5 female rats
Dosing scheme: See Table 6.1.1-25

Table 6.1.1-25 Dosing scheme, Kinetics in the female rat after single oral administration of Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Tissue distribution	2	oral	5 females	Single

Pharmacokinetic investigations: not performed (no blood samples were taken in this study)
Excretion / tissue distribution investigations: During the trial the animals were housed in individual metabolism cages from which faeces and urine were collected separately. Collection intervals for urine were: 0-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h. Cage washings were performed after 0-24, 24-48 and 48-168 h. Faeces were collected after 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, ovaries, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood, plasma and rest of the body.

Results:
The overall balance of excretion and concentrations remaining in the body showed that the recovery was 94.49 ± 1.93 % following oral administration of Fenoxaprop-ethyl to female rats.

Excretion, single oral dose: More radioactivity was excreted with urine than with faeces: the mean renal excretion was 67.46 ± 6.21 % of the dose administered (including cage wash), compared with 26.29 ± 5.41 % eliminated via faeces. The profiles of the elimination of Fenoxaprop-ethyl with urine and faeces showed 2 phases with different rates of elimination. The mean biological half-lives calculated were 8.1 h for the rapid phase I in urine and 53 h for phase II. For faeces, 16.8 h was determined for phase I and 32.7 h for phase II.

Table 6.1.1-26 Mean % of the administered radioactivity, Excretion after a single oral dose of 2 mg/kg bw Fenoxaprop-ethyl to female rats

Sample	Collection interval (h)	Females
Urine	0 – 4	2.534
	4 – 8	5.454
	8 – 24	**42.22**
	24 – 48	13.26
	48 – 72	1.938
	72 – 96	0.4667
	96 – 120	0.1708
	120 – 144	0.0996
	144 – 168	0.1585
	Total (0 – 168)	**66.30**
Faeces	**0 – 24**	**14.61**
	24 – 48	7.201
	48 – 72	2.019
	72 – 96	1.631
	96 – 120	0.0938
	120 – 144	0.460
	144 – 168	0.2665
	Total (0 – 168)	**26.29**
Cage wash	0 – 24	0.6139
	24 – 48	0.4432
	48 – 168	0.0966
	Total (0 – 168)	**1.154**
∑ excreta	after 168 hours	**93.74**
Tissues / Carcass	after 168 hours	**0.7485**
Total recovery	after 168 hours	**94.49**

Maximum values in **bold**

Table 6.1.1-27 Half-lives (h) for the elimination of radioactivity in excreta after a single oral dose of 2 mg/kg bw Fenoxaprop-ethyl to female rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration Females
Urine	Phase I	8.1
	Phase II	53
Faeces	Phase I	16.8
	Phase II	32.7

Distribution, single oral dose: The radioactivity found in organs and tissues corresponded to less than 0.1 or 0.01 µg equivalents / g. Specifically, the concentration in subcutaneous fat was 0.044 µg/g and that in retroperitoneal fat was 0.036 µg/g. The concentrations in the liver and kidneys as well as in the plasma were around 0.01 µg/g. The concentration in the ovaries was nearly 0.019 µg/g. Similar figures (0.022 µg/g) were found for the rest of the body. No radioactivity above the detection limits was found in the other organs and tissues investigated. It can be estimated that about 0.75 ± 0.39 % of the administered dose was present in the body 7 days after treatment.

Table 6.1.1-28 Tissue distribution after a single oral administration of 2 mg/kg bw Fenoxaprop-ethyl to female rats, µg equiv. / g

Tissue / organ	µg equivalents / g Females	Tissue / organ	µg equivalents / g Females
Spleen	<DL	**Subcutaneous fat**	**0.0438**
Kidneys	0.0100	Retroperitoneal fat	0.0363
Ovaries	0.0189	Brain	<DL
Liver	0.0095	Bones	<DL
Heart	<DL	Blood	<DL
Lungs	<DL	Plasma	0.0097
Skeletal Muscle	<DL	Carcass	0.0217

<DL = below detection limit
Maximum values in **bold**

Conclusion:
The principal route of excretion of (dioxyphenyl-1-^{14}C)-Fenoxaprop-ethyl was via urine (67 %) while a lower rate of radioactivity was found in faeces (26 %). Most of the radioactivity was excreted during the first 48 hours after oral administration of 2 mg/kg bw. The concentration of residues in organs and tissues was low with 0.75 % of the administered dose found 7 days after treatment. The absorption rate is assumed to be larger than 68 % based on urinary excretion plus cage wash and residues in tissues/carcass.

B.6.1.1.2.3. Kinetics and residue determination - high dose administration (study 1)

Reference:	**Hoe 33171-(chlorophenyl-U-14C). Study of kinetics and residue concentrations following oral administration of 10 mg/kg body weight to rats.**
Author(s), year:	[redacted];1984b
Report/Doc. number:	01-L42-0439-84E / A30454
Guideline(s):	EPA Guideline 85-1 (1982)
Deviations from OECD 417 (2010):	- Ratio of radiolabelled and unlabelled substance not stated, however, as radiochemical purity and specific radioactivity is indicated, this is considered a minor deviation. - No pilot studies conducted and only one dose used.
GLP:	yes
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex were administered a single dose of 10 mg/kg bw Fenoxaprop-ethyl dissolved in sesame oil by oral gavage. For this experiment, Fenoxaprop-ethyl (Hoe 033171 0H ZE98 0007) was labelled with ^{14}C on the chlorophenyl ring and had a radiochemical purity of 98 %. It was then mixed with non-radioactive test substance (Hoe 033171 0H ZB99 0001).

Test material: [chlorophenyl-U-14C]-fenoxaprop-ethyl and fenoxaprop-ethyl (ratio not stated)
Specific Activity: 445 MBq/g

Test animals: SPF Wistar rat, [redacted]
16-18 weeks and mean body weights of 183 ± 10.4 g ♂ and 191 ± 5.5 g ♀.
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.1-29

Table 6.1.1-29 Dosing scheme, Kinetics in the rat after a single oral administration of 10 mg/kg bw Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Tissue distribution	10	oral	5 males 5 females	Single

Excretion / tissue distribution investigations: Following dosing, the rats were individually placed in metabolism cages and urine, cage washes and faeces were collected for 7 days. Collection intervals for urine were: 0-2, 2-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, testes/ovaries, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, blood and carcass.

Results:
The total amount of radioactivity eliminated and retained in the organism (without gastro-intestinal tract) after 7 days yielded a recovery rate of 97.96 ± 5.79 % for the males and 99.87 ± 1.98 % for the females.

Excretion, single oral dose of 10 mg/kg bw: The orally administered radioactivity was eliminated via urine as well as via faeces. In males, the rate excreted via faeces (49 %) was higher than the rate excreted via urine (44 %, including cage wash). This was contrary in females, where a higher rate was eliminated via urine (60 %, including cage wash) than via faeces (35 %). From the course of elimination via urine and faeces two phases with different elimination rates were found. The biological half-lives calculated ranged between 8 and 10 h for the rapid phase for urine and faeces regardless of sex. For the second phase, half-lives for the elimination via urine and faeces of 36 h and 45 h for males, and 69 h and 27 h for females were determined.

Table 6.1.1-30 Mean % of the administered radioactivity, Excretion after a single oral administration of 10 mg/kg bw Fenoxaprop-ethyl to rats

Sample	Collection interval (h)	Oral	
		Males	Females
Urine	0 – 2	0.3217	1.022
	2 – 4	0.7819	0.4836
	4 – 8	4.743	7.219
	8 – 24	**22.05**	**33.43**
	24 – 48	10.20	11.55
	48 – 72	2.476	3.009
	72 – 96	1.140	0.9723
	96 – 120	0.6348	0.4925
	120 – 144	0.3795	0.3801
	144 – 168	0.2856	0.3050
	Total (0 – 168)	**43.02**	**58.86**
Faeces	0 – 8	1.352	0.8750
	8 – 24	**30.80**	**18.58**
	24 – 48	13.02	11.12
	48 – 72	2.181	2.731
	72 – 96	0.9459	0.8246
	96 – 120	0.3293	0.4436
	120 – 144	0.2140	0.5749
	144 – 168	0.1573	0.1264
	Total (0 – 168)	**49.00**	**35.27**
Cage wash	0 – 24	0.5597	1.138
	24 – 48	0.2528	0.3294
	48 – 168	0.0322	0.0182
	Total (0 – 168)	**0.8446**	**1.486**
∑ excreta	after 168 hours	**92.86**	**95.62**
Tissues / Carcass	after 168 hours	**5.09**	**4.25**

Sample	Collection interval (h)	Oral	
		Males	Females
Total recovery	after 168 hours	**97.96**	**99.87**

Table 6.1.1-31 Half-lives ($t_{1/2}$, h) for the elimination of radioactivity in excreta after a single oral dose of 10 mg/kg bw Fenoxaprop-ethyl to rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration	
		Males	Females
Urine	Phase I	8.38	9.66
	Phase II	35.64	69.43
Faeces	Phase I	10.08	8.62
	Phase II	45.03	26.50

Distribution, single oral dose of 10 mg/kg bw: 7 days after treatment, the highest concentrations of radioactivity were found in the fat tissue with relatively high interindividual differences. Relatively high concentrations were also found in blood and kidneys. The concentrations in the other organs examined were lower than 1 µg/g (spleen, ovaries, liver, heart, lung), with some being lower than 0.1 µg/g (testes, bones, brain, skeletal muscle). From the concentrations measured in the organs, tissues and carcass it can be estimated that the amount of radioactivity was approximately 5 % and 4 % of the administered dose in males and females, respectively.

Table 6.1.1-32 Tissue distribution after a single oral administration of 10 mg/kg bw Fenoxaprop-ethyl to rats, µg equiv. / g

Tissue / organ	(µg equivalents / g)		Tissue / organ	(µg equivalents / g)	
	Males	Females		Males	Females
Spleen	0.1289	0.1679	**Subcutaneous fat**	**1.265**	0.8713
Kidneys	0.7420	**1.284**	**Retroperitoneal fat**	**1.972**	**1.320**
Gonads	0.0820	0.4628	Brain	0.0207	0.0233
Liver	0.3431	0.4052	Bones	0.0722	0.0822
Heart	0.2201	0.3145	**Blood**	**0.7439**	**1.531**
Lungs	0.2652	0.3144	Carcass	0.2410	0.2373
Skeletal Muscle	0.0965	0.0951			

highest values in **bold**

Conclusion:
Fenoxaprop-ethyl was rapidly absorbed and eliminated in this study. Excretion after oral treatment was mainly via faeces in males (faeces: 49 %, urine: 44 %) and mainly via urine in females (urine: 60 %, faeces: 35 %). The elimination of radioactivity (^{14}C-chlorophenyl-Fenoxaprop-ethyl) was biphasic in both sexes. The highest concentrations of radioactivity in organs and tissues were found in fat tissue, kidneys and blood. The total amount of radioactivity in organs and tissues was approximately 5 % in males and 4 % in females. The minimum absorbed quantity of radioactivity (urine excretion including cage wash and tissues/organs) was 49 % for males and 65 % for females.

B.6.1.1.2.4. Kinetics and residue determination - high dose administration (study 2)

Reference:	**Hoe 33171-(dioxyphenyl-1-14C). Investigations into the kinetics and determination of residues concentrations after oral administration of 10 mg/kg body weight to rats.**
Author(s), year:	[redacted]; 1984c
Report/Doc. number:	01-L42-0440-84 / A32612
Guideline(s):	EPA Guideline 85-1 (1982)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	yes
Acceptability:	Yes

Material and Methods:
A group of 5 female rats was administered a single dose of 10 mg/kg bw Fenoxaprop-ethyl dissolved in sesame oil by oral gavage. The test substance was labelled with ^{14}C in the 1-position of the dioxyphenyl ring and had a radiochemical purity of 96 %.

Test material: [dioxyphenyl-1-14C]-fenoxaprop-ethyl, Hoe 033171 0H ZE99 0002

Specific Activity: 420 MBq/g

Test animals: female SPF Wistar rat, [redacted]
16-18 weeks and mean body weights of 181 ± 2.2 g ♀.
Number of animals: 5 rats
Dosing scheme: See Table 6.1.1-33

Table 6.1.1-33 Dosing scheme, Kinetics in the female rat after single oral administration of 10 mg/kg bw Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Tissue distribution	10	oral	5 females	Single

Excretion / tissue distribution investigations: Following dosing, the rats were individually placed in metabolism cages and urine, cage washes and faeces were collected for 7 days. Collection intervals for urine were: 0-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, ovaries, liver, heart, lungs, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bone, blood, plasma and carcass.

Results:
The overall balance of excretion and concentrations remaining in the body showed that the recovery was 98.93 ± 8.39 % for the 7 day test period.

Excretion, single oral dose of 10 mg/kg bw: More radioactivity was excreted with urine (65 % including cage wash) than with faeces (31 %). The mean biological half-lives for renal and faecal excretion were 6 – 7 h for the first elimination phase and 37 – 38 h for the second elimination phase.

Table 6.1.1-34 Mean % of the administered radioactivity, Excretion after a single oral administration of 10 mg/kg bw Fenoxaprop-ethyl to female rats

Sample	Collection interval (h)	Oral Females
Urine	0 – 4	2.47
	4 – 8	6.989
	8 – 24	**41.99**
	24 – 48	10.51
	48 – 72	1.126
	72 – 96	0.218
	96 – 120	0.1138
	120 – 144	0.0754
	144 – 168	0.0583
	Total (0 – 168)	**63.55**
Faeces	0 – 8	0.7835
	8 – 24	**14.75**
	24 – 48	14.63
	48 – 72	1.020
	72 – 96	0.1471
	96 – 120	0.0595
	120 – 144	0.0284
	144 – 168	0.0244
	Total (0 – 168)	**31.44**
Cage wash	0 – 24	1.144
	24 – 48	0.2207
	48 – 168	0.0148
	Total (0 – 168)	**1.38**
∑ excreta	after 168 hours	**96.37**
Tissues / Carcass	after 168 hours	**2.558**
Total recovery	after 168 hours	**98.93**

Maximum values in **bold**

Table 6.1.1-35 Half-lives (h) for the elimination of radioactivity in excreta after a single oral dose of 10 mg/kg bw Fenoxaprop-ethyl to female rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration Females
Urine	Phase I	7
	Phase II	38.1
Faeces	Phase I	6.1
	Phase II	37.3

Distribution, single oral dose of 10 mg/kg bw: The highest amounts of radioactivity were found in subcutaneous and retroperitoneal fat (0.34 µg/g and 0.53 µg/g, resp.). 0.27 µg/g were found in the carcass, and 0.1254 µg in the ovaries. In the other organs and tissues examined, the radioactivity corresponded to less than 0.1 µg/g. From the concentrations in the various organs and tissues investigated it was calculated that 7 days after treatment, 2.56 ± 1.60 % of the administered dose were still present in the body.

Table 6.1.1-36 Tissue distribution after a single oral administration of 10 mg/kg bw Fenoxaprop-ethyl to female rats, µg equiv. / g

Tissue / organ	µg equivalents / g Females	Tissue / organ	µg equivalents / g Females
Spleen	0.0156	**Subcutaneous fat**	**0.3432**
Kidneys	0.0543	**Retroperitoneal fat**	**0.5278**
Ovaries	0.1254	Brain	<DL
Liver	0.0411	Bones	0.0871
Heart	0.0350	Blood	0.0183
Lungs	0.0350	Plasma	0.0385
Skeletal Muscle	0.0216	Carcass	0.2704

<DL = below detection limit
Highest values in **bold**

Conclusion:
After oral administration of ^{14}C-dioxyphenyl-Fenoxaprop-ethyl to female rats, absorption and excretion took place rapidly. Excretion was mainly via urine (urine: 65 %, including cage wash) and less via faeces (31 %). The elimination of radioactivity was biphasic and showed rates of 6 – 7 h for the first phase and 37 – 38 h for the second phase for both renal and faecal excretion. Highest amounts of radioactivity in the examined tissues and organs were found in fat compartments (subcutaneous, retroperitoneal) and in the carcass. The total concentration of administered radioactivity in the body 7 days after treatment was 2.6 %. Based on urinary excretion including cage wash and tissues/organs, the minimum absorbed amount of test substance was 68 % of the administered dose.

B.6.1.1.2.5. Kinetics and residue determination - repeated low dose administration

Reference:	**Hoe 33171-(chlorophenyl-U-14C). Study of kinetics and residue concentrations following repeated oral applications of 2 mg/kg body weight in rats.**
Author(s), year:	[redacted]; 1984d
Report/Doc. number:	01-L42-442-84E / A30456
Guideline(s):	EPA Guideline 85-1 (1982)
Deviations from OECD 417 (2010):	- No information on batch and purity stated. - No pilot studies conducted and only one dose used.
GLP:	yes
Acceptability:	Yes

Material and Methods:
Groups of 5 rats per sex were treated with 14 daily doses of 2 mg/kg bw Fenoxaprop-ethyl dissolved in sesame oil by oral gavage. 24 h after the last dosing, 2 mg/kg bw of radioactively labelled Fenoxaprop-ethyl (^{14}C-chlorophenyl) were administered on the 15th day of the study. ^{14}C-chlorophenyl-Fenoxaprop-ethyl had a radiochemical purity of 98 %. No information on batch and purity of the unlabelled test substance is presented in the study report.

Test material: [chlorophenyl-U-14C]-fenoxaprop-ethyl, Hoe 033171 0H ZE98 0007

Specific Activity: 845 MBq/g

Test animals: Wistar rat, WISKf (SPF71), [redacted]
16-18 weeks and mean body weights of 248 ± 19.6 g ♂ and 213 ± 2.7 g ♀.
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.1-37

Table 6.1.1-37 Dosing scheme, Kinetics in the rat after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Tissue distribution	2	oral	5 males 5 females	repeated

Excretion / tissue distribution investigations: The test animals were individually placed in metabolism cages and urine, cage washes and faeces were collected for 7 days after the last dosing. Collection intervals for urine were: 0-2, 2-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed after 0-24, 24-48 and 48-168 hours. Faeces were collected after 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. The following organs and tissues were removed immediately after sacrifice of the animals 7 days after treatment: spleen, kidneys, testes/ovaries, liver, heart, lung, skeletal muscle, subcutaneous fat, retroperitoneal fat, brain, bones, carcass and blood.

Results:
7 days after the last treatment there was a total recovery of 94.56 ± 1.34 % for males and 100.36 ± 0.67 % for females.

Excretion, repeated oral dose of 2 mg/kg bw: More radioactivity was excreted with the urine than with faeces. The renally eliminated portion in females (66 %) was higher than in males (50 %), including cage washings. Correspondingly, the amounts excreted via faeces were higher for males (40 %) than for females (31 %). Elimination was biphasic for renal and faecal excretion. The biological half-lives for the rapid phase were similar for urine and faeces and ranged from 8.5 to 12.5 h. For the second slower elimination phase, half-lives ranged from 41 – 73 h for renal excretion and from 27 to 34 h for faecal excretion.

Table 6.1.1-38 Mean % of the administered radioactivity, Excretion after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-ethyl to rats

Sample	Collection interval (h)	Oral	
		Males	Females
Urine	0 – 2	< DL	0.627
	2 – 4	0.928	0.1311
	4 – 8	3.95	3.761
	8 – 24	**27.70**	**36.58**
	24 – 48	11.93	16.29
	48 – 72	3.045	3.222
	72 – 96	1.116	1.190
	96 – 120	0.5362	0.6900
	120 – 144	0.3906	0.5190
	144 – 168	0.3389	0.3421
	Total (0 – 168)	**48.95**	**64.15**
Faeces	0 – 8	**23.84 (0-24 h)**	0.5600
	8 – 24		**16.04**
	24 – 48	12.30	14.54
	48 – 72	2.785	2.004
	72 – 96	0.6532	0.5902
	96 – 120	0.3633	0.1952
	120 – 144	0.3215	0.2199
	144 – 168	0.1094	0.3049
	Total (0 – 168)	**40.37**	**31.13**
Cage wash	0 – 24	0.4038	1.721
	24 – 48	0.4311	0.2305
	48 – 168	0.0208	0.0989
	Total (0 – 168)	**0.8556**	**2.051**
∑ excreta	after 168 hours	**90.17**	**97.33**
Tissues / Carcass	after 168 hours	**4.39**	**3.03**

Sample	Collection interval (h)	Oral	
		Males	Females
Total recovery	after 168 hours	**94.56**	**100.36**

<DL = below detection limit for at least some of the animals
Maximum values in **bold**

Table 6.1.1-39 Half-lives (h) for the elimination of radioactivity in excreta after repeated doses of 2 mg/kg bw Fenoxaprop-ethyl to rats

Sample	Elimination phase	$t_{1/2}$ (h) after oral administration	
		Males	Females
Urine	Phase I	10.53	8.64
	Phase II	72.52	41.33
Faeces	Phase I	8.49	12.50
	Phase II	27.27	33.70

Distribution, repeated oral dose of 2 mg/kg bw: Concentrations of radioactivity were the highest in the kidneys with about 0.30 and 0.22 µg equivalents/g, and the blood with 0.24 and 0.21 µg equivalents/g, for females and males, respectively. Fatty tissues contained between 0.1 and 0.2 µg/g (higher in males than females). In the liver, concentrations were approximately 0.1µg/g while in all the other organs concentrations were lower than 0.1 µg/g. The concentrations found in the examined tissues and organs amounted to approximately 4.4 % of the administered radioactivity in the males and 3.0 % in the females.

Table 6.1.1-40 Tissue distribution after repeated dose oral administration of 2 mg/kg bw Fenoxaprop-ethyl to rats, µg equiv. / g

Tissue / organ	Oral (µg equivalents / g)		Tissue / organ	Oral (µg equivalents / g)	
	Males	Females		Males	Females
Spleen	0.0425	0.0390	Subcutaneous fat	0.1315	0.1082
Kidneys	**0.2206**	**0.3007**	**Retroperitoneal fat**	**0.1871**	0.0743
Testes / Ovaries	0.0239	0.0618	Brain	0.0074	0.0051
Liver	0.1257	0.0859	Bones	0.0228	0.0173
Heart	0.0651	0.0420	**Blood**	**0.2355**	**0.2071**
Lungs	0.0786	0.0783	Carcass	0.0691	0.0372
Skeletal muscle	0.0222	0.0163			

Highest values in **bold**

Conclusion:
Excretion was rapid and took place to a greater extent via urine than via faeces in both sexes. The renal portion among females (64 %) was higher than among males (49 %). Elimination was largely completed by the end of the study 7 days after treatment. However, the test substance was still present in the organs and tissues of the test animals (males: 4.4 %, females: 3.0 %). The total amount of absorbed test substance is assumed to be at least 54 % in males and 69 % in females, based on urinary excretion, cage washes and tissues/organs.

B.6.1.1.2.6. Metabolism - low and high dose administration

Reference:	**Hoe 33171-(dioxyphenyl-1-14C). Metabolism in rats orally administered at 2 doses, 2 and 10 mg/kg body weight.**
Author(s), year:	[redacted]; 1985
Report/Doc. number:	Hoechst Report No. (B)3/85 / A30377
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	- Individual body weights of animals not stated - No pilot studies conducted.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 10 rats per sex received a single dose of 10 mg/kg bw Fenoxaprop-P-ethyl dissolved in sesame oil by oral gavage. An additional group of 15 females received a dose of 2 mg/kg bw. The test substance was labelled with ^{14}C on the dioxyphenyl ring and had a radiochemical purity of 96 %.

Test material: [dioxyphenyl-1-14C]-fenoxaprop-p-ethyl, Hoe 033171 0H ZE 99 0002
Specific Activity: 420 MBq/g

Test animals: SPF Wistar rat, [redacted]
16-18 weeks and mean bw of 190 g ±2 g ♂ in low-dose group, and 191 ± 4 g ♂ and 166 ± 4 g ♀ in high-dose group.
Number of animals: 10 rats per sex at high-dose
15 females for low-dose
Dosing scheme: See Table 6.1.1-41

Table 6.1.1-41 Dosing scheme, Metabolism and kinetics in the rat after single oral administration of 2 and 10 mg/kg bw Fenoxaprop-ethyl

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Excretion / Metabolism	10	oral	10 males 10 females	Single
	2	oral	25 females	single

Excretion / tissue distribution investigations: The rats were housed in metabolism cages in groups of two. Urine and faeces from each dose group of animals were pooled. The sample collection intervals were 0-24, 24-48, 48-72 and 72-96 hours.
Laboratory investigations: The following parameters were measured or calculated:
- radioactivity concentrations in urine and faeces
- metabolite pattern in urine and faeces samples (0-24 h after application)
- identification and characterization of the main metabolites in urine and faeces

Results:
Excretion, single oral dose of 10 mg/kg bw: The predominant portion of the administered radioactivity was excreted within one day after treatment (high dose males: 73 %, high dose females: 65 %, low dose females: 80 %). Another significant portion was excreted on the second day (21 %, 17 % and 25 %, respectively). The total renal excretion of radioactivity was slightly higher in female rats (55 %) than in male rats (48 %) at the high dose level. On the contrary, the total faecal excretion rate amounted to a higher percentage in males (53 %) than in females (33 %). The dose level, too, influenced the excretion rate. At the low dose level of 2 mg/kg bw, 71 % of the applied radioactivity was renally excreted whereas only 55 % was renally excreted at the high dose level. On the contrary, the faecal excretion rate did not differ significantly (low dose: 38 %, high dose: 33 % of applied radioactivity). However, the difference between excretion rates in the high and the low dose females has to be seen in the light of the big difference in recovery rates in excreta after 96 h (87.4 % in the high dose group, 108.8 % in the low dose group).

Table 6.1.1-42 Mean % of the administered radioactivity, Excretion after a single oral administration of 2 or 10 mg/kg bw Fenoxaprop-ethyl to rats; pooled analysis of all animals from one group

Sample	Collection interval (h)	Oral Males 10 mg/kg bw	Oral Females 10 mg/kg bw	Oral Females 2 mg/kg bw
Urine	**0 – 24**	**34.0**	**40.7**	**54.8**
	24 – 48	10.3	11.1	13.4
	48 – 72	2.9	2.4	2.2
	72 – 96	0.7	0.7	0.5
	Total (0 – 168)	**47.9**	**54.9**	**70.9**
Faeces	**0 – 24**	**39.3**	24.9	**25.4**
	24 – 48	10.5	5.8	11.3
	48 – 72	3.0	1.0	1.0
	72 – 96	0.6	0.8	0.2
	Total (0 – 168)	**53.4**	**32.5**	**37.9**
∑ excreta	after 168 hours	**101.3**	**87.4**	**108.8**

Maximum values in **bold**

Metabolites in the urine: No parent compound was found in the urine. Males excreted predominantly HPP-acid (2-(4-hydroxyphenoxy)-propionic acid, Hoe 020686, 47.5 % of the applied dose), whereas females excreted both

the HPP-acid and the free acid of the parent compound (Hoe 053022). In females of the high dose group both compounds were excreted at a ratio of 1:1 (27.5 % HPP-acid, 27.0 % free acid) while the ratio was 2:1 in the low dose group (49.6 % HPP-acid, 21.3 % free acid). Only a small portion (0.4 %) was converted to polar not identified metabolites in the high dose animals independent of sex.

Metabolites in the faeces: The composition of fecally excreted compounds was almost independent of sex. A significant portion (7 – 20 % of the applied dose) could be attributed to the unchanged parent compound (Hoe 033171). Another main portion proved to be the free acid (11 – 17.5 %). A small part (up to 1 %) was further hydrolysed HPP-acid. The dose level influenced the ratio between the fecally excreted parent compound and the free acid in female rats. At the high dose level the ratio amounted to approximately 1:1 (sum = 20 %) whereas at the low dose level free acid was excreted at an approximately threefold higher rate than the parent compound (sum = 24 %). Another small portion (up to 2 % of the applied dose) consisted of two unidentified medium-polar metabolites. The remaining fecally excreted radioactivity was equally distributed over the total elution period and did not exceed the noise level. Thus, more than the half of the radioactivity excreted with the faeces could be identified (64 – 72 %).

Table 6.1.1-43 % of the administered dose, Metabolites in excreta of rats after a single oral administration of 2 or 10 mg/kg bw Fenoxaprop-ethyl

Metabolites	Metabolites in excreta of rats (% of the administered dose)								
	Urine			Faeces			Total excreta		
	♂ 10 mg/kg	♀ 10 mg/kg	♀ 2 mg/kg	♂ 10 mg/kg	♀ 10 mg/kg	♀ 2 mg/kg	♂ 10 mg/kg	♀ 10 mg/kg	♀ 2 mg/kg
Hoe 046360 parent compound	-	-	-	**20.1**	9.0	6.6	20.1	9.0	6.6
Hoe 053022 (free acid)	-	27.0	21.3	16.6	11.3	**17.5**	16.6	**38.3**	38.8
Hoe 020686 (HPP-acid, 2-(4-hydroxyphenoxy)-propionic acid)	**47.5**	27.5	**49.6**	0.2	1.0	0.3	**47.5**	28.5	**49.9**
Sum of known metabolites	47.5	54.5	70.9	36.9	21.3	24.4	84.4	75.8	95.3
Sum of unknown metabolites	0.4	0.4	-	16.5	11.2	13.5	16.9	11.6	13.5
Non-extractable residues	47.9	54.9	70.9	53.4	32.5	37.9	101.3	87.4	108.8

Highest values in **bold**

Conclusion:
Most of the orally administered dose (2 or 10 mg/kg bw of Fenoxaprop-ethyl) was excreted during the first 2 days after administration. A higher renal excretion was found in females (55 %) than in males (48 %) at the dose level of 10 mg/kg bw. In females receiving 2 mg/kg bw, the renal excretion was higher (71 %) than in females receiving 10 mg/kg bw (55 %).
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 and the free acid appearing in the faeces of male and female rats. 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 %.

B.6.1.2. Additional ADME studies

B.6.1.2.1. ADME study fenoxaprop-P-ethyl with the safener Hoe 107892

Reference:	**Hoe 046360-14C Metabolism in rats following single oral administration of test substance at dose level of 10 mg kg^{-1} body weight in the presence of co-administered Hoe 107892**
Author(s), year:	[redacted]; 1993
Report/Doc. number:	CT1D241192 / A49483
Guideline(s):	EPA Guideline 85-1 (1994)
Deviations from OECD 417 (2010):	No pilot studies conducted and only one dose used.
GLP:	Yes
Acceptability:	Yes

The objective of this study was to gain information on the influence of the safener Hoe 107892 on the metabolism of Hoe 046360 in rats. The metabolism of Hoe 046360 was therefore investigated in the presence and absence of Hoe 107892 for direct comparison.

Material and Methods:
Dose levels of 10 mg/kg bw for Hoe 046360 and the safener 107892 were chosen because the intended formulation will contain the safening additive Hoe 107892 in a mass ratio of 1:1. The test substance (Code: Hoe 046360 00 ZB98 0001) was labelled on the chlorophenyl-U-^{14}C position and had a radiochemical purity of 97.5 %. The non-labelled safener (Code: Hoe 107892 00 ZB99 0002) had a purity of 99.4 %. Groups of 5 male and 5 female rats received single oral doses of 10 mg/kg bw Hoe 046360 and 10 mg/kg bw Hoe 107892, or 10 mg/kg bw Hoe 046360 alone, by gavage. Both substances were dissolved in sesame oil.

Test material: [chlorophenyl-U-14C]-fenoxaprop-p-ethyl and safening additive Hoe 107892
Specific Activity: 1090.2 MBq/g
Test animals: Wistar rat, [redacted]
8-12 weeks and mean body weights of 216.9 ± 8.0 g ♂ and 191.7 ± 6.8 g ♀.
Number of animals: 5 rats per sex
Dosing scheme: See Table 6.1.2-1

Table 6.1.2-1 Dosing scheme, Metabolism and kinetics in the rat after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl and the safener Hoe 107892

Group	Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
Hoe 046360 + Hoe 107892	10 + 10	oral	5 males 5 females	Single
Hoe 046360	10	oral	5 males 5 females	single

Excretion investigations: The rats were kept individually and urine, cage washes and faeces were collected for 7 days. Collection intervals for urine and faeces were 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Cage washings were performed 24 h after dosing. At the end of the study, the animals were sacrificed and the carcass retained for radioassay.
Laboratory investigations: The following parameters were assessed:
- radioactivity concentrations in urine, faeces and tissue samples
- metabolite pattern in 0-24 h and 24-48 h urine and faecal extracts

Results:
The total balance of radioactivity recovered at the end of the study was 93.47 % (males) and 89.13 % (females) for the animals treated with a combination of Hoe 046360 and Hoe 107892, and 93.30 % (males) and 94.12 % (females) for the animals treated with Hoe 046360 alone.

Excretion of Hoe 046360 with and without co-administration of Hoe 107892: Total renal excretion accounted for 35 % and 44 % of the administered dose for males and females respectively which received the co-administered Hoe 107892. The corresponding values for those animals dosed Hoe 046360 alone were 35 % and 51 %. Total faecal excretion in rats co-administered with Hoe 107892 was 54 % for males and 41 % for females, respectively. For rats dosed Hoe 046360 alone, faecal excretion accounted for 54 % and 38 % respectively. The radioactivity remaining in the carcass at the end of the 168 h collection period represented means of 4 % for both sexes for the group co-administered Hoe 107892. For the groups dosed Hoe 046360 alone the corresponding values were 4 % for males and 5 % for females. Thus, Hoe 107892 had no effect on the excretion of Hoe 046360 and its metabolites in these experiments.

Table 6.1.2-2 Mean % of the administered radioactivity, Excretion after a single oral administration of 10 mg/kg bw Fenoxaprop-P-ethyl and the safener Hoe 107892 to rats

Sample	Collection interval (h)	Hoe 046360 + Hoe 107892		Hoe 046360	
		Males	Females	Males	Females

Sample	Collection interval (h)	Hoe 046360 + Hoe 107892		Hoe 046360	
		Males	Females	Males	Females
Urine + Cage wash	**0 – 24**	**26.96**	**28.48**	**26.85**	**34.34**
	24 – 48	5.35	9.83	5.66	10.55
	48 – 72	1.34	2.99	1.37	3.07
	72 – 96	0.62	1.20	0.60	1.18
	96 – 120	0.36	0.64	0.40	0.69
	120 – 144	0.32	0.49	0.30	0.53
	144 – 168	0.23	0.38	0.26	0.42
	Total (0 – 168)	**35.19**	**44.01**	**35.44**	**50.79**
Faeces	**0 – 24**	**38.42**	**21.32**	**36.46**	**21.16**
	24 – 48	12.68	14.44	14.30	12.02
	48 – 72	2.14	3.97	2.21	3.66
	72 – 96	0.44	0.84	0.43	0.69
	96 – 120	0.20	0.24	0.18	0.27
	120 – 144	0.15	0.17	0.14	0.18
	144 – 168	0.11	0.14	0.11	0.14
	Total (0 – 168)	**54.14**	**41.12**	**53.83**	**38.12**
∑ excreta	after 168 hours	**89.33**	**85.13**	**89.27**	**88.91**
Tissues / Carcass	after 168 hours	**4.14**	**4.00**	**4.03**	**5.21**
Total recovery	after 168 hours	**93.47**	**89.13**	**93.30**	**94.14**

Maximum values in **bold**

Metabolites in excreta: Four major metabolites were detected in male urine and six in female urine. Statistical analysis showed that there was no significant difference between the samples of animals dosed with and without Hoe 107892. One of the metabolites detected only in the urine of the females was the free acid Hoe 088406. In faeces samples, one or two major metabolites were found. The difference between the mean values for each metabolite of the animals dosed with and without Hoe 107892 was small and well within two standard deviations. One of the two metabolites detected in the faeces was again the free acid Hoe 088406. All other metabolites found in urine or faeces did not co-chromatograph with any reference compound. No further identification of these metabolites was performed in this study.

Conclusion:
At the mass ratio of 1:1 and a dose level of 10 mg/kg bw there was no influence of the safener Hoe 107892 on the excretion or metabolism of Hoe 046360 in male and female rats. The rate of renal and faecal excretion and the amount of Hoe 046360 in the carcass were very similar between the animals treated with a combination of Hoe 046360 and Hoe 107892 or with Hoe 046360 alone. Also, HPLC and TLC analysis of the 0-24 h and the 24-48 h urine and faecal extracts showed no qualitative or quantitative differences in metabolite profiles between the two groups. The free acid Hoe 088406 was found as a major metabolite in the urine of females and in the faeces of both sexes. No further identification of metabolites was conducted. The minimum absorbed quantity of the administered Hoe 046360 was 39 % (males) and 48 % (females) in the combination treatment groups and 39 % (males) and 56 % (females) after treatment with Hoe 046360 alone, based on urinary excretion and carcass.

B.6.1.2.2. Newly submitted study: Comparative metabolism

Reference:	Fenoxaprop-P-ethyl: Mouse, rat, rabbit, dog and human liver S9 metabolism
Author(s), year:	[redacted], 2017
Report/Doc. number:	NX60QS / MEFPN011
Guideline(s):	None
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
Incubations were conducted in triplicates using mouse, rat, rabbit, dog and human liver S9 fractions characterized in Table 6.1.2-3. The metabolic viability of the mouse, rat, rabbit, dog and human liver S9 fraction was assessed using testosterone as a standard substrate. The viability of the S9 fractions was confirmed by the production of 6β-hydroxytestosterone and the consumption of parent.

Test material:	fenoxaprop-P-ethyl, AE F046360-PU-01, purity 98.4% (fenoxaprop-ethyl: 99.4%) [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl, KML 10311, specific activity 3.97 MBq/mg, purity >98%

Test system:	4 mg/mL S9 fractions from mouse, rat, rabbit, dog and human liver stored at -70 °C ± 10 °C

Table 6.1.2-3 Characterization of liver S9 fractions (provided by Xenotech)

Species (sex)	Strain	Product number	Lot no	Number of donors in pool
Mouse (male)	CD-1	M1000.S9	1510255	1143
Rat (male)	Wistar	R3000.S9	0910239	200
Rabbit (male)	New Zealand White	L1000.S9	1210284	8
Dog (male)	Beagle	D1000.S9	1310285	8
Human (mixed gender)	Not applicable	H0630.S9	1210091	50

Incubation in all test systems was started by mixing 50 mM Potassium orthophosphate buffer (pH 7.4) containing 3.3 mM MgCl2 with 1 mM NADPH/NADH/NAD+. Afterwards the Liver S9 fraction of the tested species containing 4 mg protein/mL was added. Following an initial 3-minute pre-incubation period at 37°C (± 1˚C) in a shaking water bath, either 0.1 mM or 1 mM [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl was added to the incubation mixture. This resulted in [chlorophenyl-UL-^{14}C] fenoxaprop- P-ethyl final concentrations of 1 µM and 10 µM, respectively in a final volume of 0.5 mL each. All incubations in presence of Liver S9 fractions were conducted as triplicate samples. The incubations were performed for 0, 30 and 120 minutes in a shaking water bath set at 50 strokes per minute and 37°C (± 1°C). Reactions were terminated after the appropriate incubation time by the addition of chilled acetonitrile (0.5 mL) with vortex mixing and standing on ice for at least 10 minutes thereafter. Duplicate control incubations in the absence of S9 and cofactor were conducted in parallel, for 30 and 120 minutes, at both substrate concentrations to check the stability of [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl under the incubation conditions. Following incubation, duplicate aliquots (25 µL) of each incubate were taken for liquid scintillation counting (LSC). Samples were then stored at -70ºC ± 10°C when not in use.

Terminated incubation mixtures from all incubations were centrifuged to sediment the protein. Duplicate aliquots (10 µL) of each resulting supernatant were taken for liquid scintillation counting (LSC). An aliquot (500 µL) of each supernatant was then concentrated to dryness under nitrogen gas. Dried residues were reconstituted in acetonitrile: purified water 3 : 7 (v/v) prior to direct injection into the HPLC system. Duplicate aliquots (8 µL) of each reconstituted sample were taken for liquid scintillation counting (LSC). All samples were analysed with radiodetection.

For each chromatogram obtained from the incubations of [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl with mouse, rat, rabbit, dog and human liver S9, regions of radioactivity were assigned metabolite fraction identities of M1 – M16 and parent. Each metabolite fraction represents either a separated radioactive component or components where complete resolution could not be attained. Not all metabolite fractions were present in every sample and some were only present in trace quantities. Regions of radioactivity that contained ≥5% of sample radioactivity were considered major whilst those that contained 1 to 4.9% of sample radioactivity were considered minor. Where regions of radioactivity were present at ≥1% but not in all replicates were considered to be trace metabolites.

Stability

The test item [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl was found to be relatively unstable under the incubation conditions of this study at both concentrations in the absence of liver S9 and cofactor (duplicates).

Results:

The test item [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl rapidly degraded in all experiments resulting in mean levels of 0.3-95.7 already in the 0 minutes samples. After 30 minutes incubation levels had decreased to be constantly below 1 %. Further development of the experiments revealed residues of <1 to ND after 120 minutes. Over all species a total number of 16 metabolites could be detected. Ten of these metabolites (M1, M2, M3, M7, M9, M10, M12, M13, M14, and M16) appeared in all species only in trace levels (below 1 % of the total radioactivity). Further 5 metabolites (M4, M5, M6, M8, M14) occurred in mouse, rat and humans also at levels below 1 % but occasionally appeared in rabbit and/or dog at levels up to 4 % at maximum. The major metabolite present in all experiments over all species and both concentration levels was M11. It often was already visible in the 0 minutes sample. Further development of the experiments showed residue levels between 79.3 and 96.8 % after 30 minutes up to 73.9 to 98.2 % after 120 minutes. Mean results of the experiments are presented in Table 6.1.2-5.

Table 6.1.2-4 Stability of [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl (1 and 10 µM) in the absence of liver S9

Species	Radioactive residue in % of total radioactivity																
Incubation time [min]	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**M 13**	**M 14**	**M 15**	**M 16**	**AI**
1µM (used as control in Mouse S9 test)																	
30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**56.1**	ND	ND	ND	ND	ND	**38.6**
120	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**11.9**	ND	ND	ND	ND	ND	**76.6**
10 µM																	
30	ND	ND	ND	ND	ND	ND	ND	<1	ND	<1	**27.1**	<1	ND	ND	ND	ND	**72.8**
120	ND	ND	ND	ND	ND	ND	ND	**0.6**	<1	<1	**74.9**	ND	ND	ND	ND	ND	**23.9**
1 µM (used as control in rat S9 test)																	
30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**54.1**	ND	ND	ND	ND	ND	47.6
120	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**1.6**	ND	ND	ND	ND	ND	61.4
10 µM																	
30	ND	ND	ND	ND	ND	ND	ND	**0.6**	ND	<1	**18.4**	ND	ND	ND	ND	ND	79.9
120	ND	ND	ND	ND	ND	ND	ND	1.1	ND	<1	29.8	ND	ND	ND	ND	ND	68.8
1 µM (used as control in rabbit S9 test)																	
30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	56.1	ND	ND	ND	ND	ND	38.6
120	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	11.9	ND	ND	ND	ND	ND	76.6
10 µM																	
30	ND	ND	ND	ND	ND	ND	ND	<1	ND	<1	27.1	<1	ND	ND	ND	ND	72.8
120	ND	ND	ND	ND	ND	ND	ND	0.6	<1	<1	74.9	ND	ND	ND	ND	ND	23.9
1 µM (used as control in dog S9 test)																	
30	ND	ND	ND	ND	ND	ND	ND	<1	ND	0.6	3.4	ND	ND	ND	ND	ND	74.9
120	ND	ND	ND	ND	ND	ND	ND	2.25	ND	ND	6.4	ND	ND	ND	ND	ND	72.3
10 µM																	
30	ND	ND	ND	ND	ND	ND	ND	<1	ND	ND	1.4	ND	ND	ND	ND	ND	98.1
120	ND	ND	ND	ND	ND	ND	ND	1.6	ND	ND	4.5	ND	ND	ND	ND	ND	91.5
1 µM (used as control in human S9 test)																	
30	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**54.1**	ND	ND	ND	ND	ND	47.6
120	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	**1.6**	ND	ND	ND	ND	ND	61.4
10 µM																	
30	ND	ND	ND	ND	ND	ND	ND	**0.6**	ND	<1	**18.4**	ND	ND	ND	ND	ND	79.9
120	ND	ND	ND	ND	ND	ND	ND	**1.1**	ND	<1	**29.8**	ND	ND	ND	ND	ND	68.8

Values represent mean of two replicates

Table 6.1.2-5 Metabolite pattern of [chlorophenyl-UL-14C] fenoxaprop-P-ethyl after incubation with S9 fractions from mouse, rat, rabbit, dog and human liver

Species	Radioactive residue in % of total radioactivity																
Incubation time [min]	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**M 13**	**M 14**	**M 15**	**M 16**	**a.i.**
Mouse																	
0	ND-<1	ND-<1	ND-<1	ND-<1	ND	ND-<1	ND	<1	ND-<1	<1	**50-67**	<1	ND-<1	ND-<1	ND-<1	ND	**19-49**
30	ND-<1	ND-<1	ND	ND-<1	ND	ND-<1	ND-<1	<1	<1	ND-<1	**92-97**	ND	ND-<1	ND	ND-<1	ND-<1	<1
120	ND-<1	<1	ND-<1	ND-<1	ND	ND-<1	<1	<1	ND-<1	ND-<1	**91-96**	ND	ND	ND	ND-<1	ND-<1	ND-<1
Rat																	
0	<1	ND	ND-<1	ND	ND	<1	ND	<1	ND-<1	<1	**74-86**	ND	ND	ND	ND	ND	<1-**24**
30	<1	<1	ND-<1	ND	ND-<1	ND-<1	ND	<1	ND-<1	ND-<1	**79-98**	ND	ND	ND	ND	ND-<1	ND-<1
120	ND	<1	ND-<1	ND	ND	<1	ND	ND-<1	ND-<1	ND-<1	**98**	ND	ND	ND	ND	ND-<1	ND-<1
Rabbit																	
0	ND-<1	ND	ND-<1	ND-<1	ND	ND-<1	ND-<1	<1	ND-<1	ND-<1	**26-85**	ND-<1	ND	ND	ND	ND	**3-72**
30	ND-<1	ND-<1	ND	<1	ND-<1	**3**	ND-<1	<1	<1	ND	**83-95**	ND	ND	ND	ND-<1	ND	<1
120	<1	<1	ND	**3-4**	**2-3**	**3-4**	<1	<1	ND-<1	ND-<1	**81-85**	ND	ND	ND	ND	<1	ND-<1
Dog																	
0	ND-<1	ND-<1	ND-<1	ND-<1	ND-<1	ND	ND-<1	<1	ND	<1	ND-<1	ND-<1	ND	ND	ND	ND	**94-96**
30	ND-<1	ND-<1	ND	ND-<1	ND	<1-3	ND	<1	<1	<1	**90-95**	ND	ND	ND	ND-<1	ND	<1
120	ND-<1	ND	ND-<1	<1	<1	**3**	ND	<1-**3**	ND-<1	<1	**74-95**	ND	ND	ND-**2**	ND	ND	<1
Human																	
0	ND-<1	ND	ND	ND-<1	<1	ND	<1	<1	ND	ND-<1	**9-24**	ND-<1	ND	ND	ND	ND-<1	**71-89**
30	ND-<1	ND	ND	ND-<1	ND	ND	ND-<1	ND-<1	ND-<1	ND-<1	**92-97**	ND	ND	ND	ND	ND	<1
120	ND-<1	ND	ND	ND-<1	ND	ND	ND-<1	ND-<1	ND-<1	ND-<1	**94-96**	ND	ND	ND	ND	ND	<1

ND is given where residues in all replicates were ND. If, in one or more replicates, a residue below the limit of quantification (1 % of total radioactive residue) was determined and no quantifiable residue appeared <1 is given by the table. In case one or more replicates showed quantifiable residues the sum of the quantifiable residues divided by the number of replicates is given even if it is below 1. Mean values which include one or more replicates containing residues above 1 % are given in bolt.

Following the incubation of [chlorophenyl-UL-^{14}C] Fenoxaprop-P-ethyl with no S9/no cofactor controls showed evidence of a degradation product that eluted at the same time as M11. This was observed both at 30 and 120 minutes incubation. Therefore the test compound seems also prone to degradation which is often observed with ester-type molecules. M11 formation was likely a pH dependent reaction observed in aqueous solutions. Due to the usage of a buffer solution metabolite M11 may have been formed by hydrolytic reaction and M11 is therefore supposed to be the fenoxaprop free acid metabolite AEF088406.

Conclusion:
In all the species, at 1 µM and 10 µM, the most prominent metabolite was M11, to such an extent that generally no parent was detected following 30 minutes. The chromatograms demonstrate that under the incubation conditions used, [chlorophenyl-UL-^{14}C] fenoxaprop-P-ethyl is extensively metabolised in all species as well as human. Following 120 minutes incubation the profiles were very similar. In experiments with human liver S9 fractions as well as with the other species only one major metabolite (M11) could be detected. Other metabolites (M1, M4, M8, M9 and M10) were observed only in trace levels. Nevertheless in table XXX-10 the occurrence of these metabolites is compared to the other tested species.

Table 6.1.2-6 Comparison of metabolite pattern after 120 minutes incubation

Metabolite No.	Mouse	Rat	Rabbit	Dog	Human
M1	*trace*	*Trace*	*Trace*	*trace*	*Trace*
M4	*trace*	-	minor	*trace*	*trace*
M8	*trace*	*Trace*	minor	minor	*trace*
M9	*trace*	*Trace*	*trace*	*trace*	*trace*
M10	*trace*	*Trace*	*trace*	*trace*	*trace*
M11	**major**	**major**	**major**	**major**	**major**

No radiolabelled metabolites unique to human were observed. The unique major metabolite M11 was present in all species tested at comparable levels. Beside M4 in rat all metabolites detected in the final human liver S9 tests were also present in all other species tested. Therefore the metabolism patterns are considered comparable in all species tested.

B.6.1.3. Comparison of ADME studies with Fenoxaprop-P-ethyl and Fenoxaprop-ethyl

Reference:	**Hoe 33171 and Hoe 046360. Comparison and evaluation of the metabolism and pharmacokinetics in rats.**
Author(s), year:	[redacted]; 1988
Report/Doc. number:	Hoechst Report No. (B)258/88 / A38647
Acceptability	Yes.

In this report, the metabolism and pharmacokinetic behaviour of both Hoe 046360 and Hoe 033171 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. Conclusions of this report will be integrated in the following comparison of ADME studies with Fenoxaprop-P-ethyl and Fenoxaprop-ethyl. 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 6.1.6-1 in this chapter).

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 6.1.3-1 Overview on absorption and excretion profile of Hoe 046360 and Hoe 033171 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
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 (Schwalbe-Fehl M. *et al..*, 1988). 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 6.1.1-1).

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.

B.6.1.4. Absorption, distribution, metabolism and excretion by other routes

With regard to absorption, distribution, metabolism and excretion studies by other routes, apart from the studies including intravenous administration, which have been revised in B.6.1.1, a dermal penetration study is available.

Reference:	**Dermal penetration of 14C Hoe 046360 in the rat**
Author(s), year:	[redacted]; 1992a
Report/Doc. number:	BF-ME-08-90-01-DPR-1 / A48898
Guideline(s):	"Procedure for studying dermal absorption" edited by R.P. Zendzian PhD, Toxicology Branch, HED, October 9, 1985
GLP:	Yes
Acceptability:	No, because the study is of limited validity due to low recovery rates (mean: 78 %, worst case: 58 %). Furthermore, it was not conducted according to current guidelines (e.g. application periods 4 h and 10 h instead of 8 h). The study was performed with a formulation (containing the safener fenchlorazole) different from the representative formulation proposed by the notifier.

Material and Methods:

The rats (source: not specified) were treated with a single topical application of 1 mg Fenoxaprop-P-ethyl/animal, 0.1 mg/animal or 0.01 mg/animal. The test substance was applied as a mixture of ^{14}C-labelled Hoe 046360 (charge: 18 051 II, radiochemical purity 97 %, chemical purity: 98.5 %), unlabelled Hoe 046360, and the safener Hoe 070542 (fenchlorazole) in a mass ratio of 2:1 (Hoe 046360 : Hoe 070542). These substances were dissolved in aqueous solutions of the blank formulation Hoe 046360 01 EW 00 A 105 resulting in three different stock solutions for each dose group. Regarding the highest dose of 1 mg Fenoxaprop-P-ethyl/rat, 100 µl of the mixed solution were applied leading to a nominal dose of 1.08 mg/rat. For the 0.1 mg/rat dose group, 100 µl application volume resulted in a nominal dose of 0.1 mg/rat, and for the 0.01 mg/rat dose group, 100 µl resulted in a nominal dose of 0.015 mg/rat. 24 h before application, the back and shoulders of the animals were shaved taking care that the skin was not wounded. The formulation of the test substance was spread on an area of 11.25 cm^2. After the treated skin area had dried it was covered with a non-occlusive cover. Rats were kept in metabolism cages. After 0.5, 1, 2, 4, 10 and 24 h, 4 rats per dose group were sacrificed and the following samples were collected: blood, faeces (including gastro-intestinal contents), urine (including bladder content), liver (including bile-duct), kidney (including suprarenal glands), skin (application site) and carcass. Prior to necropsy, the application site was washed three times with cellulose made pads using a dish washing reagent (2 % v/v). The pads and the wash water were collected and radioactivity determined.

Test material:	Mixture of unlabelled and [chlorophenyl-U-14C]-labelled fenoxaprop-p-ethyl and safener Hoe 070542 (ratio 2:1)
Specific Activity:	1177.8 MBq/g
Test animals:	Male Wistar rat, source not specified mean body weights of 217 ± 15.5 g, 231 ± 11.1 g and 240 ± 11.1 g for the 1 mg, 0.1 and 0.01 dose group, respectively.
Number of animals:	4 rats per group
Dosing scheme:	See Table 6.1.4-1

Table 6.1.4-1 Dosing scheme, Dermal penetration of 14C Hoe 046360 in the rat

Dose (mg/rat)	Dose route	Times of necropsy per dose (h)	Number of animals	Frequency of administration
1.00	dermal	0.5 1 2 4 10 24	24 males	Single
0.10	dermal		24 males	single
0.01	dermal		24 males	single

Dose (mg/rat)	Dose route	Times of necropsy per dose (h)	Number of animals	Frequency of administration
- (control)	dermal	24	1	single

Findings

The general state of health of the test animals is not reported. The actual dosages differed from the nominal dosages and reached 90.7 % for the high dose group, 84.4 % for the medium dose group and 77.2 % for the low dose group.

Table 6.1.4-2 Applied Dose, Dermal penetration of 14C Hoe 046360 in the rat

Nominal dose (µg/rat)	Actual dose, mean value (µg/rat)	Applied dose (%)
1080	977 ± 27 (2.8%)	90.7
100	84.4 ± 5.2 (6.2%)	84.4
15	11.6 ± 0.6 (5.4%)	77.2

The mean recovery of radioactivity for each sampling point was highly variable with a mean of 78.6 % and a standard deviation of 10.5 % (range: 58.39 – 94.15 %) which limits the validity of the absorption and the maximal dermal penetration rate. The maximum dermal penetration rate was calculated by addition of the absorbed radioactivity and the radioactivity remaining on the skin of the application site. It showed no consistent trend over the time points of 0.5 h and 24 h and reached values from 5.77-11.2 % in the high dose group, 13.08-25.73 % in the medium dose group and 11.07-30.01 % in the low dose group.

Table 6.1.4-3 Percentage of radiochemical material of Fenoxaprop-P-ethyl following a single topical application of a (^{14}C) formulation, nominal dosage: 1.08 mg/rat

Nominal dosage: 1.08 mg/rat						
Duration of exposure (h)	**0.5**	**1**	**2**	**4**	**10**	**24**
Actual dose applied (µg)	973	1002	967	957	1003	973
Absorbed	**0.55**	**0.89**	**1.79**	**2.54**	**4.03**	**4.49**
urine	No sample	0.01	0.03	0.08	0.37	0.18
faeces	<0.01	<0.01	0.02	0.06	0.23	0.73
blood	0.03	0.06	0.02	0.27	0.56	0.64
liver and kidney	0.02	0.05	0.11	0.15	0.35	0.38
carcass	0.50	0.77	1.61	1.98	2.52	2.56
Application site	**10.65**	**4.88**	**4.74**	**4.81**	**4.63**	**2.98**
Maximal dermal penetration rate (absorbed + application site)	11.2	5.77	6.53	7.35	8.66	7.47
Skin washings	4.77	3.79	3.60	2.02	2.46	1.00
Dressing (“alliance of protection”)	74.9	79.44	83.49	78.80	73.20	85.68
Total recovery	**90.87**	**89.00**	**93.62**	**88.07**	**84.32**	**94.15**

Table 6.1.4-4 Percentage of radiochemical material of Fenoxaprop-P-ethyl following a single topical application of a (^{14}C) formulation, nominal dosage: 0.1 mg/rat

Nominal dosage: 0.1 mg/rat						
Duration of exposure (h)	**0.5**	**1**	**2**	**4**	**10**	**24**
Actual dose applied (µg)	83.3	86.8	88.1	81.5	80.6	86.0
Absorbed	**0.74**	**1.17**	**1.57**	**4.91**	**6.88**	**17.41**
urine	no sample	<0.01	0.02	0.07	0.51	3.05
faeces	<0.01	0.01	0.03	0.17	0.40	1.82
blood	0.04	0.13	0.29	1.09	1.24	2.55
liver and kidney	0.04	0.11	0.19	0.65	0.73	1.27
carcass	0.66	0.92	1.04	2.93	4.00	8.72
Application site	**14.89**	**15.63**	**11.51**	**16.34**	**11.54**	**8.32**

Nominal dosage: 0.1 mg/rat						
Duration of exposure (h)	**0.5**	**1**	**2**	**4**	**10**	**24**
Actual dose applied (µg)	83.3	86.8	88.1	81.5	80.6	86.0
Maximal dermal penetration rate (absorbed + application site)	**15.63**	**16.8**	**13.08**	**21.25**	**18.42**	**25.73**
Skin washings	9.70	7.80	4.21	5.95	4.00	2.38
Dressing ("alliance of protection")	47.2	49.90	51.86	48.98	43.79	53.28
Total recovery	**72.53**	**74.50**	**69.15**	**76.18**	**66.21**	**81.39**

Table 6.1.4-5 Percentage of radiochemical material of Fenoxaprop-P-ethyl following a single topical application of a (14C) formulation, nominal dosage: 0.015 mg/rat

Nominal dosage: 0.015 mg/rat						
Duration of exposure (h)	**0.5**	**1**	**2**	**4**	**10**	**24**
Actual dose applied (µg)	12.0	11.0	11.6	11.5	12.1	11.3
Absorbed	**0.25**	**2.06**	**3.33**	**4.32**	**8.89**	**21.64**
urine	no sample	no sample	<0.01	0.14	0.60	3.93
faeces	0.01	<0.01	0.03	0.13	0.55	1.60
blood	0.02	0.07	0.25	0.93	1.58	3.44
liver and kidney	0.06	0.07	0.22	0.79	1.21	1.67
carcass	0.16	1.92	2.83	2.33	4.95	11.00
Application site	**19.22**	**11.07**	**30.01**	**21.80**	**18.55**	**13.41**
Maximal dermal penetration rate (absorbed + application site)	**19.47**	**13.13**	**33.34**	**26.12**	**27.44**	**35.05**
Skin washings	12.98	21.82	20.70	10.67	5.27	5.28
Dressing ("alliance of protection")	25.94	34.35	41.93	40.48	33.69	38.16
Total recovery	**58.39**	**69.3**	**85.97**	**76.27**	**66.40**	**78.49**

Conclusion:

Fenoxaprop-P-ethyl was administered once as a single topical application of a formulation containing the safener Hoe 070542 (fenchlorazole), which is not the representative formulation submitted by the notifier. Three concentrations (0.01, 0.1 and 1 mg Fenoxaprop-P-ethyl per animal) were tested over several time points from 0.5 to 24 hours. The mean recovery of radioactivity for each sampling point was highly variable with a mean of 78.6 % and a standard deviation of 10.5 % (range: 58.39 – 94.15 %) which limits the validity of the study. Additionally, results of the maximum dermal penetration rate (absorption plus application site) showed no consistency over the period of time. In conclusion, the results of this study will not be used to derive the dermal absorption rate necessary for risk assessment, as a valid rat *in vivo* study with the respective formulation is available ([redacted], 2002).

B.6.2. ACUTE TOXICITY

All studies for acute oral, dermal and inhalation toxicity as well as skin irritation, eye irritation and skin sensitization were evaluated in the DAR (May 2005). In addition, an in-vitro phototoxicity study is included in response to updated data requirements under EU Regulation No 283/2013.

Fenoxaprop-P-ethyl is of moderate toxicity via the oral route and of low toxicity via the dermal and inhalation route. The active substance did not show any skin or eye irritating properties and is classified as a skin sensitizer. The *in-vitro* phototoxicity study for fenoxaprop-P-ethyl was demonstrated to present no phototoxic hazard. A summary of all original submitted and evaluated studies (EC review report (SANCO/3777/08-rev.1, 14 December 2007)) as well as newly submitted studies is presented in the following tables.

Summary of acute toxicity studies with fenoxaprop-P-ethyl

Study, reference	Dose levels	Results	Classification: CLP 1272/2008
Acute oral toxicity LD_{50} in rats [redacted]., *1992* A47470, CA 5.2.1/01	2,000; 3,150; 4,000 and 5,000 mg/kg bw	4,000>LD_{50}>3,150 mg/kg bw	No classif.
Acute oral toxicity LD_{50} in mice [redacted] *1985a* A37268, CA 5.2.1/04	5,000 mg/kg bw	>5,000 mg/kg bw	No classif.
Acute oral toxicity LD_{50} in rats [redacted] *2008* 271 FPE, CA 5.2.1/07	2,000 mg/kg bw and 300 mg/kg bw	2,000>LD_{50}>300 mg/kg bw	Acute Tox. 4 H302: harmful if swallowed
Acute oral toxicity LD_{50} in rats [redacted] *2005* 127 FPE, CA 5.2.1/08	175-2,000 mg/kg bw	1,098 mg/kg bw	Acute Tox. 4 H302: harmful if swallowed
Acute dermal toxicity LD_{50} in rats [redacted] *1985b* A36023, CA 5.2.2/01	2,000 mg/kg bw	>2,000 mg/kg bw	No classif.
Acute inhalation toxicity LC_{50} in rats [redacted] *1991* A46998, CA 5.2.3/01	1.224 mg/L	>1.224 mg/L*	No classif.
Acute inhalation toxicity LC_{50} in rats [redacted] *2005* 131 FPE, CA 5.2.3/03	3.4 mg/L	>3.40 mg/L* (supplementary information)	No classif.
Acute skin irritation in rabbits [redacted] *1985d* A36061, CA 5.2.4/01	500 mg	Slight irritant	No classif.
Acute skin irritation in rabbits [redacted] *2005* 125 FPE, CA 5.2.4/03	500 mg	Not irritating	No classif.
Acute eye irritation in rabbits [redacted] *1985e* A36022, CA 5.2.5/01	100 mg	Slight irritant	No classif.
Acute eye irritation in rabbits [redacted] *2005* 124 FPE, CA 5.2.5/03	31 mg	Slight irritant	No classif.
Skin sensitization (MK-GPMT) [redacted] *1986a* A37243, CA 5.2.6/01	5% intradermal, 50% dermal induction	Sensitizing	Skin Sens. 1 H317: may cause an allergic skin reaction
Skin sensitization (Bühler) [redacted] *1986b* A36040, CA 5.2.6/02	50% topical induction, 2, 10 and 25% challenge	Inconclusive	-
Skin sensitization (Bühler) [redacted] *1992* A47403, CA 5.2.6/03	75% induction, 75% challenge	Not sensitizing +	No classif.

Study, reference	Dose levels	Results	Classification: CLP 1272/2008
Local Lymph Node in mice [redacted] *2005* 123 FPE, CA 5.2.6/05	10, 25 and 50%	Not sensitizing	No classif.
Cytotoxicity Assay *In-vitro* with BALB/c 3T3 Cells *Wason S., 2014* Nr. 1637600, CA 5.2.7/01	w/o irr: 6.25-200 µg/ml w/ irr: 0.125- 4.0 µg/ml	Non-phototoxic	No classif.

* Highest technically attainable atmosphere concentration
[+] Induction phase non-irritating

The racemate, fenoxaprop-ethyl is of low toxicity via the oral, dermal and inhalation route. The racemate did not show any skin or eye irritating properties and is not classified. As no new studies were submitted for fenoxaprop-ethyl, the following table includes all originally submitted and evaluated studies (EC review report (SANCO/3777/08-rev.1, 14 December 2007)).

Summary of acute toxicity studies with fenoxaprop-ethyl

Study, reference	Dose levels	Results	Classification: CLP 1272/2008
Acute oral toxicity LD_{50} in male rat [redacted], *1979a* A24696, CA 5.2.1/02	1,600-5,000 mg/kg bw	2,357 mg/kg bw	No classif.
Acute oral toxicity LD_{50} in female rat [redacted] *1979b* A24698, CA 5.2.1/03	2,000-5,000 mg/kg bw	2,500 mg/kg bw	No classif.
Acute oral toxicity LD_{50} in male mouse [redacted], *1979a* A24692, CA 5.2.1/05	3,150-6,300 mg/kg bw	4,670 mg/kg bw	No classif.
Acute oral toxicity LD_{50} in female mouse [redacted], *1979b* A24694, CA 5.2.1/06	2,500-6,300 mg/kg bw	5,490 mg/kg bw	No classif.
Acute dermal toxicity LD_{50} in female rat [redacted], *1978b* A24673, CA 5.2.2/02	2,000 mg/kg bw	>2,000 mg/kg bw	No classif.
Acute dermal toxicity LD_{50} in female rat [redacted], *1979c* A24702, CA 5.2.2/03	2,000 mg/kg bw	>2,000 mg/kg bw	No classif.
Acute inhalation toxicity LC_{50} in rat [redacted] *1982* A24752, CA 5.2.3/02	0.151 and 0.511 mg/L [§]	Mortality: 1 / 24 [§]	No classif.
Acute skin irritation in rabbit [redacted] *1979d* A24688, CA 5.2.4/02	500 mg	Slight irritant	No classif.
Acute eye irritation in rabbit *(reference as in skin irritation study)*	100 mg	Slight irritant	No classif.
Skin Sensitization (Bühler) [redacted], *1982* A30110, CA 5.2.6/04	10% topical induction, 5% challenge	Not sensitizing [x] (supplementary information)	-

[§] Highest concentration tested: 0.511 mg/L
[x] Number of animals low

B.6.2.1. Acute Oral studies with Fenoxaprop-P-ethyl

B.6.2.1.1. Acute oral toxicity - Rat

Reference:	Testing for acute oral toxicity in the male and female Wistar rat
Author(s), year:	[redacted] 1992
Report/Doc. number:	A47470 / Hoechst Report No. 92.0049
Guideline(s):	EPA guideline 81-1 (1984), OECD 401 (1987)
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Groups of 5 rats/sex/dose received single doses of 2000, 3150, 4000 or 5000 mg/kg bw of Fenoxaprop-p-ethyl by oral gavage. Fenoxaprop-P-ethyl was suspended in sesame oil at concentrations of 20% w/v for 2000 mg/kg bw, 31.5% for 3150 mg/kg bw, and (due to viscosity of the test substance from a concentration of 40% onwards) at concentrations of 20% for 4000 mg/kg bw and 25% for 5000 mg/kg bw. The volume applied was 10 ml/kg bw (2000, 3150 mg/kg bw) or 20 ml/kg bw (4000, 5000 mg/kg bw), with 2 x 10 ml/kg bw being dosed over an interval of 30 minutes at 4000 and 5000 mg/kg bw. Animals were observed at least daily for 15 days. Body weights were recorded on days 1 (just prior to dosing), 8 and 15. Animals found dead during observation period and surviving animals sacrificed at study termination were examined for macroscopic abnormalities.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002
Purity: 97.7 %

Test animals: Wistar rat, WISKf (SPF71), [redacted]
7-8 weeks, mean bw of 196.6 ± 4.3 g (♂) and 173.8 ± 2.8 g (♀).
Number of animals: 5 rats per sex

Table 6.2.1-1 Dosing scheme, Testing for acute oral toxicity in the male and female Wistar rat

Dose level (mg/kg)	Dose route	Number of rats	Frequency of administration
2,000	oral	5 males 5 females	Single
3,150	oral	5 males 5 females	single
4,000	oral	5 males 5 females	Single
5,000	oral	5 males 5 females	Single

Findings:
Mortality: No animal died in the 2000 mg/kg bw dose group. The mortality rates were 1/5 for males and females at 3150 mg/kg bw, and 5/5 for males and females at 4000 and 5000 mg/kg bw, respectively. All deaths occurred between study day 2 and 3.

Table 6.2.1-2 Acute oral toxicity of fenoxaprop-P-ethyl to rats, number of deaths

	Dose [mg/kg bw]			
	2,000	**3,150**	**4,000**	**5,000**
Male	0 / 5	1 / 5	5 / 5	5 / 5
Female	0 / 5	1 / 5	5 / 5	5 / 5
Male + Female	0 / 10	2 /10	10 / 10	10 / 10

Body weight gains were markedly impaired (females) or even negative (males) up to the time of death at 4000 and 5000 mg/kg bw. At 3150 mg/kg bw there was a transient reduction in body weight of one male only which recovered until end of study.

Clinical signs were observed from 1 hour after administration and persisted up to study day 15 in some animals. Generally females were more affected than males. At the lowest dose all animals of both sexes showed decreased spontaneous activity, while for females additionally a squatting posture and flanks drawn in were noted.

At day 5 and day 7, all males and females, respectively, had recovered. At 3,150 mg/kg bw, some animals showed ataxic gait and coat bristling, and in male animals an irregular respiration as well as stained blood-stained snoud and lid margin was noted additionally. These effects persisted up to day 15 and day 10 in males and females. At the higher doses the general condition in most of the animals was poor and other symptoms were observed additionally. A summary for both sexes is given in Table 6.2.1-3 and Table 6.2.1-4.

Table 6.2.1-3 Clinical signs in male animals post-treatment, acute oral toxicity study in rats

Signs	Dose (mg / kg bw)			
	2,000 $^{4h-d4}$	3,150 $^{2h-d15}$	4,000 $^{4h-d2}$	5,000 $^{0.5h-d2}$
Flanks drawn in	1 / 5	4 / 5	2 / 5	2 / 5
Gait stilted	0 / 5	4 / 5	0 / 5	2 / 5
ataxic	0 / 5	1 / 5	1 / 5	3 / 5
Squatting posture	1 / 5	4 / 5	2 / 5	3 / 5
Decreased spontaneous activity	5 / 5	3 / 5	2 / 5	3 / 5
Coat bristling	0 / 5	1 / 5	2 / 5	3 / 5
Respiration irregular	0 / 5	1 / 5	2 / 5	3 / 5
increased		0 / 5	0 / 5	1 / 5
Lid margin blood-encrusted	0 / 5	1 / 5	2 / 5	1 / 5
Snoud blood-encrusted	0 / 5	1 / 5	1 / 5	2 / 5
General condition poor	0 / 5	0 / 5	2 / 5	3 / 5
Palpebral fissure narrow	0 / 5	0 / 5	1 / 5	3 / 5
closed	0 / 5	0 / 5	1 / 5	0 / 5
Blood-encrusted lid margin	0 / 5	0 / 5	0 / 5	0 / 5
Prone position	0 / 5	0 / 5	1 / 5	0 / 5
Stupor	0 / 5	0 / 5	1 / 5	3 / 5
Trembling	0 / 5	0 / 5	2 / 5	3 / 5
Placing reaction reduced	0 / 5	0 / 5	2 / 5	1 / 5
none	0 / 5	0 / 5	0 / 5	0 / 5
Cold to touch	0 / 5	0 / 5	0 / 5	3 / 5

Maximal values observed during designated time (d …day; h …hours); last digit refers to the time point before no symptoms were observed or before all animals had died.

Table 6.2.1-4 Clinical signs in female animals post-treatment, acute oral toxicity study in rats

Signs	Dose (mg / kg bw)			
	2,000 $^{d2-d6}$	3,150 $^{d2-d10}$	4,000 $^{6h-d2}$	5,000 $^{0.5h-d2}$
Flanks drawn in	5 / 5	5 / 5	3 / 5	4 / 5
Gait stilted	2 / 5	5 / 5	0 / 5	2 / 5
ataxic	0 / 5	1 / 5	0 / 5	2 / 5
Squatting posture	5 / 5	5 / 5	2 / 5	2 / 5
Decreased spontaneous activity	5 / 5	5 / 5	3 / 5	4 / 5
Coat bristling	1 / 5	2 / 5	2 / 5	4 / 5
Respiration irregular	0 / 5	0 / 5	3 / 5	2 / 5
increased	0 / 5	0 / 5	0 / 5	0 / 5
Lid margin blood-encrusted	0 / 5	0 / 5	3 / 5	0 / 5
Snoud blood-encrusted	0 / 5	0 / 5	0 / 5	0 / 5
General condition poor	0 / 5	0 / 5	3 / 5	3 / 5
Palpebral fissure narrow	0 / 5	0 / 5	1 / 5	2 / 5
closed	0 / 5	0 / 5	2 / 5	1 / 5
Blood-encrusted lid margin	0 / 5	0 / 5	0 / 5	0 / 5
Prone position	0 / 5	0 / 5	1 / 5	2 / 5
Stupor	0 / 5	0 / 5	3 / 5	4 / 5
Trembling	0 / 5	0 / 5	2 / 5	4 / 5
Placing reaction reduced	0 / 5	0 / 5	2 / 5	1 / 5
none	0 / 5	0 / 5	1 / 5	0 / 5
Cold to touch	0 / 5	0 / 5	2 / 5	3 / 5

Maximal values observed during designated time (dx..day x; xh …x hours); last digit refers to the time point before no symptoms were observed or day before all animals had died.

Pathology: Animals of the high dose group that were found dead during the study showed light liver discoloration, stomach filled with feed mash, test compound, gas and haemorrhages, intestinal tract filled with test compound and haemorrhages. The animals sacrificed at the end of the observation period were free of visible changes.

Conclusion:
Fenoxaprop-P-ethyl (suspended in sesame oil) is of low acute toxicity in Wistar rats after oral administration. The LD_{50} for males and females is greater than 3150 mg/kg bw and less than 4000 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute oral toxicity is not required.

B.6.2.1.2. Acute oral toxicity - Mouse

Reference:	Testing for acute oral toxicity in the male and female NMRI mouse
Author(s), year:	[redacted] 1985a
Report/Doc. number:	A37268 / Hoechst Report No. 85.1176
Guideline(s):	EPA guideline 81-1 (1984), OECD 401 (1987)
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Only one dose (5000 mg/kg bw) was examined in this study. Groups of 5 mice/sex received fenoxaprop-P-ethyl by oral gavage. 20 ml/kg bw of a 25% w/v suspension of Fenoxaprop-P-ethyl in sesame oil were dosed to the animals. During the 14-day observation period the animals were observed daily and weighed weekly. At termination all animals were examined for macroscopic abnormalities.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 %

Test animals: NMRI mouse, strain NMRKf(SPF71), [redacted]
5 weeks, mean bw of 25.8 ± 0.8 g (♂) and 21.6 ± 1.8 g (♀).
Number of animals: 5 rats per sex

Findings:
Clinical signs and mortality: No deaths occurred among either the male or female mice. No clinical signs were observed during the study. There was a loss of body weight in two males one week after dosing but the weights returned to normal by the end of the study. No effect was noted on the body weight of females.

Table 6.2.1-5 Number of deaths, Acute oral toxicity of fenoxaprop-P-ethyl to mice

	5,000 mg/kg bw
Male	0 / 5
Female	0 / 5
Male + Female	0 / 10

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
Fenoxaprop-P-ethyl (suspended in sesame oil) is of low acute toxicity to NMRI mice after oral application. The LD_{50} for males and females is greater than 5000 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute oral toxicity is not required.

B.6.2.1.3. Newly submitted study: Acute oral toxicity – Rat (study 1)

Reference:	Fenoxaprop-P-ethyl: Acute oral toxicity in the rat – fixed dose method
Author(s), year:	[redacted]; 2008
Report/Doc. number:	271 FPE
Guideline(s):	OECD 420 (2001), Method B1 of Commission Directive 2004/73/EC
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
For sighting test, one female rat was administered with 2,000 mg/kg bw orally by gavage. Due to mortality, another rat was administered 300 mg/kg bw fenoxaprop-P-ethyl. Further 4 rats were treated the same way with 300 mg/kg bw fenoxaprop-P-ethyl. The test substance was suspended in arachis oil BP. The animals were observed daily for 14 days and weighed weekly. At termination, all animals were examined for macroscopic abnormalities.

Test material:	fenoxaprop-P-ethyl CHA 480, batch 2008-03-01
Purity:	99.2 %
Test animals:	Female rat, Sprague-Dawley CD, strain Hsd:Sprague Dawley®™, [redacted] 8-12 weeks, mean bw of 178.7 ± 13.8 g
Number of animals:	5 animals (1+1 for sighting, 4 for main study)

Findings:
Clinical signs and mortality: In the sighting study, the rat died after oral administration with 2,000 mg/kg bw fenoxaprop-P-ethyl. The rat administered with 300 mg/kg bw test substance did survive and no clinical findings were observed. In the main study, upon administration of 300 mg/kg bw fenoxaprop-P-ethyl, no mortalities were observed. In two animals, hunched posture and pilo-erection were observed on day 1 after dosing, which diminished on day 2. No abnormalities were found at the necropsy.

Table 6.2.1-6 Number of deaths, Acute oral toxicity of fenoxaprop-P-ethyl in the rat – fixed dose method

Dose (mg / kg bw)	Mortality
2,000	1 / 1
300	0 / 0
300	0 / 0

Table 6.2.1-7 Clinical findings observed in rats orally dosed with fenoxaprop-P-ethyl

Signs	Dose (mg / kg bw)		
	2,000	**300**	**300**
Hunched posture	1 / 1	0 / 1	2 / 4
Pilo-erection	1 / 1	0 / 1	2 / 4
Lethargy	1 / 1	0 / 1	0 / 4
Ataxia	1 / 1	0 / 1	0 / 4
Dehydration	1 / 1	0 / 1	0 / 4
Hypothermia	1 / 1	0 / 1	0 / 4
Decreased respiratory rate	1 / 1	0 / 1	0 / 4
Laboured respiration	1 / 1	0 / 1	0 / 4
Animal killed *in extremis*	1 / 1	0 / 1	0 / 4

Body weight and necropsy: One animal showed bodyweight loss during the first week but recovered during the second week. The other surviving animals showed expected gains in body weight. No abnormalities were noted at necropsy.

Conclusion:
The acute oral median lethal dose of the test material in the female SD CD strain rat was estimated to be in the range of 300-2,000 mg/kg bw.

According to the Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), fenoxaprop-P-ethyl is to be classified as Acute Tox. Cat. 4 and labelled with H302, "Harmful if swallowed".

B.6.2.1.4. Newly submitted study: Acute oral toxicity – Rat (study 2)

Reference:	Fenoxaprop-P-ethyl: Acute oral toxicity in the rat – up and down procedure
Author(s), year:	[redacted] 2005
Report/Doc. number:	127 FPE
Guideline(s):	OECD 425 (2001), US EPA OPPTS 870.1100 (2002)
GLP:	Yes
Deviations to OECD GD 425 (2008):	None.
Acceptability:	Yes

Material and Methods:
A total of eight female animals were dosed fenoxaprop-P-ethyl orally in suspension and individually in sequence with sufficient time (at least 48 hours) between each animal, to confirm survival of the previously dosed animal. Dose levels ranged from 175 mg/kg bw to 2,000 mg/kg bw. The test was complete after eight animals had been dosed as five reversals occurred in any six animals tested.

Test material:	fenoxaprop-P-ethyl CHA 480, batch 660-PSH-45
Purity:	95.6 %
Test animals:	Female rat, Sprague-Dawley CD, strain Crl:CD® (SD) IGS BR, [redacted] 12 weeks, mean bw of 214.5 ± 13.7 g
Number of animals:	8 animals

Findings:
Clinical signs and mortality: Signs of systemic toxicity noted in animals treated at a dose level of 2,000 mg/kg bw were hunched posture, lethargy, pilo-erection, ptosis, ataxia, decreased respiratory rate, laboured respiration, loss of righting reflex, pallor of the extremities, dehydration, emaciation and tiptoe gait.

Table 6.2.1-8 Number of deaths, Acute oral toxicity of fenoxaprop-P-ethyl in the rat – up and down procedure

Dose (mg / kg bw)	Mortality
2,000	4 / 4
550	0 / 3
175	0 / 1

Table 6.2.1-9 Clinical findings observed in rats orally dosed with fenoxaprop-P-ethyl

Signs	Dose (mg / kg bw)		
	2,000	**550**	**175**
Hunched posture	4 / 4	0 / 3	0 / 1
Ataxia	3 / 4	0 / 3	0 / 1
Lethargy	4 / 4	0 / 3	0 / 1
Pilo-erection	4 / 4	0 / 3	0 / 1
Decreased respiratory rate	4 / 4	0 / 3	0 / 1
Laboured respiration	2 / 4	0 / 3	0 / 1
Loss of righting reflex	1 / 4	0 / 3	0 / 1
Pallor of the extremities	3 / 4	0 / 3	0 / 1
Dehydration	3 / 4	0 / 3	0 / 1
Emaciation	2 / 4	0 / 3	0 / 1
Tiptoe gait	3 / 4	0 / 3	0 / 1
Ptosis	1 / 4	0 / 3	0 / 1
Animal killed *in extremis*	3 / 4	0 / 3	0 / 1

Body weight and necropsy: The surviving animals showed expected gains in body weight over the study period. Abnormalities noted at necropsy of the animal that died during the study were abnormally red lungs, dark liver, dark kidneys, haemorrhage and epithelial sloughing of the gastric mucosa and haemorrhage of the non-glandular region of the stomach. Abnormalities noted at necropsy of animals that were killed in extremis during the study were epithelial sloughing and/or haemorrhage of the gastric mucosa and epithelial sloughing of the non-glandular region of the stomach. No abnormalities were noted at necropsy of animals that were killed at the end of the study.

Conclusion:
The acute and median lethal dose (LD50) and 95% confidence limits of the test material in the female SD CD strain rat were calculated to be 1,098 (550-2,000) mg/kg bw (based on an assumed sigma of 0.5).
According to the Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), fenoxaprop-P-ethyl is to be classified as Acute Tox. Cat. 4 and labelled with H302, "Harmful if swallowed".

B.6.2.2. Acute Dermal study with Fenoxaprop-P-ethyl

Reference:	Testing for acute dermal toxicity in the male and female Wistar rat
Author(s), year:	[redacted] 1985b
Report/Doc. number:	A36023 / Hoechst Report No. 85.1175
Guideline(s):	EPA Guideline 81-2 (1984)
GLP:	Yes
Deviations to OECD GD 402 (1987):	Initial bodyweight of female rats lower than recommended in the guideline.
Acceptability:	Yes

Material and Methods:
Groups of 5 rats/sex received a topical application of 2,000 mg/kg bw Fenoxaprop-P-ethyl. The test substance was moistened (ratio 1 g + 1 ml) with PEG 400 and occluded with 6 x 8 cm aluminium foil to the dorsal skin and covered with an elastic plaster bandage. After 24 h of exposure the bandage and the foil were removed and the treated skin was washed with water. During the 14-day observation period the animals were observed daily and weighed weekly. At termination all animals were examined for macroscopic abnormalities.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 %

Test animals: Wistar rat, Strain WISKf(SPF71), [redacted]
7-9 weeks, mean bw of 200.4 ± 7.8 g (♂) and 184.8 ± 6.7 g (♀).
Number of animals: 5 rats per sex

Findings:
Clinical signs and mortality: No deaths occurred among either the male or female rats. No clinical signs were observed during the study and no effect on body weight was noted. A substance-related dermal effect in the form of partial scaling of the skin was observed in all of the males between days 1 and 4, and in three of the females from days 1 to 3.

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
Fenoxaprop-P-ethyl (moistened in PEG 400) is of low acute toxicity in Wistar rats after dermal application. The LD_{50} for males and females is greater than 2000 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute dermal toxicity is not required.

B.6.2.3. Acute Inhalation studies with Fenoxaprop-P-ethyl

B.6.2.3.1. Acute inhalation study - Rat

Reference:	Testing for acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC_{50}
Author(s), year:	[redacted] 1991
Report/Doc. number:	A46998 / Hoechst Report No. 91.1089
Guideline(s):	EPA Guideline 81-3 (1984), OECD guideline 403 (1981)
GLP:	Yes
Deviations to OECD GD 403 (2009):	Individual body weights of animals before start of study not stated.
Acceptability:	Yes

Material and Methods:
Groups of 5 rats/sex were exposed (nose-only) to the technically highest administrable aerosol concentration of 1.224 mg/L Fenoxaprop-P-ethyl (actual concentration in chamber) dissolved in 10% w/v PEG 400 for 4 hours. Evaluation of the particle size distribution revealed a MMAD of 1.4 µm with a geometric standard deviation ranging from 2.1 to 2.2. During the 14-day observation period the animals were observed daily and weighed weekly. At termination all animals were examined for macroscopic abnormalities.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002
Purity: 97.7 %

Test animals: Wistar rat, WISKf (SPF71), [redacted]
8-10 weeks, mean bw of 198.8 ± 2.9 g (♂) and 191.8 ± 3.6 g (♀).
Number of animals: 5 rats per sex

Table 6.2.3-1 Main exposure parameters of the acute inhalation study

Parameter		Value
Chamber concentration (mg/L)	Chemical analysis	1.224
	Gravimetric analysis	Not stated
Particle size (µm)	MMAD (± GSD)	1.4 (± 2.1-2.2)
	% respirable (< 7µm)	100
Chamber air temperature (°C)	Control group	21.9-22.4
	Test group	
Relative humidity (%)	Control group	8.4-11.1
	Test group	

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation

Findings:
Clinical signs and mortality: No mortality occurred under the conditions of the present study. The following clinical signs were observed up to study day 4 in both males and females: irregular respiration, ruffled coat, and stilted gait. Body weight was not affected.

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
The acute inhalative LC_{50} of Fenoxaprop-P-ethyl (moistened in PEG 400) is higher than 1.224 mg/L in male and female rats after 4 hours of nose-only inhalation. 1.224 mg/L air was reported to be the technically highest administrable dose.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute inhalation toxicity is not required.

B.6.2.3.2. Newly submitted study: Acute inhalation study - Rat

Reference:	Fenoxaprop-P-ethyl technical: Acute toxicity (nose only) study in the rat
Author(s), year:	[redacted] 2005
Report/Doc. number:	131 FPE
Guideline(s):	EPA Guidelines OPPTS 870.1300, OECD Guideline 403, Method B2 of Commission Directive 92/69/EEC
GLP:	Yes
Deviations to OECD GD 403 (2009):	MMAD was too high (26.8µm) than the respirable range (1-4µm) as recommended in the guideline, leading to inadequate exposure conditions due to low respirable fraction.
Acceptability:	Supplementary, due to major deviations.

Material and Methods:
A group of 5 rats/sex was exposed (nose-only) to the technically highest administrable aerosol concentration of 3.4 mg/L Fenoxaprop-P-ethyl (ground using a small amount of diethyl ether), for four hours using a nose only exposure system. Prior to use, the diethyl ether was removed via evaporation from the test material. The animals were observed for a period of 14 days.

Test material: fenoxaprop-P-ethyl technical CHA 480, batch 660-PSH-45
Purity: 95.6 %

Test animals: Rat, Sprague-Dawley Crl:CD® (SD) IGS R[redacted]
8-12 weeks, mean bw of 292.8 ± 10.8 g (♂) and 246.4 ± 13.7 g (♀).
Number of animals: 5 rats per sex

Table 6.2.3-2 Main exposure parameters of the acute inhalation study

Parameter		Value
Chamber concentration (mg/L)	Chemical analysis	3.40 (± 1.49)
	Gravimetric analysis	Not stated
Particle size (µm)	MMAD (± GSD)	26.8 (± 3.44)
	% respirable (< 7µm) < 4µm	10.38 6.1
Chamber air temperature (°C)	Control group	21-23
	Test group	
Relative humidity (%)	Control group	46-20
	Test group	

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation

It was stated in the study report that due to physical characteristics of the material, the MMAD exceeded the range given in the test guideline. As the use of a separator reduced the concentration (0.14 mg/L), it was considered more appropriate by the study authors to run the study at a higher concentration in order expose the animals to a much greater concentration of particles below 4µm.

Findings:
Clinical signs and mortality: No mortality occurred under the conditions of the present study. During exposure both male and female animals had wet fur and increased respiratory rates. Clinical signs observed after removal from chamber were wet fur, hunched posture and piloerection. On the first day after exposure 2 female animals showed red/brown staining around snout. No further clinical signs were noted.

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
The acute inhalative LC_{50} of Fenoxaprop-P-ethyl (moistened in diethyl ether) was greater than the mean maximum attainable concentration of 3.40 mg/L in male and female rats after 4 hours of nose-only inhalation.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute inhalation toxicity is not required.

B.6.2.4. Skin Irritation studies with Fenoxaprop-P-ethyl

B.6.2.4.1. Skin irritation - Rabbit

Reference:	Testing for primary dermal irritation in the rabbit
Author(s), year:	[redacted]; 1985d
Report/Doc. number:	A36061 / Report No 85.1125
Guideline(s):	EPA Guideline 81-5 (1984)
GLP:	Yes
Deviations to OECD Guideline 404 (2015):	- Sex of animals not reported. - Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. However, as symptoms disappeared on the second day already, no (persisting) effect on body weights is to be expected.
Acceptability:	Yes

Material and Methods:
Six rabbits (sex not reported) were treated with 500 mg Fenoxaprop-P-ethyl moistened with 0.55 ml PEG 400 on a 2.5 x 2.5 cm cellulose patch covered with a semi-occlusive bandage on the dorsal region. After 4 h exposure period the test substance was removed with warm tap water and examinations of the skin took place 30-60 minutes, 24 h, 48 h and 72 h after removal of the patches according to the criteria of Draize.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 %

Test animals: Rabbit, New Zealand albino rabbits, [redacted]
3-5 months, 2.9 to 3.7 kg.
Number of animals: 6 rabbits

Findings:
30-60 minutes after removal of the bandage, very slight erythema (grade 1) was observed in all animals. After 24 hours 2 of 6 rabbits were still affected with very slight erythema (grade 1). At 48 and 72 hours all animals were free of erythema. No oedemas were observed in any of the rabbits at any time.

Table 6.2.4-1 Individual and mean skin irritation scores

Time after removal of patch (hours)	**0.5-1**						**24**						**48**						**72**					
Animal no	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
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
Total	**6**						**2**						**0**						**0**					
Irritancy index (erythema):	**8/18 = 0.44**																							

Conclusion:
Slightly irritating effects were observed on the skin of rabbits. These effects do not lead to a classification of Fenoxaprop-P-ethyl as irritating to the skin.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding dermal irritation is not required.

B.6.2.4.2. Newly submitted study: Skin irritation - Rabbit

Reference:	Fenoxaprop-P-ethyl Technical: Acute dermal irritation in the rabbit
Author(s), year:	[redacted]; 2005
Report/Doc. number:	125 FPE
Guideline(s):	OECD Guideline 404 (2002), Method B4 of the Commission Directive 2004/73/EC, US EPA OPPTS 870.2500 (1998)
GLP:	Yes
Deviations to OECD GD 404 (2015):	- Sex of animals not reported. - Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. However, as no symptoms were observed, no effect on body weights is to be expected.
Acceptability:	Yes

Material and Methods:
Three rabbits (sex not reported) were treated with 500 mg fenoxaprop-P-ethyl moistened with 0.5 ml distilled water on a 2.5 x 2.5 cm cotton gauze patch on the dorsal region. The patch was secured in position with a strip of surgical adhesive tape and the trunk of each rabbit was wrapped in an elasticated corset. After 4 h exposure period the test substance was removed with cotton wool soaked in distilled water and examinations of the skin took place 60 minutes, 24 h, 48 h and 72 h after removal of the patches according to the criteria of Draize.

Test material:	fenoxaprop-P-ethyl CHA 480, batch 660-PSH-45
Purity:	95.6 %
Test animals:	Rabbit, New Zealand albino rabbits, [redacted] 12-20 weeks, 2.0 to 3.5 kg.
Number of animals:	3 rabbits

Findings:
No oedemas and no erythema/eschar formation were observed in any of the rabbits at any time.

Table 6.2.4-2 Individual and mean skin irritation scores

Time after removal of patch (hours)	**1**			**24**			**48**			**72**		
Animal no	1	2	3	1	2	3	1	2	3	1	2	3
Erythema	0	0	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0	0	0
Total	**0**			**0**			**0**			**0**		
Mean score	**0/9 = 0**											

Conclusion:
No irritating effects were observed on the skin of rabbits.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding dermal irritation is not required.

B.6.2.5. Eye Irritation studies with Fenoxaprop-P-ethyl

B.6.2.5.1. Eye irritation - Rabbit

Reference:	Testing for primary eye irritation in the rabbit
Author(s), year:	[redacted] 1985e
Report/Doc. number:	A36022 / Report No 85.1215
Guideline(s):	EPA Guideline 81-4 (1982)
GLP:	Yes
Deviations to OECD Guideline 405 (2012):	Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. However, as symptoms disappeared on the second day already, no (persisting) effect on body weights is to be expected.
Acceptability:	Yes

Material and Methods:
Nine rabbits (sex not reported) were treated with 100 mg of undiluted Fenoxaprop-P-ethyl. The test substance was applied to the conjunctival sac of the left eyes of all rabbits. 1 minute after application the treated eyes of 3 animals were washed out for 1 minute with physiological saline at 37°C. The treated eyes of the other 6 animals were washed out the same way after 24 hours. The eyes of all animals were examined 1, 24, 48 or 72 hours after application. At 24 and 72 hours the eyes were also examined for corneal lesions under UV light after instillation of one drop of 0.01% fluorescein-sodium solution.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 %

Test animals: Rabbit, New Zealand albino rabbits, [redacted]
3-5 months, 3.0 to 4.0 kg.
Number of animals: 9 rabbits

Findings:
In the eyes washed out after 24 hours, redness and/or swelling of the conjunctivae (grades 1 and 2) were noted in all rabbits up to 24 hours after application. These findings were accompanied by slight to considerable quantities of clear discharge up to 48 hours. Inflammation of the iris (grade 1) was noted in one animal at 24 hours.
In the eyes washed out after 1 minute, redness (grade 2) and swelling (grade 1) of the conjunctivae were observed 1 hour after application. After 24 hours, only light discharge was noted.

Table 6.2.5-1 Individual and mean acute eye irritation scores after 1 min application

Animal	h	Conjunctivae		Iritis	Cornea	
		Chemosis	Redness		Opacity	Area
1	1	1	2	0	0	0
	24	0	0	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
2	1	1	2	0	0	0
	24	0	0	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
3	1	0	2	0	0	0
	24	0	0	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
Mean score (24h-72h)		**0**	**0**	**0**	**0**	**0**

Table 6.2.5-2 Individual and mean eye irritation scores after 24 h application

Animal	h	Conjunctivae		Iritis	Cornea	
		Chemosis	Redness		Opacity	Area
1	1	1	1	0	0	0
	24	0	1	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
2	1	1	2	0	0	0
	24	0	2	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
3	1	1	2	0	0	0
	24	1	2	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
4	1	1	2	0	0	0
	24	0	2	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
5	1	2	2	0	0	0
	24	1	2	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
6	1	1	2	0	0	0
	24	2	2	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
Total (24h-72h)		**4**	**11**	**0**	**0**	**0**
Mean score (24h-72h)		**0.17**	**0.61**	**0**	**0**	**0**

Conclusion:
Slightly irritating effects were observed on the eyes of rabbits. These effects do not lead to the classification of Fenoxaprop-P-ethyl as irritating to the eyes.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding eye irritation is not required.

B.6.2.5.2. Newly submitted study: Eye irritation - Rabbit

Reference:	Fenoxaprop-P-ethyl technical: Acute eye irritation in the rabbit
Author(s), year:	[redacted] 2005
Report/Doc. number:	124 FPE
Guideline(s):	OECD 405, Method B5 of Commission Directive 2004/73/EC, US EPA OPPTS 870.2400, 1998
GLP:	Yes
Deviations to OECD GD 405 (2012):	Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. However, as symptoms were minimal and disappeared on the second day already, no (persisting) effect on body weights is to be expected.
Acceptability:	Yes

Material and Methods:
A single rabbit was treated with 0.1 ml of the test material (found to weigh approximately 31 mg) by placing into the conjunctival sac of the right eye. Upper and lower eyelids were held together for a second and then released. The left eye remained untreated and was used for control purposes.
After consideration of the ocular responses, two additional animals were treated the same way. Assessment of ocular damage/irritation was made approximately 1 hour, 24, 48 and 72 hours following treatment.

Test material: fenoxaprop-P-ethyl technical CHA 480, 660-PSH-45

Purity:	95.6 %
Test animals:	Male Rabbit, New Zealand White rabbits, [redacted] 12-20 months, 2.0-3.5 kg
Number of animals:	3 rabbits

Findings:
No corneal or iridial effects were noted during the study.
Minimal conjunctival irritation was noted in all treated eyes one hour after treatment and in one treated eye at the 24-hour observation. Two treated eyes appeared normal at the 24-hour observation and the remaining eye appeared normal at the 48-hour observation.

Table 6.2.5-3 Individual scores and individual total scores for ocular irritation

Animal	h	Conjunctivae		Iritis	Cornea	
		Chemosis	Redness		Opacity	Area
1	1	0	1	0	0	0
	24	0	0	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
2	1	0	1	0	0	0
	24	0	1	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
3	1	0	1	0	0	0
	24	0	0	0	0	0
	48	0	0	0	0	0
	72	0	0	0	0	0
Total score		**0**	**1**	**0**	**0**	**0**
Mean score (24h-72h)		**0**	**0.11**	**0**	**0**	**0**

Conclusion:
Slightly irritating effects were observed on the eyes of rabbits, which lead to no classification of fenoxaprop-P-ethyl regarding eye irritation according to Regulation (EC) 1272/2008.

B.6.2.6. Skin Sensitization studies with Fenoxaprop-P-ethyl

B.6.2.6.1. Skin sensitisation (GPMT)

Reference:	Hoe 04630 - active ingredient technical (Code: Hoe 046360 0H ZC96 0002) Testing for sensitizing properties in the Pirbright-White guinea pig in a maximisation test
Author(s), year:	[redacted] 1986a
Report/Doc. number:	A37243 / Report No 86.0003
Guideline(s):	EPA Guideline 81-6 (1982)
GLP:	Yes
Deviations to OECD Guideline 406 (1992):	No
Acceptability:	Yes

Material and Methods:
Female guinea pigs were given Fenoxaprop-P-ethyl 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.

Test material:	fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity:	95.6 %
Test animals:	Female guinea pigs, Pirbright-White guinea pigs (DHPK), [redacted]

10 weeks old, 263.7 ± 19.7 g.
Number of animals: 30 animals for main study, excluding 6 for determination of primary non-irritant concentration, 3 for determination of intradermic tolerance, 5 for escort group

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.

Table 6.2.6-1 Dose levels for the main study

	Treated group			Control group		
	Site 1	**Site 2**	**Site 3**	**Site 1**	**Site 2**	**Site 3**
Induction intradermal injection	50 % CFA	5 % fenoxaprop-P-ethyl in paraffin	5 % fenoxaprop-P-ethyl in 50 % CFA	50 % CFA	Paraffin	50 % CFA
Induction topical application (48 h)	50 % fenoxaprop-P-ethyl in vaseline			Vaseline		
Topical challenge	Left flank: 50 % fenoxaprop-P-ethyl in vaseline Right flank: Vaseline					

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.

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 oedema 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 oedema (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 oedema (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.

Table 6.2.6-2 Number of animals exhibiting skin reactions after challenge with fenoxaprop-P-ethyl

	48 hours		72 hours	
	Control	**Treated**	**Control**	**Treated**
Erythema	0 / 10	19 / 20	0 / 10	20 / 20
- Very slight	-	3 / 20	-	6 / 20
- Well-defined	-	9 / 20	-	13 / 20
- Moderate to severe	-	7 / 20	-	1 / 20
Oedema	0 / 10	14 / 20	0 / 10	11 / 20

	48 hours		72 hours	
	Control	**Treated**	**Control**	**Treated**
- Very slight	-	14 / 20	-	11 / 20

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.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), fenoxaprop-P-ethyl is classified as Skin Sens. Cat. 1 and labelled with H317, "May cause an allergic skin reaction". Distinction between sub-category 1A and 1B is not possible because intradermal induction dose was >1%.

B.6.2.6.2. Skin Sensitisation (Buehler – study 1)

Reference:	Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler
Author(s), year:	[redacted] 1986b
Report/Doc. number:	A36040 / Report No 86.0466
Guideline(s):	EPA Guideline 81-6 (1982)
GLP:	Yes
Deviations:	Induction phase performed under non-irritating conditions.
Acceptability:	Limited scientific validity of this study due to technical reasons.

Material and Methods:
Female guinea pigs were given Fenoxaprop-P-ethyl 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 vaseline) 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.

Test material:	fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity:	95.6 %
Test animals:	Female guinea pigs, Pirbright-White guinea pigs (DHPK), [redacted] 10 weeks old, 227.4 ± 24.3 g.
Number of animals:	30 animals for the main test, excluding 6 for determination of the non-irritant concentration

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.) led 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.

Table 6.2.6-3 Number of animals exhibiting skin reactions after challenge with fenoxaprop-P-ethyl

1st challenge (25% f. in vaseline)	24 hours		48 hours	
	Control	Treated	Control	Treated
Erythema	1 / 10	3 / 19*	7 / 10	12 / 19
- Very slight	1 / 10	3 / 19	7 / 10	11 / 19
- Well-defined	-	-	-	1 / 19
Oedema	0 / 10	0 / 20	0 / 10	0 / 19
2nd challenge (10% f. in vaseline)	**24 hours**		**48 hours**	
	Control	**Treated**	**Control**	**Treated**
Erythema	1 / 10	3 / 19	0 / 10	1 / 19
- Very slight	1 / 10	3 / 19	-	1 / 19
Oedema	0 / 10	0 / 19	0 / 10	0 / 10
3rd challenge (2% f. in vaseline)	**24 hours**		**48 hours**	
	Control	**Treated**	**Control**	**Treated**
Erythema	0 / 10	5 / 19	0 / 10	0 / 19
- Very slight	-	5 / 19	-	-
Oedema	0 / 10	0 / 19	0 / 10	0 / 19
4th challenge (2% f. in vaseline)	**24 hours**		**48 hours**	
	Control	**Treated**	**Control**	**Treated**
Erythema	0 / 10	0 / 19	0 / 10	0 / 19
Oedema	0 / 10	0 / 19	0 / 10	0 / 19

*one animal died

Conclusion:
The results of this study are inconclusive. It is reported that technical reasons (clipping) might have led 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.

B.6.2.6.3. Skin Sensitisation (Buehler – study 2)

Reference:	Testing for sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler
Author(s), year:	[redacted] 1992
Report/Doc. number:	A47403 / Report No 91.1199
Guideline(s):	EPA Guideline 81-6 (1984), OECD Guideline 406 (1987), MAFF (1985)
GLP:	Yes
Deviations:	Induction phase performed under non-irritating conditions.
Acceptability:	Yes.

Material and Methods:
Female guinea pigs were given Fenoxaprop-P-ethyl 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.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002
Purity: 90.0 % , sum of (D+)- and (L-)-isomer 97.7%

Test animals: Female guinea pigs, Pirbright-White guinea pigs (DHPK), [redacted]
10 weeks old, 266.4 ± 14.4 g.
Number of animals: 30 animals, excluding 6 animals used for determination of 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.

Table 6.2.6-4 Number of animals exhibiting skin reactions after challenge with fenoxaprop-P-ethyl

challenge (75% f. in PEG400)	24 hours		48 hours	
	Control	Treated	Control	Treated
Erythema	0 / 10	0 / 20	0 / 10	0 / 20
Oedema	0 / 10	0 / 20	0 / 10	0 / 20

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.

B.6.2.6.4. Newly submitted study: Skin Sensitisation (LLNA)

Reference:	Fenoxaprop-p-ethyl technical: Local lymph node assay in the mouse
Author(s), year:	[redacted] 2005
Report/Doc. number:	SPL Project Number 545/339 / 123 FPE
Guideline(s):	OECD 429 (2002), Method B42 of Commission Directive 2004/72/EC
GLP:	Yes
Deviations to OECD GD 429 (2010):	No
Acceptability:	Yes

Material and Methods:
A preliminary screening test was performed with one mouse being treated by daily application of 25 µl of the test material at a concentration of 50% w/w in acetone/olive oil (4:1) to the dorsal surface of each ear for three consecutive days (d1, d2, d3). The mouse was observed twice daily, and once daily on d4, d5 and d6. Any signs of toxicity or excessive local irritation noted during this period were recorded. The bodyweight of the mouse was recorded on d1 (prior to dosing) and on d6.

The main test was conducted with four animals per group, which were treated the test material as a solution at concentrations of 10, 25 or 50 % w/w in acetone/olive oil (4:1). The mice were treated by daily application of 25 µl of the appropriate concentration of the test material to the dorsal surface of each ear for three consecutive days. A further group of four animals received the vehicle alone in the same manner. Five days following the first topical application of the test material (d6) all mice were injected via the tail vein with 250 µl of phosphate buffered saline (PBS) containing ^{3}H-methyl thymidine (^{3}HTdR: 80 µCi/ml, specific activity 2.0 Ci/mmol) giving a total of 20 µCi to each mouse. All mice were killed by CO_2 asphyxiation and draining auricular lymph nodes were analysed.

Test material: fenoxaprop-P-ethyl technical CHA 480, batch 660-PSH-45

Purity:	95.6 %
Test animals:	Female Mice, CBA/Ca (CBA/Ca CruBR) strain, [redacted] 8-12 weeks old, 19.1 ±1.9 g.
Number of animals:	16 animals, excluding one animal used for preliminary screening test

Evaluation criteria: The test material will be regarded as a sensitiser if at least one concentration it results in a 3-fold or greater increase in ^{3}HTdR incorporation (radioactive disintegrations per minute, dpm) compared to control values. In case this is not fulfilled, the test material will be classified as a "non-sensitizer"

Findings:

Preliminary screening test: No signs of systemic toxicity were noted. White residual test material was noted one hour post dosing on d3. Based on this information the dose levels selected for the main test were 10%, 25% and 50% w/w in acetone olive oil (4:1).

Main test: The radioactive disintegrations per minute (dpm) per lymph node and the stimulation index (SI) are given in Table 6.2.6-5. A stimulation index of less than 3 was recorded for the three concentrations of the test material.

There were no deaths. No signs of systemic toxicity were noted in the test or control animals during the test. White residual test material was noted in animals treated with the test material at a concentration of 50% w/w in acetone/olive oil 4:1 one hour post dosing on d2.

Bodyweight changes of the test animals between d1 and d6 were comparable to those observed in the corresponding control group animals over the same period.

Table 6.2.6-5 Radioactive disintegrations per minute (dpm), dpm/Node and Stimulation Index (SI)

Concentration (% w/w) in acetone /olive oil 4:1	Dpm	Dpm/Node [a]	SI [b]	Result
Vehicle	9769.20	1221.15	N/A	N/A
10	12557.62	1569.70	1.29	Negative
25	16654.83	2081.85	1.70	Negative
50	10439.48	1304.94	1.07	Negative

The following table summarizes a selection of historical control data for positive controls (α-Hexylcinnamaldehyde dissolved in 4:1 acetone/olive oil).

Table 6.2.6-6 Historical control data, Fenoxaprop-p-ethyl technical: Local lymph node assay in the mouse

Experiment date	Test material	Concentration	Vehicle	Stimulation index	Classification
10-2003	α-Hexylcinnamaldehyde	5, 10, 25% v/v	4:1 acetone/olive oil	1.49, 1.73, 5.26	Positive
05-2004	α-Hexylcinnamaldehyde	5, 10, 25% v/v	4:1 acetone/olive oil	1.40, 2.23, 6.09	Positive
04-2004	α-Hexylcinnamaldehyde	5, 10, 25% v/v	4:1 acetone/olive oil	1.74, 2.20, 8.89	Positive
03-2005	α-Hexylcinnamaldehyde	5, 10, 25% v/v	4:1 acetone/olive oil	2.76, 3.34, 8.91	Positive
04-2005 (latest study)	α-Hexylcinnamaldehyde	5, 10, 25% v/v	70% ethanol in distilled water	2.60, 8.40, 12.90	Positive

Conclusion:

Fenoxaprop-P-ethyl did not induce skin sensitization after an LLNA test in mice.

According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding skin sensitization is not required.

B.6.2.7. Phototoxicity study with Fenoxaprop-P-ethyl

According to new data requirements for active substances (Regulation (EU) No 283/2012) an *in vitro* phototoxicity study is required where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution.

If the Ultraviolet/visible molar extinction/absorption coefficient of the active substance is less than 10 L x mol^{-1} x cm^{-1}, no toxicity testing is required.
Fenoxaprop-P-ethyl absorbs electromagnetic radiation mostly below 300 nm. However, at 290 nm the extinction coefficient is still > 1000 L x mol^{-1} x cm^{-1}, which is above the trigger of 10 L x mol^{-1} x cm^{-1}. Therefore, testing of fenoxaprop-P-ethyl for cytotoxicity is justified.

Newly submitted study

Reference:	Fenoxaprop-P-ethyl, technical: Cytotoxicity assay *in vitro* with Balb/c 3T3 cells: Neutral Red (NR) test during simultaneous irradiation with artificial sunlight
Author(s), year:	Heppenheimer A.; 2014
Report/Doc. number:	M-496758-01-1
Guideline(s):	Method B 41 Commission Regulation (EC) No. 440/2008, CMPM/SWP/398/01 (2002), OECD 432 (2004)
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Materials and Methods:
The test item was dissolved in DMSO. The final concentration of the solvent in EBSS was 1% (v/v). The highest applied concentration of the test item was 500 µg/mL and thus in accordance with the OECD Guideline.
The experiment was performed twice. The first experiment ranged as range finding experiment (RFE), the second one was the main experiment (ME).

Test material:	fenoxaprop-P-ethyl technical, batch AE F046360-01-12
Purity:	94.3 % (w/w, optically active enantiomer alone, dose calculation was not adjusted to purity)
Stability of test item:	Not indicated by sponsor
Storage conditions:	At room temperature, protected from light
Test system:	BALB/c 3T3 cells clone $2x10^4$ per well
Incubation medium:	EBSS containing 1% (v/v) DMSO
Temperature and Atmosphere:	37 ± 1.5 °C 7.5 ± 0.5 % CO_2

Tested Concentrations:
The following concentrations were tested (each concentration of the test item was measured 6 times) with and without irradiation: 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250 and 500 µg/mL.

Controls:
The solvent control for the test item was EBSS containing 1% (v/v) DMSO. The solvent control for the positive control was EBSS.
Solvent controls were performed as follows and were each tested in 12 replicates:

- Cultures exposed to the solvent controls, stored in the dark during exposure
- Cultures exposed to the solvent controls, irradiated for 50 min during exposure

Chlorpromazine (Sigma) dissolved in EBSS was used as positive control. The following concentrations were applied:

- Absence of Irradiation: 6.25, 12.5, 25, 37.5, 50, 75, 100, 200 µg/mL chlorpromazine
- Presence of Irradiation: 0.125, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0 µg/mL chlorpromazine

Each concentration of the positive control was measured 6 times in both experiments.

Solar Simulator:
The irradiation was performed with a Dr. Hönle Sol 500 solar simulator. The filter H1 was used to keep the UVB irradiation as low as possible. The produced wavelength of the solar simulator with the filter was > 320 nm.

Experimental Procedure:
2 x 10^4 cells per well were seeded in 100 µL culture medium (two plates, one was exposed to artificial sunlight and one was kept in the dark). Approximately 24 hours after seeding the cultures were treated with the test item.

After pre-incubation for one hour in the dark, one plate was irradiated through the lid at 1.65 mW/cm^2 (approx. 5 J/cm^2), for 50 min at 28 °C, the other plate was stored for 50 min at 28 °C in the dark. After irradiation, the test item was removed and both plates were washed twice with EBSS and incubated with culture medium overnight. Cytotoxicity was determined by Neutral Red Uptake determination.

Analysis:
The ED50 values, the Photo-Irritancy-Factor (PIF), as well as the Mean Phototoxic Effect (MPE), were calculated using the software Phototox (Version 2.0) (distributed by ZEBET, 12277 Berlin, Germany, and recommended by the OECD guideline).

Interpretation of Results:
Based on the results obtained, the test item is evaluated as follows:
- If PIF < 2 or MPE < 0.1: no phototoxic potential predicted.
- If PIF > 2 and < 5 or MPE >0.1 and <0.15 a probable phototoxic potential is predicted.
- If PIF > 5 or MPE > 0.15 a phototoxic potential predicted

The assay meets the acceptance criteria:
- If after irradiation with a UVA dose of 5 J/cm² the cell viability of the solvent control is > 80% of non-irradiated cells;
- If for the positive control CPZ the factor (PIF) between the two ED50 values is > 6; and
- If the mean OD540 of solvent controls is > 0.4.

Findings:
Cytotoxic effects did not occur after exposure of the test item to the cells, neither in the presence nor in the absence of irradiation with artificial sunlight in both experiments. Therefore, ED50-values or a PIF could not be calculated. The resulting MPE values were -0.117 and -0.235, for the range finding (RFE) and main experiment (ME) respectively. The results demonstrate that the test item is not phototoxic under the conditions of this study.

Table 6.2.7-1 ME: Treatment of BALB/c 3T3 with fenoxaprop-P-ethyl technical

With artificial sunlight			Without artificial sunlight		
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value ± SD**	**% of SC**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value ± SD**	**% of SC**
0	1.1290* ± 0.0540	100.00	**0**	1.0607* ± 0.1229	100.00
0.244	1.1010 ± 0.0779	97.52	**0.244**	0.7923 ± 0.0739	74.70
0.488	1.0851 ± 0.0492	96.11	**0.488**	0.7567 ± 0.0959	71.34
0.977	1.1141 ± 0.0559	98.68	**0.977**	0.7827 ± 0.0501	73.79
1.953	1.1105 ± 0.0856	98.36	**1.953**	0.7913 ± 0.0530	74.61
3.906	1.0520 ± 0.0840	93.18	**3.906**	0.7454 ± 0.0845	70.28
7.813	1.0488 ± 0.1026	92.90	**7.813**	0.7563 ± 0.0757	71.30
15.63	1.0890 ± 0.1290	96.45	**15.63**	0.7036 ± 0.0577	66.33
31.25	1.0660 ± 0.0918	94.42	**31.25**	0.7620 ± 0.0402	71.85

* mean O.D.$_{540\ nm}$ out of 12 wells
SD = standard deviation
SC = solvent control

Table 6.2.7-2 ME: Treatment of BALB/c 3T3 with the positive Control (chlorpromazine)

With artificial sunlight			Without artificial sunlight		
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value ± SD**	**% of SC**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value ± SD**	**% of SC**
0	1.1056* ± 0.0898	100.00	**0**	0.8419* ± 0.0510	100.00
0.244	1.0580 ± 0.0840	95.69	**0.244**	0.6664 ± 0.0686	79.15
0.488	0.9721 ± 0.0684	87.92	**0.488**	0.1446 ± 0.0296	17.18
0.977	0.5687 ± 0.0853	51.44	**0.977**	0.0610 ± 0.0082	7.24
1.953	0.2451 ± 0.0344	22.17	**1.953**	0.0623 ± 0.0097	7.40
3.906	0.1187 ± 0.0381	10.74	**3.906**	0.0565 ± 0.0043	6.70
7.813	0.0946 ± 0.0397	8.56	**7.813**	0.0593 ± 0.0062	7.04
15.63	0.0734 ± 0.0105	6.64	**15.63**	0.0565 ± 0.0055	6.71
31.25	0.0825 ± 0.0306	7.46	**31.25**	0.0543 ± 0.0013	6.45

* mean $O.D._{540\,nm}$ out of 12 wells
SD = standard deviation
SC = solvent control

The positive control chlorpromazine induced phototoxicity in the expected range after irradiation with artificial sunlight. The PIF values were 50.49 and 17.45, and the resulting MPE values were 0.744 and 0.512.
The positive control chlorpromazine induced phototoxicity in the expected range.

Table 6.2.7-3 Summary of Results

	Test Item	ED_{50} [µg/mL] +UV	-UV	PIF	MPE	% viability of SC of irradiated vs non-irradiated plate
RFE	Fenoxaprop-P-ethyl technical	-	-	-	-0.117	93.3
	Positive control	0.21	10.81	50.49	0.744	100.6
ME	Fenoxaprop-P-ethyl technical	-	-	-	-0.235	106.4
	Positive control	0.51	8.83	17.45	0.512	131.3

RFE … range finding experiment
ME … main experiment

Conclusion:
In conclusion, under the experimental conditions reported in this study, fenoxaprop-P-ethyl technical did not have any phototoxic effects on BALB/c 3T3 cells.

B.6.2.8. Acute Oral studies with Fenoxaprop-ethyl

B.6.2.8.1. Acute oral study – Rat (male)

Reference:	Acute oral toxicity of HOE 33171 0H AT203 to the male rat
Author(s), year:	[redacted]; 1979a
Report/Doc. number:	A24696 / Hoechst Report No. 576/79
Guideline(s):	None, but similar to OECD 401
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Groups of 10 rats/dose received single doses of 1,600, 2,000, 2,250, 2500 or 5,000 mg/kg bw of a 25% suspension of Fenoxaprop-ethyl in sesame oil by oral gavage. The animals were starved 16 hours before and 2 hours after treatment. Clinical symptoms, body weight gain and mortality were registered during the 14-day follow-up period.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT203
Purity: 97.0 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: Male Wistar rat, WISKf (SPF71), [redacted]
Age not stated, mean bw of 180.4 ± 8.7 g
Number of animals: 10 rats per group

Findings:
Clinical signs and mortality: No animal died in the 1600 and 2000 mg/kg bw dose groups, respectively. The mortality rates were 4/10 at 2250 mg/kg bw, 7/10 at 2500 mg/kg bw and 10/10 at 5000 mg/kg bw. The LD50 was calculated to be 2357 mg/kg bw by probit analysis. All deaths occurred 1 to 7 days after application. Clinical signs included passiveness, disequilibrium, squatting, crawling or crouching, bristled hair, blepharophimosis, seromucous and sanguineous rhinorrhoea. The time frame in which clinical signs showed up is not reported. One week after dosing, body weight gains were impaired in some of the animals at 1600 and 2000 mg/kg bw and in all of the surviving animals at higher doses. Body weights were generally normal after two weeks.

Pathology: Animals found dead during the study showed bright spots on the liver, lobular marking of the liver, diffuse reddening of the pancreas, petechial haemorrhages in the gastric mucosa (fundic part) and in the duodenum, and a red-black liquid in the entire region of the small intestine. The only finding in animals killed at the end of study was a diffuse reddening of all abdominal viscera.

Conclusion:
Fenoxaprop-ethyl (suspended in sesame oil) is of low acute toxicity in male Wistar rats after oral administration. The LD_{50} was calculated to be 2357 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute oral toxicity is not required.

B.6.2.8.2. Acute oral study – Rat (female, study 1)

Reference:	Acute oral toxicity of HOE 33171 0H AT203 to the female rat
Author(s), year:	[redacted]; 1979b
Report/Doc. number:	A24698 / Hoechst Report No. 57/79
Guideline(s):	No, but similar to OECD 401
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Groups of 10 rats/dose received single doses of 2,000, 2,500, 3,150, 4,000 or 5,000 mg/kg bw of a 25% suspension of Fenoxaprop-ethyl in sesame oil by oral gavage. The animals were starved 16 hours before and 2 hours after treatment. Clinical symptoms, body weight gain and mortality were registered during the 14-day follow-up period.

Test material:	fenoxaprop-ethyl, batch Hoe 33171 0H AT203
Purity:	97.0 %; not included in the study report, but presented by the notifier in a separate report (A18371)
Test animals:	female Wistar rat, WISKf (SPF71), [redacted] Age not stated, mean bw of 165.6 ± 5.3 g
Number of animals:	10 rats per group

Findings:
Clinical signs and mortality: The mortality rates were 1/10 at 2000 mg/kg bw, 5/10 at 2500 mg/kg bw, 9/10 at 3150 mg/kg bw, 10/10 at 4000 mg/kg bw, and 9/10 at 5000 mg/kg bw. The LD_{50} was calculated to be 2500 mg/kg bw by probit analysis. All deaths occurred 1 to 4 days after dosing. Clinical signs included passiveness, disequilibrium, squatting, crawling or crouching, bristled hair, blepharophimosis, chromodacryorrhoea, and increased respiratory rate. The time frame in which clinical signs showed up is not reported. One week after dosing, body weight gains were impaired in some of the animals at 2000 mg/kg bw and in all of the surviving animals at higher doses. After two weeks, body weights recovered at 2000 mg/kg bw but only partially at higher doses.

Pathology: Animals found dead during the study showed bright spots on the liver, lobular marking of the liver, diffuse reddening of the small intestine and pancreas, petechial haemorrhages in the gastric mucosa (fundic part) and in the duodenum, uterus reddened, and a red-black liquid in the entire region of the small intestine. The only finding in animals killed at the end of study was slight lobular marking of the liver.

Conclusion:
Fenoxaprop-ethyl (suspended in sesame oil) is of low acute toxicity in male Wistar rats after oral administration. The LD_{50} was calculated to be 2357 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute oral toxicity is not required.

B.6.2.8.3. Acute oral study – Rat (female, study 2)

Reference:	HOE 33171 0H AT203 Acute oral toxicity to the female mouse
Author(s), year:	[redacted]; 1979b
Report/Doc. number:	A24694 / Hoechst Report No. 424/79
Guideline(s):	No, but similar to OECD 401
GLP:	Yes
Deviations:	Individual body weights of animals in the 2,500 mg/kg bw group not stated.
Acceptability:	Yes

Material and Methods:
Groups of 10 mice/dose received single doses of 2,500, 3,150, 4,000, 5,000, 5,600 or 6,300 mg/kg bw of a 25% suspension of Fenoxaprop-ethyl in sesame oil by oral gavage. The animals were deprived of food for 2 hours after treatment. Clinical symptoms, body weight gain and mortality were registered during the 14-day follow-up period.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT203
Purity: 97.0 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: female NMRI mouse, NMRKf (SPF71), [redacted]
Age not stated, mean bw of 20.52 ± 3.0 g, individual body weights of animals in low dose group not reported
Number of animals: 10 mice per group

Findings:
Clinical signs and mortality: No animals died in the 2500, 3150 or 4000 mg/kg bw dose group, resp.. The mortality rates were 3/10 at 5000 mg/kg bw, 8/10 at 5600 mg/kg bw, and 6/10 at 6300 mg/kg bw. The LD_{50} was calculated to be 5490 mg/kg bw by probit analysis. All deaths occurred 1 to 7 days after application. Clinical signs included passiveness, blepharophimosis, increased respiratory rate, disequilibrium, abdominal position, drowsiness, increased lacrimation and jerky respiration. Surviving animals were free from clinical symptoms within 48 or 72 hours after treatment. In some of the animals slight effects on body weight gain were recorded at higher doses.

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

Conclusion:
Fenoxaprop-ethyl (suspended in sesame oil) is of low acute toxicity in female NMRI mice after oral administration. The LD_{50} was calculated to be 5490 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-P-ethyl regarding acute oral toxicity is not required.

B.6.2.9. Acute Dermal studies with Fenoxaprop-ethyl

B.6.2.9.1. Acute dermal study – Rat (study 1)

Reference:	Hoe 33171 0H AT202 Op. No. 1619 I. Acute percutaneous toxicity to the female SPF-Wistar rat
Author(s), year:	[redacted]; 1978
Report/Doc. number:	A24673 / Hoechst Report No. 443/78
Guideline(s):	No, but similar to OECD 402
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Six rats received a topical application of 2,000 mg/kg bw Fenoxaprop-ethyl. The test substance was applied in the form of a 40 % suspension in sesame oil to the mechanically shaven dorsal skin of the rats. The area of exposure was covered for 24 hours with a strip of aluminium foil (6 x 8 cm) which was secured with an elastic plaster bandage. After 24 h of exposure the bandage and foil were removed and the treated skin was washed with water.

During the 14-day observation period the animals were observed and body weight was recorded. At the end of the study all animals were examined for macroscopic abnormalities.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT202 Op.No.1618I
Purity: >95.0 % (not reported in the study report; provided in the MCA section 6)

Test animals: Female Wistar rat, SPF, [redacted]
Age not stated, mean bw of 177.3 ± 6.7 g
Number of animals: 6 rats

Findings:
Clinical signs and mortality: No deaths occurred after treatment with 2000 mg/kg bw. Slight passiveness, ruffled pelage and blepharophimosis were observed at the beginning of the study but no longer seen 24 hours after treatment. Body weight was not affected at the end of the follow-up period. It is not reported if local effects on the skin had been observed.

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
Fenoxaprop-ethyl (suspended in sesame oil) is of low acute toxicity in female Wistar rats after dermal application. The LD_{50} for females is greater than 2000 mg/kg bw.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-ethyl regarding acute dermal toxicity is not required.

B.6.2.9.2. Acute dermal study – Rat (study 2)

Reference:	Acute percutaneous toxicity of Hoe 33171 0H AT203 to the female rat
Author(s), year:	[redacted]; 1979c
Report/Doc. number:	A24702 / Hoechst Report No. 578/79
Guideline(s):	No, but similar to OECD 402
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Six rats received a topical application of 2,000 mg/kg bw Fenoxaprop-ethyl. The test substance was applied in the form of a 40 % suspension in sesame oil to the shaven dorsal skin of the rats. The area of exposure was covered for 24 hours with a strip of aluminium foil (6 x 8 cm) which was secured with an elastic plaster bandage. After 24 h of exposure the bandage and foil were removed and the treated skin was washed with water. During the 14-day observation period the animals were observed and body weight was recorded. At the end of the study all animals were examined for macroscopic abnormalities.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT203
Purity: 97.0 %; not reported in the study report, but presented by the notifier in a separate report (A18371)

Test animals: Female Wistar rat, Strain WISKf(SPF71), [redacted]
Age not stated, mean bw of 178.8 ± 6.1 g
Number of animals: 6 rats

Findings:
Clinical signs and mortality: No deaths occurred after treatment with 2000 mg/kg bw. Passiveness was observed in all animals up to 24 hours after treatment. Body weight was not affected during follow-up period. It is not reported if local effects on the skin had been observed.

Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
Fenoxaprop-ethyl (suspended in sesame oil) is of low acute toxicity in female Wistar rats after dermal application. The LD_{50} for females is greater than 2000 mg/kg bw.

According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-ethyl regarding acute dermal toxicity is not required.

B.6.2.10. Acute Inhalation study with Fenoxaprop-ethyl

Reference:	Aerosol inhalation of Hoe 33171 active ingredient (Code: Hoe 33171 0H AT204) in male and female SPF-Wistar rats. 4-hour LC_{50}
Author(s), year:	[redacted]; 1982
Report/Doc. number:	A24752 / Hoechst Report No. 352/82
Guideline(s):	No, but similar to OECD 403
GLP:	Yes
Deviations:	No
Acceptability:	Yes

Material and Methods:
Groups of 6 rats/sex/dose were exposed nose-only to 0.151 or 0.511 mg/L fenoxaprop-ethyl (nominal concentrations). The test substance was supplied as a 5 % preparation in ethanol / polyglycol (1:1). The animals received the aerosol during a time period of 4 hours. The actual concentrations measured in the inhalation chamber were 0.140 mg/L for the lower dose group (nominal 0.151 mg/L) and 0.475 mg/L for the higher dose group (nominal 0.511 mg/L). In the lower dose group, the percentage of particles was 24.8 % at a size of 0.34 – 0.49 µm, 40.5 % at 0.5 – 1.49 µm, 15.8 % at 1.5 – 2.01 µm, with the remaining particles being larger than 2.02 µm of size. In the higher dose group, the percentage of particles was 21.0 % at a size of 0.34 – 0.49 µm, 31.0 % at 0.5 – 1.49 µm, 15.5 % at 1.5 – 2.01 µm, with the remaining particles being larger than 2.02 µm of size. Following inhalation the animals were observed for further 14 days and, with the exception of weekends, weighed daily and their behaviour noted. At the end of the observation period the animals were examined macroscopically.

Test material:	fenoxaprop-ethyl, batch Hoe 33171 0H AT 204
Purity:	93 %
Test animals:	Wistar rat, SPF, [redacted] Age not stated, mean bw of 185.6 ± 4.0 g (♂) and 187.2 ± 2.2 g (♀).
Number of animals:	6 rats per sex per dose

Findings:
Clinical signs and mortality: One male rat from the highest dose group died between day 1 and 2 following treatment. Due to cannibalism autopsy could not be carried out. Clinical symptoms were observed during the first 24 hours after inhalation and occurred dose-dependently in both treatment groups: narrowed lid openings, irregular and jerky respiration, spasmodic respiration, sneezing, balance disturbances, ataxia, lateral positioning, weakened reflexes or no reflexes. As these symptoms also occurred in control studies with carrier substance only, they were not considered to be drug related. Body weight was impaired one day after exposure but recovered during the follow-up period.

Pathology: The animals killed at termination showed no macroscopically visible changes. A single male which died in the highest dose group could not be examined due to cannibalism.

Conclusion:
The acute inhalative LC50 of Fenoxaprop-ethyl (vehicle ethanol / polyglycol 1:1) is higher than 0.475 mg/L (actual concentration) in male and female rats after 4 hours of nose-only exposure. One death occurred at the highest dose tested (0.475 mg/L) and no assumptions can be made for concentrations above especially for the range up to the limit concentration of 5 mg/L. Furthermore it cannot be ruled out that the clinical symptoms were exclusively caused by the vehicle alone and not at least partially by the test substance.

B.6.2.11. Skin irritation with Fenoxaprop-ethyl

Reference:	Hoe 33171 0H AT203 (active ingredient techn.) Irritance to the rabbit skin and eye mucosa
Author(s), year:	[redacted]; 1979d
Report/Doc. number:	A24688 / Report No 406/79
Guideline(s):	EPA Guideline 81-5 (1978)
Deviations:	24 hour exposure period, occlusive dressing
Deviations to OECD Guideline 404 (2015):	- Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. - Age of animals not stated
GLP:	Yes
Acceptability:	Yes

Material and Methods:
6 rabbits were treated with 500 mg Fenoxaprop-ethyl moistened with 0.3 ml PEG 400 on a 2.5 x 2.5 cm cellulose patch covered with an impervious PVC-foil. The application site (flank) was clipped free of hair, with one half of the area being additionally scarified. The exposure period was 24 hours and the first evaluation immediately took place after removal of the patches. Further evaluations were carried out 48 and 72 hours after application. The irritating effects were classified according to EPA (Federal Register 38, 1973).

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT203
Purity: 97 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: Albino-Himalayan Rabbit, [redacted],
Age not stated, bw of 1.5 to 2.5 kg. Sex not reported
Number of animals: 6 rabbits

Findings:
The irritating effects of Fenoxaprop-ethyl are shown in the following table:

Table 6.2.11-1 Irritating effects of Fenoxaprop-ethyl on the intact and the scarified skin of rabbits

Time after removal of patch (hours)		24						48						72						Mean value
Animal no		1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	
Intact skin	Erythema	1	3	3	2	2	1	1	1	2	1	1	2	0	0	0	0	0	1	1.2
	Oedema	2	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0.5
Scarified skin	Erythema	1	3	2	2	2	2	1	1	1	1	1	2	0	0	0	0	0	1	1.1
	Oedema	2	2	2	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0.6

Conclusion:
After an exposure period of 24 hours under occlusive conditions, very slight to moderate erythema (grades 1 to 3) and very slight to slight oedema (grades 1 and 2) had been observed immediately after exposure. These effects do not lead to the classification of Fenoxaprop-ethyl as irritating to the skin.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-ethyl regarding dermal irritation is not required.

B.6.2.12. Eye irritation study with Fenoxaprop-ethyl

Reference:	Hoe 33171 0H AT203. Irritance to the rabbit skin and eye mucosa.
Author(s), year:	[redacted]; 1979d
Report/Doc. number:	A24688 / Report No 406/79
Guideline(s):	EPA Guideline 81-5 (1978)
GLP:	Yes
Deviations to OECD Guideline 405 (2012):	- Individual and mean body weights of animals at beginning and at end of test not stated. Only range was given. - Age of animals not stated.
Acceptability:	Yes

Material and Methods:
9 rabbits weighing were treated with 100 mg Fenoxaprop-ethyl which was applied to the conjunctival sac of the left eye. The right eye served as control. 1 minute after application the eyes of 3 animals were flushed with sodium chloride solution. The eyes of the remaining 6 animals were not washed out. The irritant effects were evaluated 1, 7, 24, 48 and 72 hours after treatment. At 48 and 72 hours the eyes were also examined after the addition of one drop of 0.01% fluorescein-sodium solution. The classification of effects was performed according to FDA Guidelines (1975).

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT 203
Purity: 97.0 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: Albino-Himalayan Rabbit, [redacted]
Age not stated, bodyweight of 1.5 to 2.5 kg. Sex not reported
Number of animals: 9 rabbits

Findings:
The exact scores are given in Table 6.2.12-1 (for simplicity, readings after 1 hour and 7 hours were left out).
In the eyes not washed out, all animals developed redness of the conjunctivae (grades 1 and 2) up to 24 hours after treatment. At 48 and 72 hours, only slight redness (grade 1) was still observed in some of the rabbits. Swelling of the conjunctivae (grades 1 and 2) was noted up to 7 hours in all animals. At 24 hours only 3 rabbits showed slight swelling which disappeared afterwards. No effects on the iris were seen at any point of time. Opacity of the cornea was noticed in some of the rabbits and lasted up to 72 hours in one rabbit. In the eyes washed out after 1 minute, similar results were observed.

Table 6.2.12-1 Eye irritation scores, Hoe 33171 0H AT203 Irritance to the rabbit skin and eye mucosa

Time after removal of patch (hours)	**24**									**48**									**72**									**Mean score**
Animal no	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	
Discharge	1	0	0	1	1	1	1	2	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0.44
Conjunctivae																												
- **Chemosis**	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.22
- **Redness**	2	2	2	2	2	2	2	2	2	0	0	1	1	0	1	1	2	1	0	0	1	1	0	0	1	1	0	1.07
Iritis	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	0	0	0
Cornea																												
- **Degree of opacity**	1	0	0	1	1	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0.26
- **Area involved**	1	0	0	1	1	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0.26

Conclusion:
Slightly irritating effects were observed on the eyes of rabbits. These effects do not lead to the classification of fenoxaprop-ethyl as irritating to the eyes.
According to Annex VI of Regulation (EC) 1272/2008, ATP01 (Regulation (EC) 790/2009), classification of fenoxaprop-ethyl regarding eye irritation is not required.

B.6.2.13. Skin sensitization with Fenoxaprop-ethyl

Reference:	Testing for sensitizing properties of Hoe 33171 0H AS201 in the guinea pig according to Buehler
Author(s), year:	[redacted]; 1982
Report/Doc. number:	A30110 / Report No 573/82
Guideline(s):	Corresponding to OECD 406 (1987)
GLP:	Yes
Deviations to OECD Guideline 406 (1992):	- Age of animals not stated. - Individual body weight at start and end of study not reported.
Acceptability:	Supplementary due to small number of animals.

Material and Methods:
Female Pirbright-White guinea pigs were given Fenoxaprop-ethyl in the Buehler test. 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.

Test material:	fenoxaprop-P-ethyl, batch Hoe 33171 0H AS201
Purity:	94.0 %; not included in the study report, but presented by the notifier in a separate report (A36866)
Test animals:	Female Pirbright-White guinea pigs, DHPK(SPCLac), [redacted] Age not stated, mean body weight of 288 g (range 247-320 g).
Number of animals:	10 for treatment group + 5 for control group in the main test 1 + 5 animals for first and second preliminary test

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 were used in this study, which limits the validity of this study.

B.6.3. SHORT-TERM TOXICITY

All required data were evaluated during the first Annex I review of fenoxaprop-p and were presented in the fenoxaprop monograph (Vol.3, Annex B, Section B6, Point B.6.3, August 2005) and addenda to the monograph (January 2007). The 90-day (13-week) rat and dog studies are required according to data requirements under Regulation (EC) No. 1107/2009. These studies were considered in general compliance with test guidelines and fit for purpose. Percentages to the values of untreated group were calculated and differences were added to the result tables.

4- and 13-week shorter term toxicity studies with fenoxaprop-P-ethyl were conducted in rats, mice and dogs. However, 4-week studies were regarded as supplementary information only.

In addition to the studies already submitted and reviewed, a 21-day dermal toxicity study in the rat was conducted (2014) for data registration requirements outside the E.U. Fenoxaprop-P-ethyl is classified as STOT RE 2 H373 (kidneys).

Summary of short-term toxicity with fenoxaprop-P-ethyl

Rats: Fenoxaprop-P-ethyl induced comparable effects in the 28 day dose finding study and the 13 week feeding studies in Wistar rats. Reductions of body weights were found at doses of 640 ppm and above and were more distinct in males than in females. Severe toxicity was observed in all animals receiving 5,210 ppm in the 28 day study leading to an interim kill in extremis. Slight, but not biologically significant effects on haematology were observed in both sexes. In clinical chemistry, the most striking effects were observed on lipid metabolism and liver enzymes at 80 ppm and above in both sexes. Total cholesterol, HDL-cholesterol and HDL-phospholipid levels were decreased while triglyceride levels were increased. Regarding liver enzymes, ALP and LDH levels were increased. Additional investigations on mixed function oxidase, catalase and glutathione in liver revealed a distinct increase at 1,280 ppm. Slight effects on plasma electrolytes were noted in both sexes, with decreased calcium and increased sodium levels at 80 ppm and above. All these effects were reversible after a 4 week recovery period. Slight to moderate ketonuria and urobilinogenuria were noted for males at mid and high doses. Also bilirubinuria were observed at the high dose in males. However, both findings were within the normal range of biological variation. 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. In the 13 week study, 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.

The oral short-term toxicity NOAEL of Fenoxaprop-P-ethyl in rats 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).

Other routes: Similar effects (organ weight changes, lipid metabolism) were observed in the repeated subchronic inhalation study as well as the subchronic dermal study, where additionally dry/chapped skin and/or fine/coarse scales were noted. Inhalative and dermal short-term toxicity NOAELs were determined as 0.015 mg/L and 20 mg/kg bw/d, respectively.

Mice: Fenoxaprop-P-ethyl was tested in a 28 day dose finding study and a 13 week feeding study in NMRI mice. 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 and only marginal effects were noticed in the highest dose group (640 ppm) of the 13 week study. Clinical chemistry evaluations in both studies revealed marked effects on lipid metabolism and liver enzymes at concentrations of 320 ppm and above. 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 in males and females at 640 ppm and above. Additional investigations on mixed function oxidase, catalase and glutathione in liver indicated induction of peroxisome proliferation through markedly increased catalase starting from 80 ppm in males and from 320 ppm and onwards in females. 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 and above. In the 13 week study, 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 both studies. 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 80 ppm.

The oral short-term toxicity NOAEL of Fenoxaprop-P-ethyl in mice 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).

Dogs: Two studies were conducted in Beagle dogs. 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. 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 at 2000 ppm. Also, total protein levels were increased in this dose group. Relative liver weight was increased in females at 2000 ppm. However, no statistically significant changes were noted at organ weight analysis. No treatment-related effects were seen at macroscopical and microscopical examination.

The oral short-term toxicity NOAEL of Fenoxaprop-P-ethyl in dogs is considered to be 400 ppm (equivalent to 15.6 mg/kg bw/d in males and 16.2 mg/kg bw/d in females).

A summary of all submitted data is presented in the following table.

Summary of short-term toxicity studies, fenoxaprop-P-ethyl

Study, reference	Dose levels	NOAEL	Main effects/target organs
Oral 28-day studies			
28 days oral Wistar rat [redacted]., *1987a*, A36568, CA 5.3.1/01 Addendum [redacted] *1990*, A42820, CA 5.3.1/02 Supplement [redacted], *1987b* A36955, CA 5.8.2/01	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) Supplementary information only	- haematology, clinical chemistry and urinalysis findings - increase of catalase levels at 1,280 ppm
28 days oral NMRI mice [redacted] *1987b* A36557, CA 5.3.1/04 Supplements [redacted] *H., 1987c* A36958, CA 5.8.2/03 [redacted] *1987d* A36960, CA 5.8.2/04	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)	80 ppm (♂: 14 mg/kg bw/d; ♀: 16 mg/kg bw/d) Supplementary information only	- clinical chemistry findings - increased organ weights (liver, kidney) - histopathological findings (tubular injury, hepatocellular hypertrophy, single cell necrosis, mitotic hepatocytes) - increased catalase in ♂ at 80 ppm and in ♀ at 320 ppm onwards - at 640 ppm: induction of N-demethylase in ♀; increased CP450 levels observed in ♂; increase in catalase activity; decreased testis weight
28 days oral Beagle dog [redacted] *1987a*, A36558, CA 5.3.1/07 Supplement [redacted] *1987c*, A36597, CA 5.8.2/05	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).
Oral 90-day studies			

Study, reference	Dose levels	NOAEL	Main effects/target organs
13 weeks oral Wistar rat [redacted].., *1987* A36566, CA 5.3.2/01 [redacted] *1987* A36954, CA 5.8.2/02	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)	- haematology, clinical chemistry and urinalysis findings - increased organ weights (liver, kidney) - macroscopically enlarged kidneys - at 640 ppm: changes in glutathione levels, slight increase in CP450; in ♂: increased activity of catalase
13 weeks oral NMRI mouse [redacted] *1987a* A36567, CA 5.3.2/05	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 organ weights (liver) - histopathological findings (tubular injury)
13 weeks oral Beagle dog [redacted].., *1987b*, A36617, CA 5.3.2/07 Supplement [redacted]., *1987d*, A36959, CA 5.8.2/06	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 - N-demethylase decreased in ♂ at 2,000 ppm
Other routes			
28 day inhalation Wistar rat [redacted] *1989* A40799, CA 5.3.3/01	0, 0.015, 0.07 and 0.3 mg/L air	0.015 mg/L	- haematology and clinical chemistry findings - increased organ weights (liver)
21 day dermal application Wistar rat [redacted] *1988* A40800, CA 5.3.3/02	0, 10, 20, 100 and 500 mg/kg bw/d	20 mg/kg bw/d	- dry/chapped skin, fine/coarse scales - haematology and clinical chemistry findings - increased organ weights (liver, kidney)

Summary of short-term toxicity studies with fenoxaprop-ethyl

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. In addition, a study investigating microscopic (via electron microscopy) changes in the liver from the 13 week mouse study of fenoxaprop-ethyl was also undertaken. A 1-year oral administration toxicity study in the dog was also undertaken.

Rats: Fenoxaprop-ethyl was tested in a 32-day and a 3-month-feeding study in Wistar rats. Excessive toxicity was found at a dose level of 5000 ppm in the 32-day study leading to a premature sacrifice of these animals. A reduction in body weight gain was observed at a dose level of 1250 ppm in the 32-day study but not at the highest dose (320 ppm) in the 3-month-study. Slight haematological effects were only observed in the 3-month study at 320 ppm (decreased haemoglobin and erythrocyte levels). Changes in lipid status were observed in both studies at doses of 20 ppm and above (decreased cholesterol and total lipids). Signs of hepatotoxicity were demonstrated by increased ALP levels at 320 ppm and above. In both studies 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.

The oral short-term toxicity NOAEL of Fenoxaprop-ethyl in rats 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).

Mice: A 32-day and a 30-day feeding study in NMRI mice were conducted because no NOAEL could be defined in the 32-day study as effects were already observed at the lowest dose level of 80 ppm. Furthermore, a 3-month feeding study in NMRI mice was done to establish a MTD for a chronic toxicity study and to further investigate the mechanistic action of Fenoxaprop-ethyl in hepatocytes. Again, no NOAEL could be established as effects were evident at the lowest dose level of 320 ppm in this 3-month study. 5000ppm Fenoxaprop-ethyl led to excessive toxicity and subsequently to an interim sacrifice of animals in the 32-day feeding study. An increased body weight was observed after 3 months at 640 ppm and higher, which was discussed to be a result of markedly increased liver weight in these dose groups. Haematological effects were observed at doses of 320 ppm and/or above including a decrease in haemoglobin, erythrocytes and thrombocytes, and an increase in MCV, reticulocytes and leucocytes. Clinical chemistry revealed effects on the lipid status (increased total lipids and cholesterol at 20 and/or 80 ppm; 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 1280 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 20 ppm and increased markedly with dose. Histopathological examination of the livers revealed enlargement of hepatocytes starting at a dose level of 20 ppm. At higher dose levels (320 ppm and above), also single cell necrosis and an increased rate of mitosis were observed. Liver peroxisome proliferation was confirmed by electron microscopy and special biochemical investigations in the 3-month study. Kidneys weights were increased at 315 ppm and above which was accompanied by tubular necrosis. 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.

The oral short-term toxicity NOAEL of Fenoxaprop-ethyl in mice 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).

Dogs: Three feeding studies were conducted in Beagle dogs: a 30-day dose finding study (supplementary information only due to limited study design, 2 dogs/sex/group), a 3-month study and a 1-year study. The dogs of the highest dose group (2,000 ppm) in the 30-day dose finding study 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, haemorrhages 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 in any of the studies. No substance related changes were observed in haematological, clinical chemistry and urinalysis parameters and at liver and renal function tests. In the 30-day dose finding study, adrenals weights seemed to be increased slightly at 400 ppm and distinctly at 2000 ppm. In the 3-month study, relative pituitary weights were increased statistically significant in males at 400 ppm. Biologically significant but not dose-related changes were observed most profoundly in absolute and relative liver weight, absolute kidney weight, absolute and relative ovary weights as well as relative thyroid weights in all dose groups in females, and absolute pituitary weights in males. Furthermore, chronic interstitial pyelonephritis was detected at histopathological investigation of males and females of the 80 and 400 ppm dose groups. In the 1-year study, dose-related but statistically not significant increases were observed starting from 3 ppm in relative prostate weight in males, absolute and relative uterus weight and absolute and relative ovaries weight in females. The applicant submitted a position paper with detailed reasoning and historical control data, which did not fulfil the criteria set out in Regulation (EC) No 283/2013 (summarized in B.6.3.6.1). However, due to high variability in organ weights and as no histopathological changes were observed these effects were considered not relevant.

The oral short-term toxicity NOAEL of Fenoxaprop-ethyl in dogs is considered to be 16 ppm (♂: 1.2 ♀: 1.0 mg/kg bw/d).

A summary of all submitted data is presented in the following table.

Summary of short-term toxicity studies, fenoxaprop-ethyl

Study, reference	Dose levels	NOAEL	Main effects/target organs
Oral 28-day studies			

Study, reference	Dose levels	NOAEL	Main effects/target organs
32 days oral Wistar rat [redacted]., *1980a* A26171, CA 5.3.1/03	0, 80, 315, 1250 and 5000 ppm / diet (values in mg/kg bw/d are not presented in the study report)	< 80 ppm (approximately ♂: 9.44 mg/kg bw/d ♀: 9.36 mg/kg bw/d)	- clinical chemistry findings (decreased cholesterol, total lipids, phosphorus (♂ only), uric acid, potassium; increased ALP - increased organ weights (kidney)
32 days oral NMRI mouse [redacted] *1980b* A26168, CA 5.3.1/05	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 (♂: 14.6 mg/kg bw/d; ♀: 14.9 mg/kg bw/d)	- increased organ weights (liver) - histopathological findings (liver)
30 days oral NMRI mouse [redacted] *1981* A26169, CA 5.3.1/06	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)
30 days oral Beagle dog [redacted] *1980* A25657, CA 5.3.1/08 Supplement [redacted] *1986* A32691, CA 5.3.1/09	0, 80, 400 and 2000 ppm / diet (values in mg/kg bw/d are not presented in the study report)	<u>Supplementary information only,</u> <u>dose finding study with two animals per group</u>	- excessive toxicity at 2000 ppm leading to premature sacrifice - haematology and clinical chemistry findings - increased organ weights (adrenals) - histopathology findings (various organs)
Oral 90-day studies			
3 months oral Wistar rat [redacted] *1981* A35788, CA 5.3.2/02 Addendum [redacted] *1986* A32697, CA 5.3.2/03 Addendum [redacted] 1986 A32985, CA 5.3.2/04	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 - increased organ weights (adrenals)
13 weeks oral NMRI mouse [redacted] *1993a* A50244, CA 5.3.2/06	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 (♂: 51.6 mg/kg bw/d; ♀: 54.4 mg/kg bw/d)	- 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)

Study, reference	Dose levels	NOAEL	Main effects/target organs
3 months oral Beagle dog [redacted] *1981a* A24131, CA 5.3.2/08 Supplement [redacted], *1986* A32690, CA 5.3.2/09	0, 16, 80 and 400 ppm / diet (equivalent to 0, 1.2, 5.4 and 28.2 mg/kg bw/d in males; 0, 1.0, 4.9 and 25.6 mg/kg bw/d in females)	16 ppm (♂: 1.2 ♀: 1.0 mg/kg bw/d)	at 400 ppm: Relative pituitary weights were increased statistically significantly in males, however not dose-related Biologically significant but not dose-related Females - absolute and relative liver weight - absolute kidney weight - absolute and relative ovary weights - relative thyroid weights in all dose groups Males: - absolute pituitary weights - histopathology findings (interstitial pyelonephritis)
Other studies			
1 year oral Beagle dog [redacted] *1984* A29692, CA 5.3.2/10	0, 3, 15 and 75 ppm / diet (equivalent to 0, 0.2, 1.0 and 5.0 mg/kg bw/d in males; 0, 0.2, 0.8 and 4.4 mg/kg bw/d in females)	> 75 ppm (♂: 5.0 ♀: 4.4 mg/kg bw/d)	dose-related but statistically not significant changes starting from 3 ppm: Males: slight ⇩ relative prostate weight Females: - ⇩ triglycerides - ⇧ total lipids (starting from mid dose:) - ⇧ abs. and relative uterus weight - ⇧ abs. and relative ovaries weight

B.6.3.1. Oral 28-day studies with Fenoxaprop-P-ethyl

B.6.3.1.1. Rat

Reference:	Hoe 046360 Technical (Code: HOE 046360 0H ZC96 0002). Repeated-dose oral toxicity: 28-day feeding study in rats
Author(s), year:	[redacted] 1987a
Report/Doc. number:	A36568 / RCC Project No. 060636
Guideline(s):	OECD 407 (1981)
Deviations to OECD 407 (2008):	According to current standards, limited organ weight analysis and very limited histopathology have been performed.
GLP:	Yes, but the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.
Acceptability:	Supplementary information.

Materials and Methods:
A group of 5 rats per sex 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. Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: Wistar rats, [redacted]
About 6 weeks old, 138-167 g (♂) and 130-145 g (♀).
Number of animals: 5 rats per sex

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. Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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. Urinalysis included 18-hour volume, specific gravity, colour, 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 6.3.1-1 Group food consumption and mean body weights, 28 day feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)											
	Males						Females					
	0	**20**	**80**	**320**	**1,280**	**5,210**[t]	**0**	**20**	**80**	**320**	**1,280**	**5,210**[t]
Food consumption (g/d)	22	22	22	20	17	4[t]	14	14	15	16	12	3[t]
Body weight on day 1 (g)	158	148 -6.3%	154 -2.6%	147 -7.0%	162 +2.5%	158[t]	136	137 +0.7%	139 +2.2%	139 +2.2%	140 +2.9%	138[t] +1.5%
Terminal body weight (g)	285	289 +1.4%	298 +4.6%	265 -7.1%	**220**** **-22.8%**	-[t]	180	183 +1.7%	186 +3.3%	181 +0.6%	**160*** **-11.1%**	-[t]
Bodyweight gain (g)	127	141 +11.0%	144 +13.4%	118 -7.1%	**58** **-54.3%**	-	44	46 +4.5%	47 +6.8%	42 -4.5%	**20** **-54.5%**	-

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

Haematology: Slightly prolonged thromboplastin times (TT) and partial thromboplastin times (PTT) were observed in males at 1,280 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 6.3.1-2 Relevant haematology findings after 28 days, 28 day feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1,280**	**0**	**20**	**80**	**320**	**1,280**
TT (s)	12.3	12.4 +0.8%	12.6 +2.4%	12.8 +4.1%	**13.6*** **+10.6%**	12.8	12.6 -1.6%	**12.2*** **-4.7%**	**12.0*** **-6.3%**	**11.5*** **-10.2%**
PTT (s)	22.5	22.6 +0.4%	23.4 +4.0%	25.3 +12.4%	**28.4*** **+26.2%**	18.5	20.7 +11.9%	20.4 +10.3%	21.3 +15.1%	17.9 -3.2%

* (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 1,280 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 1,280 ppm and in males at 1,280 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 1,280 ppm and for LAP in females at 1,280 ppm, which could be signs of liver toxicity at high doses. Male rats developed slightly decreased calcium levels (at 320 ppm and 1,280 ppm) and phosphorus levels (at 1,280 ppm). Slightly increased albumin levels were noticed in males at 320 and 1,280 ppm and females at 1,280 ppm. All other differences were considered to be incidental and of normal biological variation.

Table 6.3.1-3 Relevant clinical chemistry findings after 28 days, 28 day feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Total cholesterol (mmol/L)	2.02	1.77 -12.4%	1.78 -11.9%	1.39 -31.2%	**1.05*** **-48.0%**	1.78	1.57 -11.8%	1.83 +2.8%	1.54 -13.5%	1.90 +6.7%
HDL-cholesterol (mmol/L)	1.06	0.95 -10.4%	0.85 -19.8%	**0.53*** **-50.0%**	**0.27*** **-74.5%**	1.14	0.99 -13.2%	1.10 -3.5%	0.96 -15.8%	1.05 -7.9%
HDL-phospho-lipid (mmol/L)	1.01	0.96 -5.0%	**0.83*** **-17.8%**	**0.73*** **-27.7%**	**0.58*** **-42.6%**	1.13	1.03 -8.8%	1.07 -5.3%	1.01 -10.6%	1.25 +10.6%
Triglycerides (mmol/L)	0.31	0.32 +3.2%	0.33 +6.5%	0.40 +29.0%	**0.71*** **+129.0%**	0.17	0.16 -5.9%	0.19 +11.8%	**0.25*** **+47.1%**	**0.43*** **+152.9%**
ALP (ukat/L)	4.04	4.03	4.27 +5.7%	5.16 +27.7%	**6.54*** **+61.9%**	1.90	2.62 +37.9%	2.17 +14.2%	2.58 +35.8%	**3.83*** **+101.6%**
LAP (ukat/L)	23.65	23.54 -0.5%	25.16 +6.4%	26.84 +13.5%	27.10 +14.6%	21.65	23.78 +9.8%	22.99 +6.2%	24.62 +13.7%	**28.08*** **+29.7%**
Calcium (mmol/L)	2.57	2.55 -0.8%	2.53 -1.6%	**2.45*** **-4.7%**	**2.44*** **-5.1%**	2.51	2.50	2.55 +1.6%	2.50	2.45 -2.4%
Phosphorus (mmol/L)	2.21	2.12 -4.1%	2.23 +0.9%	2.17 -1.8%	**1.84*** **-16.7%**	1.52	1.71 +12.5%	**1.85*** **+21.7%**	1.57 +3.3%	1.49 -2.0%
Albumin (g/L)	28.8	29.6 +2.8%	29.6 +2.8%	**32.2*** **+11.8%**	**34.1*** **+18.4%**	33.0	32.9	32.7 -0.9%	32.2 -2.4%	**34.8*** **+5.5%**

* ($p < 0.05$); 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 haematuria 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) haematuria was not reported any more.

Table 6.3.1-4 Relevant urinalysis findings after 28 days, 28 day feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
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 +9.0%	72.2 -2.7%	66.3 -10.6%	**52.5*** **-29.2%**	41.1	43.4 +5.6%	43.9 +6.8%	39.4 -4.1%	35.6 -13.4%

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Creatinine Clearance (ml/min)	0.82	0.95 +15.9%	0.9 +9.8%	0.71 -13.4%	0.54 -34.1%	0.37	0.41 +10.8%	0.43 +16.2%	0.43 +16.2%	0.36 -2.7%
LDH (nkat/24h)	5.93	8.32 +40.3%	7.7 +29.8%	7.92 +33.6%	9.66 +62.9%	1.27	1.98 +55.9%	2.76 +117.3%	2.6 +104.7%	**4.08*** **+221.3%**
GGT (nkat/24h)	321.7	355 +10.4%	342.6 +6.5%	311.2 -3.3%	**107.1**** **-66.7%**	30.0	33.8 +12.7%	41 +36.7%	25.8 -14.0%	25.2 -16.0%
LAP (nkat/24h)	87.4	82.7 -5.4%	89.4 +2.3%	76.6 -12.4%	**29.4**** **-66.4%**	9.5	11.7 +23.2%	9.7 +2.1%	5.4 -43.2%	3.6 -62.1%
Potassium (mmol/24h)	1.34	1.49 +11.2%	1.42 +6%	1.18 -11.9%	**0.79*** **-41.0%**	0.66	0.69 +4.5%	0.83 +25.8%	0.6 -9.1%	0.64 -3.0%

* + (p< 0.05); significantly different from controls (* Dunnett-test, + 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 6.3.1-5 Relevant organ weight findings after 28 days, 28 day feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Liver weight										
absolute (g)	8.26	7.99 -3.3%	9.44 +14.3%	9.83 +19.0%	10.88 +31.7%	5.25	5.42 +3.2%	5.83 +11%	6.73 +28.2%	6.42 +22.3%
relative (% bw)	2.89	2.76 -4.5%	3.17 +9.7%	**3.72**** **+28.7%**	**4.93**** **+70.6%**	2.92	2.96 +1.4%	3.13 +7.2%	**3.74**** **+28.1%**	**4.01**** **+37.3%**
Kidney weight										
absolute (g)	1.86	1.83 -1.6%	1.97 +5.9%	1.94 +4.3%	1.72 -7.5%	*1.13*	*1.13*	1.23 +8.8%	1.28 +13.3%	1.21 +7.1%
relative (% bw)	0.66	0.63 -4.5%	0.66	0.73 +10.6%	0.78 +18.2%	0.63	0.62 -1.6%	0.66 +4.8%	**0.71*** **+12.7%**	**0.76**** **+20.6%**

* (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.

Analytical method: According to the analytical method described in attachment 3 of the report of Suter *et al.*., 1987 (Doc No. A36568) the LOQ was determined as 20 ppm (for details refer to Volume 3 CA B-5).

Conclusion:
Fenoxaprop-P-ethyl demonstrated excessive toxicity at 5,120 ppm so that animals had to be sacrificed in extremis on treatment day 9. There was a significantly decreased body weight at 1,280 ppm in both sexes. The target organs identified were the liver (metabolic changes, enzyme release, and 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.

Reference:	Hoe 046360 Technical. 28-day dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver
Author(s). year:	[redacted]; 1987(b)
Report/Doc. number:	A36955 / RCC Project No. 060636
Guideline(s):	Not applicable.
GLP:	Yes
Deviation:	The study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 28-day repeated dose study in Wistar rats (Suter P., Luetkemeier H., 1987(a); Doc No. A36568)

Material and Methods:
See study of Suter P. *et al.* (1987a) at the beginning of this section.

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 1,280 ppm. Due to an analytical error, no data were obtained for N-demethylase from 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 1,280 ppm, while GSSG levels were increased in females receiving 1280 ppm. A marked increase of catalase activity was measured in both sexes at 1,280 ppm.

Table 6.3.1-6 Hepatic enzyme determination after 28 days, 28 day feeding study in Wistar rats with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					**Females**				
	0	**20**	**80**	**320**	**1,280**	**0**	**20**	**80**	**320**	**1,280**
Cytochrome P-450 (nmol/g)	20.1	17.6 -12.4%	18.7 -7.0%	22.9 +13.9%	23.2 +15.4%	15.0	14.2 -5.3%	13.9 -7.3%	14.9 -0.7%	13.9 -7.3%
N-demethylase (nmol/min/g)	n.d.	n.d.	n.d.	n.d.	n.d.	125	134 +7.2%	157 +25.6%	**194*** **+55.2%**	**167*** **+33.6%**
Glutathione (µmol/g)										
-reduced (GSH)	3.28	3.44 +4.9%	3.99 +21.6%	**4.76*** **+45.1%**	**5.89*** **+79.6%**	3.77	4.03 +6.9%	3.81 +1.1%	4.72 +25.2%	4.60 +22.0%
-oxidized (GSSG)	0.98	1.05 +7.1%	0.92 -6.1%	0.80 -18.4%	1.15 +17.3%	0.74	0.78 +5.4%	0.79 +6.8%	0.80 +8.1%	**1.07*** **+44.6%**
-total (GSH+GSSG)	4.26	4.49 +5.4%	4.91 +15.3%	**5.55*** **+30.3%**	**7.04*** **+65.3%**	4.51	4.81 +6.7%	4.60 +2.0%	5.52 +22.4%	5.66 +25.5%
Catalase (k/g)	176	205 +16.5%	164 -6.8%	224 +27.3%	**318*** **+80.7%**	87	66 -24.1%	68 -21.8%	86 -1.1%	**197*** **+126.4%**

* ($p<0.05$); 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 GSH. Determination of catalase, an enzymatic marker of peroxisome proliferation, showed a distinct increase at a dose level of 1,280 ppm.

B.6.3.1.2. Mouse

Reference:	Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in mice
Author(s), year:	[redacted]; 1987b
Report/Doc. number:	A36557 / RCC Project No. 060647
Guideline(s):	OECD 407 (1981)
Deviations to OECD 407 (2008):	Limited organ weight analysis and very limited histopathology. No haematology and urinalysis have been performed.
GLP:	Yes, the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.
Acceptability:	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 mice per sex received a diet containing 0, 20, 80, 320 or 1,280 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. Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: NMRI mice, [redacted]
About 6 weeks old, 25-30 g (♂) and 20-25 g (♀).
Number of animals: 5 mice per sex

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. Haematology and urinalysis 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 1,280 ppm.

Body weight: There was a trend towards higher body weight at 1,280 ppm. However, this was statistically significant only 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 6.3.1-7 Group food consumption and mean body weight, 28 day feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	**20**	**80**	**320**	**1,280**	**0**	**20**	**80**	**320**	**1,280**
Food consumption (g/d)	5.8	5.9 +1.7%	6.4 +10.3%	6.6 +13.8%	7.3 +25.9%	5.7	5.4 -5.3%	5.5 -3.5%	5.3 -7.0%	6.2 +8.8%
Body weight on day 1 (g)	27	27	28 +3.7%	28 +3.7%	27	22	21 -4.5%	23 +4.5%	23 +4.5%	21 -4.5%
Terminal body weight (g)	33.5	33.6	35.1 +4.8%	35.5 +6.0%	37.2 +11%	24.6	**22.2*** **-9.8%**	26.3 +6.9%	24.5	**28.2**** **+14.6%**
Bodyweight gain (g)	6.5	6.6 +1.5%	7.1 +9.2%	7.5 +15.4%	10.2 56.9%	2.6	1.2 -53.8%	3.3 +26.9%	1.5 -42.3%	7.2 +176.9%

* ($p < 0.05$); ** ($p < 0.01$); 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 1,280 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 1,280 ppm and in total protein for males at 1280 ppm.

Table 6.3.1-8 Relevant clinical chemistry findings after 28 days, 28 day feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Total cholesterol (mmol/L)	4.30	4.84 +12.6%	5.2 +20.9%	4.41 +2.6%	3.39 -21.2%	3.72	3.73	3.88 +4.3%	**5.29*** **+42.2%**	3.07 -17.5%
Phospholipids (mmol/L)	3.88	3.97 +2.3%	4.18 +7.7%	3.42 -11.9%	2.92 -24.7%	2.78	2.87 +3.2%	2.99 +7.6%	**3.56*** **+28.1%**	2.44 -12.2%
ASAT (ukat/L)	1.10	1.14 +3.6%	1.47 +33.6%	1.15 +4.5%	**5.02*** **+356.4%**	1.54	1.66 +7.8%	1.25 -18.8%	1.38 -10.4%	**2.88*** **+87%**
ALAT (ukat/L)	0.78	0.8 +2.6%	0.76 -2.6%	0.92 +17.9%	**8.56*** **+997.4%**	0.95	0.71 -25.3%	0.75 -21.1%	0.86 -9.5%	**4.71*** **+395.8%**
ALP (ukat/L)	3.59	3.09 -13.9%	3.31 -7.8%	4.48 +24.8%	**19.80*** **+451.5%**	5.30	5.03 -5.1%	4.55 -14.2%	4.76 -10.2%	**8.73*** **+64.7%**
Sodium (mmol/L)	139.3	150.2* +7.8%	149.3* +7.2%	151.8* +9.0%	**153.5*** **+10.2%**	145.6	145.7	149.1 +2.4%	150 +3.0%	**153.4*** **+5.4%**
Albumin (g/L)	26.6	27.9 +4.9%	28.9 +8.6%	27.5 +3.4%	**35.3*** **+32.7%**	29.7	30.1 +1.3%	30.3 +2.0%	31.2 +5.1%	**34.7*** **+16.8%**
Protein (g/L)	54.6	57.9 +6.0%	61.2 +12.1%	56.5 +3.5%	**68.2*** **+24.9%**	60.5	61.8 +2.1%	62.2 +2.8%	63.3 +4.6%	65.3 +7.9%

* (p< 0.05); ** (p< 0.01); 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 1,280 ppm and relative kidney weights at 1,280 ppm. In males, only absolute kidney weights were increased at 1,280 ppm. Furthermore, a decrease in relative testes weight was noted at 1,280 ppm.

Table 6.3.1-9 Relevant organ weight findings after 28 days, 28 day feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Liver weight										
absolute (g)	1.48	1.52 +2.7%	1.73 +16.9%	**2.74**** **+85.1%**	**5.40**** **+264.9%**	1.19	1.05 -11.8%	1.41 +18.5%	1.59 +33.6%	**3.73**** **+213.4%**
relative (% bw)	4.44	4.55	4.92	**7.71****	**14.51****	4.84	4.73	5.34	**6.49****	**13.15****
Kidney weight										
absolute (g)	0.560	0.553 -1.3%	0.528 -5.7%	0.605 +8.0%	**0.665**** **+18.8%**	0.347	0.339 -2.3%	**0.396*** **+14.1%**	0.37 +6.6%	**0.469**** **+35.2%**
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 +2.1%	0.236 -1.7%	0.204 -15.0%	-	-	-	-	-
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 1,280 ppm. Furthermore, single cell necrosis and increased mitotic activity in the liver were observed

in some of the animals receiving 320 and 1,280 ppm. Treatment-related minimal tubular injury was noted in the kidneys of 1/5 males and 4/5 females receiving 320 ppm. 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 1,280 ppm group.

Table 6.3.1-10 Relevant histopathological findings after 28 days, 28 day feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)									
	Males					Females				
	0	20	80	320	1,280	0	20	80	320	1,280
Liver										
- hepatocellular hypertrophy	0/5	0/5	0/5	5/5	5/5	0/5	0/5	0/5	0/4	5/5
- single cell necrosis	0/5	0/5	0/5	2/5	5/5	0/5	0/5	0/5	0/4	2/5
- mitotic hepatocytes	0/5	0/5	0/5	1/5	3/5	0/5	0/5	0/5	0/4	2/5
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.

Reference:	Hoe 046360 Technical. 28-day dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver
Author(s). year:	[redacted]; 1987(c)
Report/Doc. number:	A36958 / RCC Project No. 060647
Guideline(s):	Not applicable.
GLP:	No information on GLP is presented in the study report.
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 28-day repeated dose study in NMRI mice (Suter P. *et al.*, 1987(b); Doc No. A36557)

Material and Methods:
See study of Suter P. *et al.* (1987b) at the beginning of this section.

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 6.3.1-11 Hepatic enzyme determination after 28 days, 28 day feeding study in NMRI mice with fenoxaprop-P-ethyl

	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
Cytochrome P-450 (nmol/g)	25.8	**16.5*** **-36.0%**	22.3 -13.6%	23.1 -10.5%	**17.0*** **-34.1%**	20.2	17.4 -13.9%	16.8 -16.8%	19.2 -5.0%	18.4 -8.9%
N-demethylase (nmol/min/g)	174	164 -5.7%	174	147 -15.5%	118 -32.2%	n.d.	162	142	168	n.d.
Glutathione (µmol/g)										
-reduced (GSH)	7.65	7.29 -4.7%	7.11 -7.1%	7.87 +2.9%	**9.71*** **+26.9%**	7.69	**5.89*** **-23.4%**	6.68 -13.1%	**6.29*** **-18.2%**	8.98 +16.8%
-oxidized (GSSG)	1.65	1.60 -3.0%	1.59 -3.6%	1.34 -18.8%	1.62 -1.8%	1.56	1.24 -20.5%	1.40 -10.3%	1.29 -17.3%	**1.17*** **-25.0%**
-total (GSH+GSSG)	9.29	8.89 -4.3%	8.70 -6.4%	9.21 -0.9%	**11.33*** **+22.0%**	9.24	**7.13*** **-22.8%**	8.08 -12.6%	**7.59*** **-17.9%**	10.16 +10.0%
Catalase (k/g)	125	161 +28.8%	**192*** **+53.6%**	**353*** **+182.4%**	**367*** **+193.6%**	119	124 +4.2%	126 +5.9%	**256*** **+115.1%**	**365*** **+206.7%**

* ($p<0.05$); 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.

B.6.3.1.3. Dog

Reference:	Hoe 046360 Technical. Repeated-dose oral toxicity: 28-day feeding study in dogs
Author(s), year:	[redacted]; 1987a
Report/Doc. number:	A36558 / RCC Project No. 060658
Guideline(s):	-
Deviations to OECD 407 (2008):	Only one animal per dose group was used. Organ weights for spleen and heart not analysed. Histopathology not performed for eye, spinal cord, ovaries, vagina and most accessory sex organs, skeletal muscle, bone as well as bone marrow.
GLP:	Yes, the study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.
Acceptability:	The 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 as supplementary information only.

Material and Methods:
One male and one female Beagle dogs 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 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.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: Beagle dog, [redacted]
4-5 months old, 4.4-7.2 kg (♂) and 4.8-5.4 kg (♀).
Number of animals: 1 per dose group

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 pre-test 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.

Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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, colour, 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, oesophagus, 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 diarrhoea were spontaneously observed in animals receiving 0, 80 and 320 ppm during pre-test 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 1,280 ppm during the first two weeks of treatment. However the females allocated to treatment already showed a decreased food intake during the pre-test 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 1,280 ppm when compared to control and 320 ppm animals.

Table 6.3.1-12 Body weights of single animals, 28 days feeding study in dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	320	1,280	0	80	320	1,280
Initial body weight (g)	7,924	6,755 -14.8%	6,825 -13.9%	5,115 -35.4%	6,118	5,337 -12.8%	5,668 -7.4%	5,541 -9.4%
Body weight day 28 (g)	8,388	7,454 -11.1%	7,558 -9.9%	6,052 -27.8%	7,213	6,114 -15.2%	6,695 -7.2%	6,276 -13.0%
Body weight gain	464	699 +50.6%	733 +58.0%	937 +101.9%	1,095	777 -29.0%	1,027 -6.2%	735 -32.9%

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

Haematology, clinical chemistry, and 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 6.3.1-13 Organ weights of single animals after 28 days, 28 days feeding study in dogs with fenoxaprop-P-ethyl

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

	Dose group level (ppm)							
	Males				Females			
	0	80	320	1280	0	80	320	1280
Liver weight								
absolute (g)	305.2	276.8 -9.3%	264.0 -13.5%	253.7 -16.9%	222.7	212.8 -4.4%	241.0 +8.2%	214.2 -3.8%
relative (% bw)	3.8	4.0 +5.3%	3.7 -2.6%	4.7 +23.7%	3.4	3.9 +14.7%	4.1 +20.6%	3.8 +11.8%
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 -17.9%	43.52 -13.4%	34.19 -32.0%	33.35	31.78 -4.7%	33.16 -0.6%	30.09 -9.8%
relative (% bw)	0.62	0.59 -4.8%	0.61 -1.6%	0.63 +1.6%	0.50	0.58 +16.0%	0.56 +12.0%	0.53 +6.0%
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.

Reference:	Hoe 046360 Technical. 28-day dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver
Author(s). year:	[redacted] 1987(c)
Report/Doc. number:	A36957 / RCC Project No. 060658
Guideline(s):	Not applicable.
GLP:	Yes.
Deviation:	The study protocol and the experimental phase of the study were not inspected by the Quality Assurance Unit.
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 28-day repeated dose study in Beagle dogs [redacted] 1987(a); Doc No. A36558)

Material and Methods:
See study of Sachsse K. *et al.* (1987a) at the beginning of this section.

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 6.3.1-14 Hepatic enzyme determination after 28 days, 28 day feeding study in Beagle dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	320	1,280	0	80	320	1,280
Cytochrome P-450 (nmol/g)	7.2	10.8 +50.0%	9.2 +27.8%	8.8 +22.2%	10.0	10.4 +4.0%	11.6 +16.0%	10.4 +4.0%
N-demethylase (nmol/min/g)	n.d.	n.d.	n.d.	n.d.	129	107 -17.1%	125 -3.1%	111 -14.0%
Glutathione (µmol/g)								
-reduced (GSH)	4.16	7.15 +71.9%	3.87 -7.0%	5.17 +24.3%	5.74	6.17 +7.5%	6.36 +10.8%	6.54 +13.9%
-oxidized (GSSG)	0.36	0.48 +33.3%	0.30 -16.7%	0.44 +22.2%	0.55	0.55	0.45 -18.2%	0.40 -27.3%
-total (GSH+GSSG)	4.52	7.63 +68.8%	4.17 -7.7%	5.61 +24.1%	6.29	6.72 +6.8%	6.81 +8.3%	6.94 +10.3%

n.d. not determined

Conclusion:
No change in enzyme values could be detected in this study with single animals/sex/dose group.

B.6.3.2. Oral 90-day studies with Fenoxaprop-P-ethyl

B.6.3.2.1. Rat

Reference:	Hoe 046360 Technical (Hoe 046360 0H ZC96 0002) Subchronic oral toxicity: 13-week feeding study in rats.
Author(s), year:	[redacted]; 1987
Report/Doc. number:	A36566 / RCC Project No. 060671
Guideline(s):	OECD Guideline 408 (1981), EPA Guideline 82-1 (1982)
Deviations to OECD 408 (1998):	Haematological analysis did not include measurement for BUN. Limited pathology and organ weight analysis performed. No functional observations conducted.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 10 rats per sex 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 per sex in the control and the 80 ppm and 640 ppm treatment groups over a 4-week recovery period. Diets were prepared twice monthly, and stability and homogeneity of the test substance in the food were confirmed by analysis.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: Wistar rat, [redacted]
6 weeks old, 143-172 kg (♂) and 128-153 kg (♀).
Number of animals: 10 per sex per dose group,
excluding 10 additional per sex for control, 80 and 640 ppm dose groups

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.
Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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, colour, 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), oesophagus, 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 anaesthesia (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 6.3.2-1 Group food consumption and mean bodyweight after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	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 +3.1%	20.3 -9.0%	17.5	17.0 -2.9%	16.8 -4.0%	15.9 -9.1%
17 weeks	24.3	-	25.0 +2.9%	22.9 -5.8%	18.3	-	16.8 -8.2%	17.9 -2.2%
Body weight on day 1 (g)	155	154	155	154	140	140	142	140
Terminal body weight (g)								
13 weeks	367.1	375.0 +2.2%	384.8 +4.8%	**310.2**** **-15.5%**	225.8	230.5 +2.1%	224.7 -0.5%	206.0 -8.8%
17 weeks	387.2	-	411.1 +6.2%	**332.6*** **-14.1%**	236.2	-	242.6 +2.7%	230.3 -2.5%
Bodyweight gain (g)								
13 weeks	212.1	221.0 +4.2%	229.8 +8.3%	**156.2** **-26.4%**	85.8	90.5 +5.5%	82.7 -3.6%	66.0 -23.1%
17 weeks	232.2	-	256.1 +10.3%	**178.6** **-23.1%**	96.2	-	100.6 +4.6%	90.3 -6.1%

* ($p < 0.05$); ** ($p < 0.01$); 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.

Haematology: A marginal decrease in the haemoglobin concentration, haematocrit value and mean corpuscular volume (MCV), and a marginal increase in the mean corpuscular haemoglobin concentration (MCHC) 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 (TT) and partial thromboplastin time (PTT) 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 haemoglobin concentration and haematocrit value remained slightly decreased. Other statistical differences were considered to be incidental and of normal biological variation.

Table 6.3.2-2 Relevant haematology findings after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Haemoglobin (mmol/L)								
13 weeks	10.0	9.8 -2.0%	9.9 -1.0%	**9.7*** **-3.0%**	9.8	9.8	9.8	9.8
17 weeks	10.1	-	10.0 -1.0%	**9.6*** **-5.0%**	10.0	-	10.1 +1.0%	9.8 -2.0%
Haematocrit (l/L)								
13 weeks	0.43	0.42	**0.42*** -2.3%	**0.41*** **-4.7%**	0.42	0.42	0.42	0.42
17 weeks	0.43	-	0.43	**0.41*** **-4.7%**	0.43	-	0.43	0.42 -2.3%

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
MCV (fL)								
13 weeks	45.0	44.8	45.4 +0.9%	**43.8*** **-2.7%**	47.8	47.3 -1.0%	48.3 -1.0%	46.8 -2.1%
17 weeks	45.2	-	45.7 +1.1%	44.6 -1.3%	48.0	-	**49.2*** **+2.5%**	48.6 +1.3%
MCHC (mmol/L)								
13 weeks	23.2	23.4 +0.9%	**23.6*** **+1.7%**	**23.7*** **+2.2%**	23.2	23.3	23.2	**23.7*** **+2.2%**
17 weeks	23.6	-	23.5	23.3 -1.3%	23.6	-	23.5	23.5
TT (sec)								
13 weeks	13.5	13.4	13.5	**14.0*** **+3.7%**	13.6	**13.3*** **-2.2%**	13.4	**12.8*** **-5.9%**
17 weeks	13.2	-	13.1 -0.8%	**12.8*** **-3.0%**	13.1	-	**12.7*** **-3.1%**	12.9 -1.5%
PTT (sec)								
13 weeks	22.6	22.8 +0.9%	22.5	**24.6*** **+8.8%**	21.0	19.7 -6.7%	21.6 +2.9%	21.0
17 weeks	22.9	-	22.5 -1.7%	**20.0*** **-12.7%**	20.4	-	19.2 -5.9%	20.6 +1.0%

* ($p < 0.05$); 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 6.3.2-3 Relevant clinical chemistry findings after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	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*** **-7.3%**	**5.55*** **-7.5%**	5.57	5.54 -0.5%	5.37 -3.6%	5.58
17 weeks	6.21	-	5.88 -5.3%	5.30 -14.7%	5.40	-	5.21 -3.5%	5.59 +3.5%
Urea (mmol/L)								
13 weeks	7.23	7.41 +2.5%	7.22	**8.32*** **+15.1%**	8.53	8.42 -1.3%	8.84 +3.6%	8.83 +3.5%
17 weeks	6.79	-	7.47 +10.0%	6.81	8.64	-	8.92 +3.2%	9.21 +6.6%
Total cholesterol (mmol/L)								
13 weeks	2.32	2.20 -5.2%	2.10 -9.5%	**1.46*** **-37.1%**	2.23	2.32 +4.0%	2.20 -1.3%	2.03 -9.0%
17 weeks	2.35	-	2.67 +13.6%	2.39 +1.7%	2.25	-	2.55 +13.3%	2.36 +4.9%
Triglycerides (mmol/L)								
13 weeks	0.57	0.54 -5.3%	0.62 +8.8%	0.57	0.42	0.40 -4.8%	**0.48*** **+14.3**	**0.57*** **+35.7%**
17 weeks	0.69	-	0.70 +1.4%	0.69	0.60	-	0.65 +8.3%	0.64 +6.7%

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
HDL cholesterol (mmol/L)								
13 weeks	1.06	1.08 +1.9%	1.00 -5.7%	**0.41*** **-61.3%**	1.20	1.37 +14.2%	1.22 +1.7%	**1.05*** **-12.5%**
17 weeks	1.14	-	1.24 +8.8%	1.12 -1.8%	1.37	-	1.67* +21.9%	1.48 +8.0%
HDL phospholipid (mmol/L)								
13 weeks	1.06	1.06	1.02 -3.8%	**0.72*** **-32.1%**	1.29	**1.51*** **-17.1%**	1.30 +0.8%	1.23 -4.7%
17 weeks	1.10	-	1.16 +5.5%	1.12 +1.8%	1.44	-	1.68 +16.7%	1.54 +6.9%
ALP (ukat/L)								
13 weeks	2.74	2.74	2.39 -12.8%	**4.47*** **+63.1%**	1.37	1.01* -26.3%	**1.26*** **-8.0%**	**1.68*** **+22.6%**
17 weeks	2.43	-	2.52 +3.7%	2.83 +16.5%	1.24	-	1.15 -7.3%	1.30 +4.8%
Calcium (mmol/L)								
13 weeks	2.44	2.41 -1.2%	2.42 -0.8%	**2.33*** **-4.5%**	2.56	2.60 +1.6%	**2.50*** **-2.3%**	**2.44*** **-4.7%**
17 weeks	2.40	-	2.44 +1.7%	2.40	2.45	-	**2.52*** **+2.9%**	2.44 -0.4%
Sodium (mmol/L)								
13 weeks	144.1	144.5	**145.5*** **+1.0%**	**146.4*** **+1.6%**	143.1	143.6	**144.4*** **+0.9%**	**145.2*** **+1.5%**
17 weeks	141.3	-	141.6	142.2 +0.6%	141.1	-	141.0	143.1 +1.4%
Total protein (g/L)								
13 weeks	65.6	63.3 -3.5%	65.0 -0.9%	**60.3*** **-8.1%**	63.4	64.0 +0.9%	63.4	62.9 -0.8%
17 weeks	67.2	-	**69.9*** **+4.0%**	**65.1*** **-3.1%**	70.6	-	70.8	69.0 -2.3%

* ($p < 0.05$); 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. 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 6.3.2-4 Relevant urinalysis findings after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	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 a reduction in 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 6.3.2-5 Organ weight findings after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Liver weight Week 13								
absolute (g)	9.54	9.44 -1.0%	10.21 +7.0%	**11.77*** **+23.4%**	6.11	6.58 +7.7%	6.71 +9.8%	**7.36**** **+20.5%**
relative (% bw)	2.59	2.52 -2.7%	2.65 +2.3%	**3.78**** **+45.9%**	2.70	2.87 +6.3%	**2.99**** **+10.7%**	**3.57**** **+32.2%**
Liver weight Week 17								
absolute (g)	9.59	-	10.35 +7.9%	8.89 -7.3%	6.69	-	7.23 +8.1%	**7.66**** **+14.5%**
relative (% bw)	2.49		2.51 +0.8%	2.67 +7.2%	2.83		2.98 +5.3%	**3.33**** **+17.7%**
Kidney weight Week 13								
absolute (g)	2.07	2.15 +3.9%	2.21 +6.8%	2.17 +4.8%	1.29	1.39 +7.8%	**1.49**** **+15.5%**	**1.46*** **+13.2%**
relative (% bw)	0.57	0.57	0.58 +1.8%	**0.70**** **+22.8%**	0.57	0.61 +7.0%	**0.66**** **+15.8%**	**0.71**** **+24.6%**
Kidney weight Week 17								
absolute (g)	2.09	-	2.25 +7.7%	2.05 -1.9%	1.50	-	1.45 -3.3%	1.51 +0.7%
relative (% bw)	0.54		0.55 +1.9%	**0.62*** **+14.8%**	0.64		0.60 -6.3%	0.66 +3.1%
Testes weight Week 13								
absolute (g)	3.35	3.29 -1.8%	3.56 +6.3%	3.28 -2.1%				
relative (% bw)	0.92	0.88 -4.3%	0.93 +1.1%	**1.07**** **+16.3%**				
Testes weight Week 17								
absolute (g)	3.43	-	3.49 +1.7%	3.18 -7.3%				
relative (% bw)	0.89		0.85 -4.5%	0.96 +7.9%				

* ($p < 0.05$); ** ($p < 0.01$); 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 6.3.2-6 Microscopic findings after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with fenoxaprop-P-ethyl

	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	-	-	-	-	-	-	-	-

Analytical method: According to the analytical method described in attachment 3 of the report of Tennekes *et al.*, 1987 (Doc No. A36566) the LOQ was determined as 10 ppm (for details refer to Volume 3 CA B-5).

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 were 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).

Reference:	Hoe 046360 Technical. 13-week dietary toxicity study in rats. Determinations of mixed function oxidase, catalase and glutathione in liver
Author(s). year:	[redacted] 1987
Report/Doc. number:	A36954 / RCC Project No. 060671
Guideline(s):	Not applicable.
GLP:	Yes
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 13-week repeated dose study in Wistar rats (Tennekes H. *et al.*, 1987; Doc No. A36566)

Material and Methods:
See study of Tennekes *et al.* (1987) at the beginning of this section.

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 6.3.2-7 Hepatic enzyme determination after treatment (13 w) and recovery (17 w), 13 week feeding study in Wistar rats with fenoxaprop-P-ethyl

	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 +2.4%	**20.0*** **+19.8%**	**21.7*** **+29.9%**	14.9	15.1 +1.3%	15.7 +5.4%	15.7 +5.4%
17 weeks	18.6	n.d.	17.6 -5.4%	17.0 -8.6%	12.7	n.d.	**14.3*** **+12.6%**	12.8 +0.8%
N-demethylase (nmol/min/g)								
13 weeks	404	**324*** **-19.8%**	**320*** **-20.8%**	**285*** **-29.5%**	175	174 -0.6%	196 +12.0%	**216*** **+23.4%**
17 weeks	431	n.d.	**372*** **-13.7%**	**328*** **-23.9%**	167	n.d.	183 +9.6%	**217*** **+29.9%**

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
GSH (µmol/g)								
13 weeks	1.23	0.95 -22.8%	0.92 -25.2%	**0.45*** **-63.4%**	0.85	0.42 -50.6%	0.93 +9.4%	0.73 -14.1%
17 weeks	1.66	n.d.	1.40 -15.7%	1.41 -15.1%	0.67	n.d.	1.24 +85.1%	**1.33*** **+98.5%**
GSSG (µmol/g)								
13 weeks	1.39	1.13 -18.7%	1.63 +17.3%	**1.79*** **+28.8%**	1.09	1.02 -6.4%	1.15 +5.5%	**1.44*** **+32.1%**
17 weeks	1.33	n.d.	1.40 -5.3%	1.03 -22.6%	1.08	n.d.	**1.70*** **+57.4%**	**2.25*** **+108.3%**
Total glutathione (µmol/g)								
13 weeks	2.58	2.05 -20.5%	2.55 -1.2%	2.16 -16.3%	1.96	1.46 -25.5%	2.10 +7.1%	2.21 +12.8%
17 weeks	2.98	n.d.	2.80 -6.0%	2.45 -17.8%	1.80	n.d.	**2.94*** **+63.3%**	**3.58*** **+98.9%**
Catalase (k/g)								
13 weeks	143	127 -11.2%	**110*** **23.1%**	**182*** **+27.3%**	88	74 -15.9%	**63*** **-28.4%**	100 +13.6%
17 weeks	115	n.d.	108 -6.1%	115	60	n.d.	67 +11.7%	**88*** **+46.7%**

* ($p<0.05$); 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.

B.6.3.2.2. Mouse

Reference:	Hoe 046360 Technical. Subchronic oral toxicity 13-week feeding study in mice
Author(s), year:	[redacted]; 1987a
Report/Doc. number:	A36567 / RCC Project No. 060660
Guideline(s):	OECD guideline 408 (1981), EPA guideline 82-1 (1982).
Deviations to OECD 408 (1998):	Haematological analysis did not include measurement for BUN. Limited pathological evaluation and organ weight analysis performed. No functional observations conducted.
GLP:	Yes.
Deviations:	Minor deviations in pathology compared to current guidelines.
Acceptability:	Yes.

Material and Methods:
Groups of 10 mice per sex 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. 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.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: NMRI mice, [redacted]
About 6 weeks old, 26-32 g (♂) and 22-30 g (♀).
Number of animals: 10 mice per sex

At the end of treatment (13 weeks), blood samples were taken after a fasting period of 18 hours. Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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, oesophagus, 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.

Haematology: 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 6.3.2-8 Relevant haematology findings after 13 weeks, 13 week feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
MCV (fL)	42.2	42.4 +0.5%	42.8 +1.4%	**44.6*** **+5.7%**	44.6	43.4 -2.7%	43.8 -1.8%	44.2 -0.9%
Platelets (g/L)	1407	1376 -2.2%	1235 -12.2%	1294 -8.0%	1101	1086 -1.4%	1115 +1.3%	**1260*** **+14.4%**
Reticulocytes (1)	0.024	0.025 +4.2%	0.024	**0.031*** **+29.2%**	0.029	0.028 -3.4%	0.030 +.3.4%	0.026 -10.3%

* ($p < 0.05$); 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 6.3.2-9 Relevant clinical chemistry findings after 13 weeks, 13 week feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Urea (mmol/L)	8.36	8.25 -1.3%	9.26 +10.8%	9.01 +7.8%	7.21	7.34 +1.8%	5.72 -20.7%	**13.78*** **+91.1%**
Total cholesterol (mmol/L)	4.97	4.42 -11.1%	4.63 -6.8%	**3.84*** **-22.7%**	3.66	3.97 +8.5%	4.55 +24.3%	**4.60*** **+25.7%**
Phospholipids (mmol/L)	3.61	3.42 -5.3%	3.65 +1.1%	**2.68*** **-25.8%**	2.53	2.77 +9.5%	3.00 +18.6%	2.98 +17.8%
ALAT (ukat/L)	0.90	1.27 +41.1%	0.85 -5.6%	**1.82*** **+102.2%**	1.03	1.29 +25.2%	0.98 -4.9%	1.08 +4.9%
ALP (ukat/L)	2.56	2.45 -4.3%	2.44 -4.7%	**6.95*** **+171.5%**	3.54	3.29 -7.1%	3.88 +9.6%	4.79 +35.3%
Albumin (g/L)	27.3	27.5 +0.7%	28.0 +2.6%	**30.8*** **+12.8%**	29.4	27.0 -8.2%	29.8 +1.4%	31.0 +5.4%

* ($p < 0.05$); 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 6.3.2-10 Relevant organ weight findings after 3 weeks, 13 week feeding study in mice with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	10	80	640	0	10	80	640
Liver weight								
absolute (g)	1.81	1.73 -4.4%	2.00 +10.5%	**4.28*** **+136.5%**	1.40	1.33 -5.0%	1.49 +6.4%	**2.80**** **+100.0%**
relative (% bw)	4.36	4.31 -1.1%	**5.03**** **+15.4%**	**10.46**** **+139.9%**	4.83	4.79 -0.8%	5.30 +9.7%	**9.30**** **+92.5%**
Kidney weight								
absolute (g)	*0.708*	0.700 -1.1%	0.676 -4.5%	0.724 +2.3%	0.449	0.428 -4.7%	0.450	**0.525**** **+16.9%**
relative (% bw)	1.721	1.741 +1.2%	1.716	1.771 +2.9%	1.553	1.545 -0.5%	1.617 +4.1%	1.745 +12.4%

* (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 to marked tubular injury was noted in all females receiving 640 ppm. In five males receiving 640 ppm minimal to slight tubular injury was observed. The type and incidence of other findings were considered to be similar in the treatment and control groups.

Table 6.3.2-11 Relevant histopathological findings after 13 weeks, 13 week feeding study in mice with fenoxaprop-P-ethyl

	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

Analytical method: According to the analytical method described in attachment 3 of the report of [redacted] 1987 (Doc No. A36567) the LOQ was determined as 10 ppm (for details refer to Volume 3 CA B-5).

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).

Reference:	Hoe 046360 Technical. 13-week dietary toxicity study in mice. Determinations of mixed function oxidase, catalase and glutathione in liver
Author(s). year:	[redacted] 1987(d)
Report/Doc. number:	A36960 / RCC Project No. 060660
Guideline(s):	Not applicable.
GLP:	Yes.
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 28-day repeated dose study in NMRI mice (Suter and Luetkemeier 1987(a); Doc No. A36567)

Material and Methods:
See study of Suter and Luetkemeier (1987a) at the beginning of this section.

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 6.3.2-12 Hepatic enzyme determination after 13 weeks, 13 week feeding study in NMRI mice with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	**10**	**80**	**640**	**0**	**10**	**80**	**640**
Cytochrome P-450 (nmol/g)	14.8	16.8 +13.5%	18.9 +27.7%	**20.6*** **+39.2%**	15.7	13.5 -14.0%	15.2 -3.2%	19.0 +21.0%
N-demethylase (nmol/min/g)	238	230 -3.4%	301 +26.5%	244 +2.5%	285	272.1 -4.5%	214 -24.9%	**577*** **+102.5%**
Glutathione (µmol/g) -reduced (GSH)	1.62	**0.41*** **-74.7%**	1.78 +9.9%	1.78 +9.9%	n.d.	n.d.	1.34	2.18
-oxidized (GSSG)	1.53	1.54 +0.7%	1.65 +7.8%	1.66 +8.5%	n.d.	n.d.	1.33	1.27
-total (GSH+GSSG)	3.15	1.94* -38.4%	3.42 +8.6%	3.44 +9.2%	n.d.	n.d.	2.66	3.45
Catalase (k/g)	127	129 +1.6%	130 +2.4%	**400*** **+215.0%**	68	101 +48.5%	78 +14.7%	**279*** **+310.3%**

* ($p < 0.05$); 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.

B.6.3.2.3. Dog

Reference:	Hoe 046360 Technical. Subchronic oral toxicity 13-week feeding study in Beagle dogs
Author(s), year:	[redacted]., 1987b
Report/Doc. number:	A36617 / RCC Project No. 060682
Guideline(s):	EPA guideline 82-1 (1982).
Deviations to OECD 409 (1998):	Minor deviations in pathology compared to current guidelines. No functional observations conducted.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Four dogs/sex/dose group 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 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.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 %; according to certificate of analysis No. 02912

Test animals: Beagle dogs, Kleintierfarm Madoerin AG, CH
About 4-6 months old, 4.1-8.6 kg (♂) and 4.2-6.8 kg (♀).
Number of animals: 4 mice per sex

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 pre-test and after 4 and 13 weeks of treatment. Furthermore ophthalmoscopic examinations were performed in each animal at pre-test and after 4 and 13 weeks of treatment. Blood and urine samples were taken at pre-test 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.
Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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, creatinine 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, colour, 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, oesophagus, 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 diarrhoea (all groups), faeces 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 6.3.2-13 Food consumption and bodyweights after 13 weeks, 13 week feeding study in dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	**80**	**400**	**2,000**	**0**	**80**	**400**	**2,000**
Food consumption (g/day)	298	300	300	300	294	299	291	289
Initial body weight (g)	5971	6807 +14.0%	6583 +10.2%	6956 +16.5%	6277	6166 -1.8%	6123 -2.5%	5836 -7.0%
Body weight day 90 (g)	8524	8910 +4.5%	8755 +2.7%	8456 -0.8%	8644	8685 +0.5%	7962 -7.9%	7881 -8.8%
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.

Haematology: 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 significantly increased in males receiving 2,000 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 6.3.2-14 Relevant clinical chemistry findings after 4 and 13 weeks, 13 week feeding study in dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	**80**	**400**	**2,000**	**0**	**80**	**400**	**2,000**
ASAT (ukat/L)								
4 weeks	0.78	0.80 +2.6%	0.85 +9.0%	0.91 +16.7%	0.85	0.90 +5.9%	0.83 -2.4%	0.94 +10.6%
13 weeks	0.67	0.74 +10.4%	0.75 +11.9%	**0.82*** **+22.4%**	0.71	0.82 +15.5%	0.79 +11.3%	0.79 +11.3%
ALAT (ukat/L)								
4 weeks	0.67	0.62 -7.5%	0.66 -1.5%	**0.53*** **-20.9%**	0.69	0.67 -2.9%	**0.56*** **-18.8%**	**0.49*** **-29.0%**
13 weeks	0.54	0.51 -5.6%	0.50 -7.4%	**0.37*** **-31.5%**	0.51	0.52 +2.0%	0.46 -9.8%	**0.38*** **-25.5%**
LDH (ukat/L)								
4 weeks	2.57	2.93 +14.4%	3.12 +21.4%	3.32 +29.2%	3.23	3.66 +13.3%	3.02 -6.5%	3.61 +11.8%
13 weeks	2.67	3.19 +19.5%	3.02 +13.1%	**3.80*** **+42.3%**	3.18	3.76 +18.2%	3.14 -1.3%	3.72 +17.0%
Total protein (g/L)								
4 weeks	49.5	52.2 +5.5%	53.6 +8.3%	**54.6*** **+10.3%**	51.0	53.1 +4.1%	50.9	52.1 +2.2%
13 weeks	54.1	56.0 +3.5%	55.6 +2.8%	**58.4*** **+7.9%**	55.6	56.1 +0.9%	54.4 -2.2%	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 kidney weights relative to the brain weight in males at 2,000 ppm.

Table 6.3.2-15 Organ weight findings after 13 weeks, 13 weeks feeding study in dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	400	2,000	0	80	400	2,000
Liver weight								
absolute (g)	282.5	278.4 -1.5%	272.9 -3.4%	290.1 +2.7%	257.1	236.2 -8.1%	244.9 -4.7%	276.6 +7.6%
relative (% bw)	3.6	3.4 -5.6%	3.4 -5.6%	3.7 +2.8%	3.2	3.0 -6.3%	3.3 +3.1%	3.9 +21.9%
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 +4.2%	39.38 -1.9%	43.34 +7.9%	37.55	36.75 -2.1%	34.12 -9.1%	36.43 -3.0%
relative (% bw)	0.50	0.52 +4.0%	0.49 -2.0%	0.56 +12.0%	0.47	0.46 -2.1%	0.47	0.51 +8.5%
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.

Analytical method: According to the analytical method described in attachment 1 of the report of Sachsse *et al.*, 1987 (Doc No. A36617) the LOQ was determined as 80 ppm (for details refer to Volume 3 CA B-5).

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).

Reference:	Hoe 046360 Technical. 13-week dietary toxicity study in dogs. Determinations of cytochrome P-450, N-demethylase and glutathione in liver
Author(s). year:	[redacted] 1987(d)
Report/Doc. number:	A36959 / RCC Project No. 060682
Guideline(s):	Not applicable.
GLP:	Yes.
Acceptability:	In this study, special investigations on liver enzymes were performed, which is supplementary to the 13 week repeated dose study in Beagle dogs ([redacted] 1987(b); Doc No. A36617)

Materials and Methods:
See study of Sachsse K. *et al.* (1987b) at the beginning of this section.

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 2,000 ppm. Data was lost for some glutathione determinations in females.

Table 6.3.2-16 Hepatic enzyme determination after 13 weeks, 13 week feeding study in Beagle dogs with fenoxaprop-P-ethyl

	Dose group level (ppm)	
	Males	Females

	0	80	400	2000	0	80	400	2000
Cytochrome P-450 (nmol/g)	9.8	10.3 +5.1%	9.4 -4.1%	7.5 -23.5%	9.2	9.4 +2.2%	8.5 -7.6%	8.1 -12.0%
N-demethylase (nmol/min/g)	116	114 -1.7%	77 -33.6%	**43*** **-62.9%**	101	124 +22.8%	115 +13.9%	109 +7.9%
Glutathione (µmol/g) -reduced (GSH)	3.75	2.97 -20.8%	3.77 +0.5%	4.22 +12.5%	4.02	-[1)]	-[1)]	2.69 -33.1%
-oxidized (GSSG)	2.10	1.99 -5.2%	1.82 -13.3%	1.73 -17.6%	1.02	-[1)]	-[1)]	1.68 +64.7%
-total (GSH+GSSG)	5.85	4.95 -15.4%	5.59 -4.4%	5.95 +1.7%	5.04	-[1)]	-[1)]	4.36 -13.5%

* ($p<0.05$); 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.

B.6.3.3. Other routes

B.6.3.3.1. Subchronic inhalation study - Rat

Reference:	Hoe 046360-substance technical. Testing for subchronic inhalation toxicity (28 applications within 40 days in male and female Wistar rats
Author(s), year:	[redacted]; 1989
Report/Doc. number:	A40799 / Hoechst Report No. 89.0584
Guideline(s):	OECD guideline 412 (1981), EPA guideline 82-4 (rev. 1984), EC guideline B.8 (1984)
Deviations to OECD 412 (2009):	- Animal age at beginning of study slightly younger. - Limited pathology and organ weight analysis performed. - Mostly dry exposure conditions than recommended in the guideline.
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
15 rats per sex per dose group 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 per sex per 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. 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 % was less than 1 µm.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: Wistar rat, strain WISKf(SPF71), [redacted]
About 5-6 weeks old, 121-132 g (♂) and 118-132 g (♀).
Number of animals: 15 rats per sex per dose

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.
Haematology consisted of erythrocyte count, haemoglobin, haematocrit, MCV, MCH, MCHC, leukocyte count, thrombocyte count, differential leucocyte count, red cell morphology, reticulocyte count, Heinz bodies, coagulation time, thromboplastin time, methaemoglobin and activated partial thromboplastin time.

In clinical chemistry the following parameters were assessed: sodium, potassium, inorganic 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 6.3.3-1 Food and water consumption (complete study) and body weights (terminal, recovery), Subchronic inhalation toxicity study in rats with fenoxaprop-P-ethyl

	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 +4.0%	21.0 +4.5%	20.1	16.6	16.7 +0.6%	16.8 +1.2%	16.3 -1.8%
Water consumption (g/day)	29.2	29.7 +1.7%	30.6 +4.8%	29.1	23.7	25.5 +7.6%	24.4 +3.0%	25.9 +9.3%
Body weight gain study days 1 – 41 (g)	98	107 +9.2%	109 +11.2%	87 -11.2%	51	54 +5.9%	53 +3.9%	46 -9.8%
Terminal body weight on study day 41 (g)	255	272 +6.7%	258 +1.2%	241 -5.5%	206	212 +2.9%	206	196 -4.9%
Terminal body weight recovery (g)	341	349 +2.3%	**378*** **+10.9%**	351 +2.9%	234	231 -1.3%	239 +2.1%	229 -2.1%

* (p = 0.05); significantly different from controls

Ophthalmological examinations: No abnormalities were noted at examinations.

Haematology: Haemoglobin and haematocrit 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 6.3.3-2 Relevant haematology findings on study day 41 and after recovery, Subchronic inhalation toxicity study in rats with fenoxaprop-P-ethyl

	Dose group level (mg/L air)							
	Males				Females			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**

	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 -1.3%	150 -2.6%	**139*** **-9.7%**	135	142 +5.2%	142 +5.2%	138 +2.2%
after recovery	157	**146*** **-7.0%**	149 -5.1%	**147*** **-6.4%**	140	146 +4.3%	142 +1.4%	144 +2.9%
Hematocrit (unity)								
study day 41	0.46	0.45 -2.2%	0.45 -2.2%	**0.41*** **-10.9%**	0.41	0.43 +4.9%	0.42 +2.4%	0.41
after recovery	0.48	0.45 -6.2%	0.44 -8.3%	**0.43*** **-10.4%**	0.43	0.44 +2.4%	0.43	0.43
TT (s)								
study day 41	11.8	9.9 -16.1%	**9.7*** **-17.8%**	**9.7*** **-17.8%**	9.4	9.3 -1.1%	9.7 +3.2%	9.3 -1.1%
after recovery	11.3	10.5 -7.1%	10.2 -9.7%	**9.8*** **-13.3%**	9.6	9.5 -1.0%	9.8 +2.1%	9.4 -2.1%
aPTT (s)								
study day 41	14.0	13.8 -1.4%	14.2 +1.4%	14.2 +1.4%	12.6	13.1 +4.0%	15.2 +20.6%	**14.4*** **+14.3%**
after recovery	12.5	11.9 -4.8%	13.6 +8.8%	12.7 +1.6%	16.5	16.2 -1.8%	15.0 -9.1%	14.6 -11.5%

* (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 significances 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 apparent.

Table 6.3.3-3 Relevant clinical chemistry findings on study day 41 and after recovery, Subchronic inhalation toxicity study in rats with fenoxaprop-P-ethyl

	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 -1.4%	144 -0.7%	145	146	145 -0.7%	143 -2.1%	**141*** **-3.4%**
after recovery	145	146 +0.7%	**150*** **+3.4%**	148 +2.1%	142	**150*** **+5.6%**	143 +0.7%	146 +2.8%
Calcium (mmol/L)								
study day 41	2.63	2.68 +1.9%	**2.49*** **-5.3%**	**2.47*** **-6.1%**	2.68	2.62 -2.2%	2.60 -3.0%	2.65 -1.1%
after recovery	2.63	2.62 -0.4%	**2.76*** **+4.9%**	2.67 +1.5%	2.48	**2.64*** **+6.5%**	2.62 +5.6%	**2.64*** **+6.5%**
Chloride (mmol/L)								
study day 41	104	103 -1.0%	102 -1.9%	**101*** **-2.9%**	102	103 1.0%	103 1.0%	101 -1.0%
after recovery	101	102 +1.0%	101	103 +2.0%	102	**106*** **+3.9%**	105 +2.9%	107* +4.9%
Urea nitrogen (mmol/L)								
study day 41	7.3	8.3 +13.7%	7.2 -1.4%	**9.1*** **+24.7%**	7.3	8.8 +20.5%	7.9 +8.2%	**10.0*** **+37.0%**
after recovery	8.7	9.2 +5.7%	8.3 -4.6%	7.9 -9.2%	11.0	8.9 -19.1%	9.5 -13.6%	9.9 -10.0%
Cholesterol (mmol/L)								
study day 41	1.34	1.35 +0.7%	1.19 -11.2%	**1.02*** **-23.9%**	1.25	1.15 -8.0%	1.23 -1.6%	**0.91*** **-27.2%**
after recovery	1.46	1.51 +3.4%	1.50 +2.7%	1.33 -8.9%	1.35	1.38 +2.2%	1.50 +11.1%	1.58 +17.0%

	Dose group level (mg/L air)							
	Males				Females			
	0	**0.015**	**0.07**	**0.3**	**0**	**0.015**	**0.07**	**0.3**
Triglycerides (mmol/L)								
study day 41	1.65	1.67	1.89	**2.10***	1.46	1.12	1.11	1.41
		+1.2%	+14.5%	**+27.3%**		-23.3%	-24.0%	-3.4%
after recovery	1.24	1.45	1.51	1.31	1.42	1.18	1.43	1.29
		+16.9%	+21.8%	+5.6%		-16.9%	+0.7%	-9.2%
Total lipids (g/L)								
study day 41	3.45	3.22	3.33	**3.03***	4.25	3.71	4.33	**3.71***
		-6.7%	-3.5%	**-12.2%**		-12.7%	1.9%	**-12.7%**
after recovery	3.86	4.06	4.04	4.83	4.10	3.82	4.00	4.27
		+5.2%	+4.7%	+25.1%		-6.8%	-2.4%	+4.1%
Alpha-2 globulin								
study day 41	0.057	0.059	0.049	**0.040***	0.045	0.046	0.042	0.050
		+3.5%	-14.0%	**-29.8%**		+2.2%	-6.7%	+11.1%
after recovery	0.055	0.061	0.069	0.064	0.040	0.049	0.051	0.048
		+10.9%	+25.5%	+16.4%		+22.5%	+27.5%	+20.0%

* (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). These were not considered as biologically relevant. 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 6.3.3-4 Relevant organ weight findings on study day 41 and after recovery, subchronic inhalation toxicity study in rats with fenoxaprop-P-ethyl

	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***
		+12.9%	**+22.2%**	**+41.1%**		+5.8%	+5.3%	**+12.3%**
relative (% bw)	3.202	3.386	**3.848***	**4.779***	3.769	3.873	3.966	**4.443***
		+5.7%	**+20.2%**	**+49.3%**		+2.8%	+5.2%	**+17.9%**
Liver weight Recovery								
absolute (g)	10.76	12.12	12.55	12.15	8.29	7.80	8.14	8.14
		+12.6%	+16.6%	+12.9%		-5.9%	-1.8%	-1.8%
relative (% bw)	3.154	**3.470***	3.317	**3.451***	3.555	3.377	3.409	3.545
		+10.0%	+5.2%	**+9.4%**		-5.0%	-4.1%	
Kidney weight Day 41								
absolute (g)	1.59	1.69	1.72	**1.78***	1.42	1.49	1.49	1.47
		+6.3%	+8.2%	**+11.9%**		+4.9%	+4.9%	+3.5%
relative (% bw)	0.627	0.620	0.667	**0.740***	0.692	0.702	0.727	**0.749***
		-1.1%	+6.4%	**+18.0%**		+1.4%	+5.1%	**+8.2%**
Kidney weight Recovery								
absolute (g)	2.11	1.92	2.22	2.07	1.49	1.41	1.47	1.45
		-9.0%	+5.2%	-1.9%		-5.4%	-1.3%	-2.7%
relative (% bw)	0.616	0.551	0.588	0.590	0.641	0.611	0.615	0.629
		-10.6%	-4.5%	-4.2%		-4.7%	-4.1%	-1.9%
Testes weight Day 41								
absolute (g)	2.97	2.88	2.94	**2.56***				
		-3.0%	-1.0%	**-13.8%**				
relative (% bw)	1.167	1.054	1.131	1.061				
		-9.7%	-3.1%	-9.1%				

	Dose group level (mg/L air)							
	Males				Females			
	0	0.015	0.07	0.3	0	0.015	0.07	0.3
Testes weight Recovery								
absolute (g)	3.03	2.89 -4.6%	3.29 +8.6%	3.16 +4.3%				
relative (% bw)	0.892	0.822 -7.8%	0.872 -2.2%	0.903 +1.2%				

* (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) liver weights were observed in both sexes at all dose groups in males during the study, while only the high dose group was affected in the females. In the recovery period, increased relative liver weights (0.015 mg/L and above) were recorded in males. 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.

B.6.3.3.2. Subchronic dermal toxicity study - Rat

Reference:	Hoe 046360-active ingredient technical. Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rat
Author(s), year:	[redacted]; 1988
Report/Doc. number:	A40800 / Hoechst Report No. 88.1774
Guideline(s):	OECD guideline 410 (1981), EPA guideline 82-2 (1982)
GLP:	Yes.
Acceptability:	yes

Materials and Methods:
6 rats/sex/dose group 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 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 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.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002, vehicle: sesame oil
Purity: 95.6 % according to certificate of analysis No. 02912

Test animals: Wistar rat, strain WISKf(SPF71), Hoechst
About 6 weeks old, 198-230 g (♂) and 186-214 g (♀).
Number of animals: 6 rats per sex per dose

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.

Haematology consisted of erythrocytes, haemoglobin, haematocrit, MCV, MCH, MCHC, leukocytes, thrombocytes, differential blood count, reticulocytes, Heinz bodies, coagulation time, thromboplastin time (TT) and activated partial thromboplastin time (PTT).
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 oedema 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. During the recovery period, these effects subsided and finally disappeared in all animals.

Table 6.3.3-5 Skin dryness/chapping, fine or coarse scales observed in male animals (of total), Subchronic dermal toxicity study in rats with fenoxaprop-P-ethyl

	Dose (mg/kg bw/day)				
day	Control	10	20	100	500
4	2/12	1/6	1/6	**6/12**	4/12
5	**6/12**	3/6	1/6	5/12	2/12
8	1/12	2/6	2/6	4/12	3/12
9	1/12	2/6	2/6	**6/12**	3/12
10	0/12	0/6	0/6	1/12	2/12
11-19	0/12	0/6	0/6	0/12	0/12
22-23	0/12	0/6	0/6	0/12	**12/12**
24	0/12	0/6	0/6	4/12	**12/12**
25	0/12	0/6	0/6	5/12	**12/12**
26-30	0/12	0/6	0/6	0/12	**12/12**
Recovery period:					
31-33	0/12	-	-	0/12	**6/12**
36-37	0/12	-	-	0/12	1/6
38-44	0/12	-	-	0/12	0/6

≥50% of animals affected in **bold**

Table 6.3.3-6 Skin dryness/chapping, fine or coarse scales observed in female animals (of total), Subchronic dermal toxicity study in rats with fenoxaprop-P-ethyl

	Dose (mg/kg bw/day)

day	Control	10	20	100	500
4	5/12	2/6	0/6	0/12	0/12
7	**11/12**	**6/6**	3/6	0/12	0/12
8	**11/12**	**6/6**	1/6	**9/12**	**7/12**
9	**6/12**	1/6	1/6	1/12	2/12
10-11	0/12	0/6	0/6	0/12	0/12
14	3/12	1/6	1/6	3/12	5/12
15	0/12	0/6	0/6	0/12	0/12
16	0/12	1/6	1/6	3/12	2/12
17	0/12	1/6	0/6	1/12	0/12
18	0/12	0/6	0/6	0/12	0/12
21-22	0/12	0/6	0/6	0/12	**12/12**
23	0/12	0/6	0/6	1/12	**12/12**
24	0/12	0/6	0/6	4/12	**12/12**
25-30	0/12	0/6	0/6	0/12	**12/12**
Recovery period:					
31	0/12	-	-	0/12	**6/6**
32	0/12	-	-	0/12	**4/6**
35-44	0/12	-	-	0/12	0/12

≥50% of animals affected in **bold**

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 6.3.3-7 Food consumption (complete study) and body weights (main study, recovery), Subchronic dermal toxicity study in rats with fenoxaprop-P-ethyl

	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 +5.1%	10.1 +3.1%	9.5 -3.1%	10.0 +2.0%	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 -2.4%	330 +0.9%	319 -2.4%	240	238	230 -4.2%	228 -5.0%	230 -4.2%
Bodyweight gain after main study (g)	100	100	91 -9.0%	99 -1.0%	97 -3.0%	26	25	17 -34.6%	16 -38.5%	16 -38.5%
Terminal body weight after recovery (g)	362	-	-	369 +1.9%	356 -1.7%	252	-	-	251	244 -3.2%
Bodyweight gain after recovery (g)	135	-	-	138	134	38	-	-	39	30

Haematology: Erythrocyte count, haemoglobin, and haematocrit 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 6.3.3-8 Relevant haematology findings after treatment and recovery, Subchronic dermal toxicity study in rats with fenoxaprop-P-ethyl

	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
Erythrocyte count (10^{12}/L)										
after treatment	8.06	7.89 -2.1%	7.59 -5.8%	**7.55*** **-6.3%**	**7.56*** **-6.2%**	7.80	8.04 +3.1%	7.92 +1.5%	8.15 +4.5%	7.65 -1.9%
after recovery	8.26	-	-	8.07 -2.3%	7.65 -7.4%	7.53	-	-	7.38 -2.0%	7.38 -2.0%
Haemoglobin (g/L)										
after treatment	153	149 -2.6%	146 -4.6%	**145*** **-5.2%**	**143*** **-6.5%**	146	151 +3.4%	149 +2.1%	151 +3.4%	142 -2.7%
after recovery	153	-	-	146 -4.6%	143 -6.5%	140	-	-	141 +0.7%	138 -1.4%
Hematocrit (unity)										
after treatment	0.48	0.47 -2.1%	0.45 -6.2%	**0.44*** **-8.3%**	**0.43*** **-10.4%**	0.46	0.46	0.46	0.47 +2.2%	0.44 -4.3%
after recovery	0.47	-	-	0.45 -4.3%	0.43 -8.5%	0.43	-	-	0.43	0.43
Reticulocytes (unity)										
after treatment	0.033	0.035	0.023 -30.3%	0.028 -15.2%	0.021 -36.4%	0.045	0.042 -6.7%	0.036 -20.0%	0.045	**0.026*** **-42.2%**
after recovery	0.067	-	-	0.046 -31.3%	**0.025*** **-62.7%**	0.013	-	-	0.023 +76.9%	0.010 -23.1%
TT (s)										
after treatment	13.2	13.2	12.1 -8.3%	11.2 -15.2%	**11.1*** **-15.9%**	11.7	12.2 +4.3%	10.1 -13.7%	**9.4*** **-19.7%**	9.7 -17.1%
after recovery	11.3	-	-	11.5 +1.8%	11.5 +1.8%	11.1	-	-	10.4 -6.3%	11.2 +0.9%
aPTT (s)										
after treatment	21.2	20.8 -1.9%	18.8 -11.3%	18.6 -12.3%	**18.2*** **-14.2%**	17.7	20.7 +16.9%	19.9 +12.4%	19.7 +11.3%	20.0 +13.0%
after recovery	19.3	-	-	19.8 +2.6%	20.0 +3.6%	19.2	-	-	18.4 -4.2%	-[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 significances were not dose-related and within biological variation and therefore not considered as toxicologically relevant.

Table 6.3.3-9 Relevant clinical chemistry findings after treatment and recovery, Subchronic dermal toxicity in rats with fenoxaprop-P-ethyl

	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*** **+2.8%**	144	143	143	142	**141*** **-2.1%**
after recovery	143	-	-	141	145	143	-	-	142	**140*** **-2.1%**
Chloride										
after treatment	104	102	103	102	**102*** **-1.9%**	106	104	105	102 -3.8%	**104*** **-1.9%**
after recovery	105	-	-	103	104	105	-	-	106	105
Cholesterol (mmol/L)										
after treatment	1.60	1.54 -3.8%	1.40 -12.5%	**1.19*** **-25.6%**	**1.10*** **-31.3%**	1.48	1.54 +4.1%	1.45 -2.0%	1.15 -22.3%	**1.05*** **-29.1%**
after recovery	1.92	-	-	1.66 -13.5%	**1.58*** **-17.7%**	1.77	-	-	1.73 -2.3%	1.56 -11.9%

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Total lipids (g/L)										
after treatment	3.58	3.37 -5.9%	3.33 -7.0%	**3.13*** **-12.6%**	**3.25*** **-9.2%**	3.34	3.38 +1.2%	3.34	3.41 +2.1%	3.43 +2.7%
after recovery	4.66	-	-	4.64	**4.15*** **-10.9%**	4.18	-	-	4.35 +4.1%	4.09 -2.2%

* (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). These effects on kidney weight in females were not considered as biologically relevant. 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 6.3.3-10 Statistically significant organ weight findings after treatment and recovery, Subchronic dermal toxicity in rats with fenoxaprop-P-ethyl

	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 +5.3%	12.85 +1.6%	14.70 +16.2%	**17.31*** **+36.8%**	9.02	9.41 +4.3%	8.95 -0.8%	9.50 +5.3%	10.39 +15.2%
after recovery	13.65	-	-	13.79 +1.0%	13.75 +0.7%	9.07	-	-	9.53 +5.1%	9.44 +4.1%
Liver relative										
after treatment	3.866	4.033 +4.3%	4.030 +4.2%	**4.449*** **+15.1%**	**5.414*** **+40.0%**	3.761	3.960 +5.3%	3.890 +3.4%	4.151 +10.4%	**4.526*** **+20.3%**
after recovery	3.766	-	-	3.741 -0.7%	3.867 +2.7%	3.597	-	-	3.798 +5.6%	3.863 +7.4%
Kidney absolute										
after treatment	2.12	2.23 +5.2%	2.19 +3.3%	2.34 +10.4%	**2.40*** **+13.2%**	1.55	1.67 +7.7%	1.70 +9.7%	1.69 +9.0%	1.72 +11.0%
after recovery	2.27	-	-	2.22 -2.2%	2.23 -1.8%	1.59	-	-	1.54 -3.1%	1.60 +0.6%
Kidney relative										
after treatment	0.650	0.674 +3.7%	0.688 +5.8%	**0.710*** **+9.2%**	**0.750*** **+15.4%**	0.646	0.701 +8.5%	**0.739*** **+14.4%**	**0.739*** **+14.4%**	**0.749*** **+15.9%**
after recovery	0.627	-	-	0.604 -3.7%	0.628	0.630	-	-	0.614 -2.5%	0.654 +3.8%
Spleen absolute										
after treatment	0.61	0.63 +3.3%	0.56 -8.2%	0.55 -9.8%	**0.46*** **-24.6%**	0.49	0.45 -8.2%	0.49	0.45 -8.2%	0.44 -10.2%
after recovery	0.59	-	-	0.58 -1.7%	0.62 +5.1%	0.48	-	-	0.51 +6.3%	0.44 -8.3
Spleen relative										
after treatment	0.187	0.191 +2.1%	0.177 -5.3%	0.165 -11.8%	**0.144*** **-23.0%**	0.206	0.189 -8.3%	0.215 +4.4%	0.197 -4.4%	0.193 -6.3%
after recovery	0.163	-	-	0.156 -4.3%	0.175 +7.4%	0.189	-	-	0.202 +6.9%	0.181 -4.2%
Heart absolute										
after treatment	1.26	1.26	1.15 -8.7%	1.11 -11.9%	**1.04*** **-17.5%**	0.93	0.87 -6.5%	0.94 +1.1%	0.90 -3.2%	0.94 +1.1%
after recovery	1.44	-	-	1.28 -11.1%	**1.19*** **-17.4%**	0.93	-	-	0.98 +5.4%	0.94 +1.1%

	Dose group level (mg/kg bw/d)									
	Males					Females				
	0	10	20	100	500	0	10	20	100	500
Heart relative										
after treatment	0.387	0.381 -1.6%	0.363 -6.2%	0.336 -13.2%	**0.325*** **-16.0%**	0.385	0.366 -4.9%	0.407 +5.7%	0.394 +2.3%	0.408 +6.0%
after recovery	0.398	-	-	0.349 -12.3%	**0.334*** **-16.1%**	0.369	-	-	0.391 +6.0%	0.382 +3.5%

* (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 6.3.3-11 Histopathological findings on treated skin area after treatment and recovery, Subchronic dermal toxicity study in rats with Fenoxaprop-P-ethyl

	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:
Repeated dermal exposure led to skin dryness/chapping and fine/coarse scales in some animals among the lower dose groups, while most or all animals were affected at the high dose group. According to Regulation (EC) 1272/2008, these effects would lead to the additional labelling provision with "EUH066-Repeated exposure may cause skin dryness or cracking". 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.

B.6.3.4. Oral 28-day studies with Fenoxaprop-ethyl

B.6.3.4.1. Rat

Reference:	Range-finding-test with Hoe 33171 0H AT203 in a 32-day study with SPF-Wistar-rats
Author(s), year:	[redacted] 1980a
Report/Doc. number:	A26171 / Hoechst Report No. 164/80
Guideline(s):	No guideline is mentioned in the study report. However, the study design is close to OECD Guideline 407.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
Groups of 10 male and 10 female rats received a diet containing 0, 80, 315, 1,250 or 5,000 ppm Fenoxaprop-ethyl for 32 days (the daily test substance intake in mg/kg bw/d is not presented in the study report). Diets were prepared at the beginning of the study and on days 13 and 24 of the experiment. Samples of each preparation were analysed for their content of the test substance.

Test material: fenoxaprop-ethyl, batch Hoe 33171 AT203
Purity: 97 % according to certificate of analysis No. 00792

Test animals: Wistar rat, strain WISKf(SPF71), [redacted]
36-38 days old, 95-98 g (♂) and 89-91 g (♀).
Number of animals: 10 rats per sex per dose

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 haematology the following parameters were assessed: erythrocytes, haemoglobin, haematocrit, 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 urinalysis 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, epididymis, 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 (5,000 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 1,250 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 bristled 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 5,000 ppm dosage group until the time of premature autopsy. At 1,250 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 5,000 ppm dosage group until premature necropsy. A significant reduction in body weight gain was observed in male and female rats of the 1,250 ppm dose group.

Table 6.3.4-1 Food and water consumption, body weight, 32 day feeding study in rats with fenoxaprop-ethyl

	Dose group level (ppm)									
	Males					**Females**				
	0	**80**	**315**	**1,250**	**5,000[1]**	**0**	**80**	**315**	**1,250**	**5,000[1]**
Food consumption[2] (g/100g), days 1 - 33	9.23	9.02 -2.3%	8.87 -3.9%	8.26 -10.26%	3.61[1] -60.9%	9.31	8.64 -7.2%	8.64 -7.2%	7.57 -18.7%	3.24[1] -65.2%
Water consumption[2] (g/100g), day 29	11.83	12.38 +4.6%	12.51 +5.7%	17.36 +46.7%	-[1]	11.99	10.02 -16.4%	12.85 +7.2%	16.17 +34.9%	-[1]
Body weight gain (g)	148	148	134 -9.5%	83* -43.9%	-[1]	74	71 -4.1%	67 -9.5%	**45*** **-39.2%**	-[1]
Terminal body weight (g)	255	261 +2.4%	241 -5.5%	**194*** **-23.9%**	75[1] -70.6%	180	175 -2.8%	170 -5.6%	**148*** **-17.8%**	75[1]

* ($p < 0.05$); 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

Haematology: 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 1,250 ppm; decreased uric acid in females at 315 and 1,250 ppm; decreased potassium in females at 1,250 ppm).

Table 6.3.4-2 Clinical chemistry findings after 32 days, 32 day feeding study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1,250	0	80	315	1,250
Cholesterol (mmol/L)	1.84	**1.36*** **-26.1%**	**1.24*** **-32.6%**	**0.85*** **-53.8%**	1.75	**1.45*** **-17.1%**	**1.39*** **-20.6%**	**1.23*** **-29.7%**
Total lipids (mmol/L)	4.01	3.65 -9.0%	**2.84*** **-29.2%**	**3.06*** **-23.7%**	4.07	3.37 -17.2%	**3.25*** **-20.1%**	**3.23*** **-20.6%**
ALP (U/L)	339	336 -0.9%	360 +6.2%	**415*** **+22.4%**	237	255 +7.6%	267 +12.7%	**325*** **+37.1%**
Phosphorus (mmol/L)	2.79	2.42 -13.3%	**2.06*** **-26.2%**	**1.90*** **-31.9%**	2.18	1.96 -10.1%	2.19 +0.5%	**1.70*** **-22.0%**
Urea nitrogen (mmol/L)	7.74	7.78 +0.5%	8.07 +4.3%	**9.30*** **+20.2%**	8.36	9.42 +12.7%	8.11 -3.0%	7.39 -11.6%
Uric acid (mmol/L)	126	58 -54.0%	68 -46.0%	107 -15.1%	104	109 +4.8%	**64*** **-38.5%**	**75*** **-27.9%**
Potassium (mmol/L)	7.0	6.1 -12.9%	6.6 -5.7%	6.4 -8.6%	6.1	5.6 -8.2%	6.1	**5.3*** **-13.1%**

* ($p<0.05$); 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 1,250 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 1,250 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 6.3.4-3 Organ weight findings after 32 days, 32 day feeding study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Liver weight								
absolute (g)[1]	10.02	10.82 +8.0%	11.99 +19.7%	11.52 +15.0%	7.32	7.19 -1.8%	7.66 +4.6%	8.32 +13.7%
relative (% bw)	3.933	4.147 +5.4%	**4.956*** **+26.0%**	**5.926*** **+50.7%**	4.074	4.119 +1.1%	**4.516*** **+10.8%**	**5.632*** **+38.2%**
Kidney weight								
absolute (g)[1]	1.74	2.25 +29.3%	1.78 +2.3%	1.63 -6.3%	1.19	1.34 +12.6%	1.33 +11.8%	1.20 +0.8%
relative (% bw)	0.683	**0.858*** **+25.6%**	0.739 +8.2%	**0.840*** **+23.0%**	0.666	**0.768*** **+15.3%**	**0.782*** **+17.4%**	**0.818*** **+22.8%**
Brain weight								
absolute (g)[1]	1.99	2.03 +2.0%	1.96 -1.5%	1.89 -5.0%	1.85	1.90 +2.7%	1.89 +2.2%	1.79 -3.2%
relative (% bw)	0.784	0.782	0.816 +4.1%	**0.987*** **+25.9%**	1.034	1.092 +5.6%	1.116 +7.9%	**1.216*** **+17.6%**

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Adrenals weight								
absolute (g)[1]	0.0431	0.0519 +20.4%	0.0402 -6.7%	0.0368 -14.6%	0.0578	0.0503 -13.0%	0.0517 -10.6%	0.0378 -34.6%
relative (% bw)	0.0170	0.0199 +17.1%	0.0167 -1.8%	0.0190 +11.8%	0.0322	0.0288 -10.6%	0.0305 -5.3%	**0.0256*** **-20.5%**
Testes weight								
absolute (g)[1]	2.98	3.07 +3.0%	2.81 -5.7%	2.72 -8.7%				
relative (% bw)	1.173	1.182 +0.8%	1.164 -0.8%	**1.410*** **+20.2%**				

* ($p < 0.05$); 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 1.250 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 5,000 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 (calculated dietary intake based on approximate default conversion factor of 0.118 for males and 0.117 for females according to the EFSA Guidance on selected default values to be used (EFSA Journal 2012;10(3):2579): 9.44 and 9.36 mg/kg bw/day).

B.6.3.4.2. Mouse

B.6.3.4.2.1. 32-days oral study

Reference:	Toxicity test of Hoe 33171 0H AT203 in a 32-day study with SPF-mice
Author(s), year:	[redacted] 1980b
Report/Doc. number:	A26168 / Hoechst Report No. 336/80
Guideline(s):	No guideline is mentioned in the study report. However, the study design is close to OECD Guideline 407.
GLP:	Yes.
Acceptability:	Yes.

10 male and 10 female mice per dose group received a diet containing 0, 80, 315, 1,250 or 5,000 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). Diets were prepared at the beginning of the study and twice during the study at a 14-day interval.

Test material: fenoxaprop-ethyl, batch Hoe 33171 AT203
Purity: 97 % according to certificate of analysis No. 00792

Test animals: NMRI mouse, strain NMRKf, [redacted]
Age not reported, 16-17 g (♂) and 15-16g (♀).
Number of animals: 10 mice per sex per dose

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 haematology the following parameters were assessed: haemoglobin, erythrocytes, haematocrit, 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 urinalysis 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, epididymides, 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, haematocrit and reticulocytes), all clinical chemistry data and relative organ weights.

Findings:
Mortality / Clinical Signs: All animals of the highest dose group (5,000 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 continuous refusal of food. No signs of toxicity were seen in other treatment groups.

Food and water consumption: The relative food consumption, except for the 5,000 ppm dose group was within the normal range of biological variation. The animals in the 5,000 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 5,000 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 6.3.4-4 Food consumption and bodyweight, 32 day feeding study in mice with fenoxaprop-ethyl

	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 -4.0%*	*18.00 -5.0%*	*17.20 -9.2%*	*11.14[1] -41.2%*	*19.14*	*18.59 -2.9%*	*18.62 -2.7%*	*17.82 -6.9%*	*9.27[1] -51.6%*
Body weight gain (g)	15	13 -13.3%	16 +6.7%	14 -6.7%	-[1]	7	8 +14.3%	7	7	-[1]
Terminal body weight (g)	35	33 -5.7%	36 +2.9%	34 -2.9%	**17*[1] -51.4%**	27	26 -3.7%	26 -3.7%	26 -3.7%	**16*[1] -40.7%**

* ($p < 0.05$); 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*

Haematology: Males and females of the 1,250 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 starting from 315 ppm and above. ALAT was increased in males and females at 1,250 ppm while ALP was increased in males at 315 and 1,250 ppm and in females at 1,250 ppm.

Table 6.3.4-5 Relevant haematology and clinical chemistry findings after 32 days, 32 day feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				**Females**			
	0	**80**	**315**	**1,250**	**0**	**80**	**315**	**1,250**
Haematology								

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1,250	0	80	315	1,250
Haemoglobin (g/L)	146	139 -4.8%	141 -3.4%	**134*** **-8.2%**	159	163 +2.5%	156 -1.9%	**152*** **-4.4%**
Clinical chemistry								
ALAT (U/L)	81	74 -8.6%	140 +72.8%	**244*** **201.2%**	76	95 +25.0%	92 +21.1%	**317*** **+317.1%**
ALP (U/L)	198	193 -2.5%	**471*** **+137.9%**	**1,560*** **+687.9%**	282	269 -4.6%	348 +23.4%	1,370* +385.8%

* (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 6.3.4-6 Relevant organ weight findings after 32 days, 32 day feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Liver weight *absolute (g)*[1]	*2.11*	*2.16* +2.4%	*3.63* +72.0%	*5.62* +166.4%	*1.39*	*1.64* +18.0%	*2.14* +54.0%	*3.73* +168.3%
relative (% bw)	6.02	6.47 +7.5%	**10.17*** **+68.9%**	16.43* +172.9%	5.24	**6.26*** **+19.5%**	**8.39*** **+60.1%**	**14.31*** **+173.1%**
Kidney weight *absolute (g)*[1]	*0.54*	*0.50* -7.4%	*0.54*	*0.55* +1.9%	*0.33*	*0.36* +9.1%	*0.36* +9.1%	*0.37* 12.1%
relative (% bw)	1.55	1.50 -3.2%	1.52 -1.9%	1.62 +4.5%	1.26	1.36 +7.9%	**1.40*** **+11.1%**	**1.42*** **+12.7%**

* (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 5,000 ppm dose group which were killed prematurely showed the same findings with additional necrosis of the hepatocytes and Kupffer cell proliferation. Effects on kidneys were observed in females only and started at a dose level of 315 ppm. Tubular cell necrosis 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 1,250 ppm.

Table 6.3.4-7 Microscopic findings after 32 days, 32 day feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Liver:								
isolated Kupffer cell proliferates and/or infiltrates in the periportal regions[1)]	2/10	3/10	7/10	2/10	4/10	4/10	8/10	4/10
isolated necroses	0/10	1/10	8/10		0/10	0/10	1/10	
Kidney:								
Dilation of one renal pelvis	1/10	0/10	1/10	0/10	0/10	0/10	0/10	0/10
Focal tubular atrophies	3/10	5/10	5/10	2/10	2/10	3/10	4/10	1/10

	Dose group level (ppm)							
	Males				Females			
	0	80	315	1250	0	80	315	1250
Isolated focal tubular dilatation	1/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Necroses of tubular cells or cells showing large nucleus and basophilous cytoplasm in internal renal cortex	0/10	0/10	0/10	0/10	0/10	0/10	0/10	7/10

[1)] not observed in the control groups

Conclusion:
Fenoxaprop-ethyl demonstrated excessive toxicity at 5,000 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.

B.6.3.4.2.2. 30-days oral study

Reference:	Toxicity test of Hoe 33171 0H AT204 in a 30-day study with SPF-mice
Author(s). year:	[redacted] 1981
Report/Doc. number:	A26169 / Hoechst Report No. 356/81
Guideline(s):	No guideline is mentioned in the study report. However, the study design is close to OECD guideline 407.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
10 male and 10 female mice 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). Diets were prepared at the beginning of the study and twice during the study at a 14-day interval.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity: 96% according to certificate of analysis No. 01514

Test animals: NMRI mice, strain NMRKf, [redacted]
Age not reported, 15-17 g (♂) and 14-17 g (♀).
Number of animals: 10 rats per sex per dose
+ 10 animals per sex per dose for reversibility study

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 haematology the following parameters were assessed: haemoglobin, erythrocytes, haematocrit, 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 urinalysis 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, epididymis, 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, haematocrit 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.

Haematology: 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 6.3.4-8 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 +6.4%	2.87 +14.3%	2.89 +15.1%	2.91 +15.9%	1.95	1.92 -1.5%	1.99 +2.1%	2.17 +11.3%	**3.14*** **+61.0%**
Total lipids (g/L)	6.92	7.28 +5.2%	7.34 +6.1%	**7.86*** **+13.6%**	**8.29*** **+19.8%**	5.37	5.16 -3.9%	4.84 -9.9%	5.68 +5.8%	5.57 +3.7%

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 6.3.4-9 Relevant organ weight findings after 30 days, 30 day feeding study in mice with fenoxaprop-ethyl

	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 -11.2%	1.83 +2.2%	1.70 -5.0%	2.23 -24.6%	1.39	1.40 +0.7%	1.41 +1.4%	1.60 +15.1%	1.65 +18.7%
relative (% bw)	5.338	5.323	5.457 +2.2%	5.178 -3.0%	**6.507*** **-21.9%**	5.049	5.177 +2.5%	4.997 -1.0%	5.631* +11.5%	**5.911*** **+17.1%**

* ($p < 0.05$); 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 in the 20 ppm group showed slight enlargement of the epithelia with large nuclei and dense eosinophil cytoplasm in the centrilobular 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).

B.6.3.4.3. Dog

Reference:	Repeated-dose (30 days) oral toxicity study of Hoe 33171 0H AT203 in Beagle dogs (range-finding test)
Author(s), year:	[redacted].; 1980
Report/Doc. number:	A25657 / Hoechst Report No. 165/80 A32691 (Supplement to Document No A25657; [redacted], 1986) A35547 (Amendment to Hoechst Report No. 165/80; [redacted] 1987)
Guideline(s):	-
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.
Acceptability:	This study is considered of supplementary information only.

Material and Methods:
2 dogs per sex per dose group were given Fenoxaprop-ethyl in the diet for 30 days. The concentrations in the food were 0, 80, 400 or 2,000 ppm (the actual test substance intake was not presented in the test report). As there were only a few animals in trial, no detailed calculations or statistical analyses were conducted.

Test material: fenoxaprop-ethyl, batch Hoe 33171 AT203
Purity: 97.0 % according to certificate of analysis No. 00792

Test animals: Beagle dog, strain BEAK, [redacted]
Avg. 14 months old, 12.9-15.2 kg (♂) and 10.5-13.9 kg (♀).
Number of animals: 2 dogs per sex per dose

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.
Haematological examinations consisted of haemoglobin, erythrocyte count, leucocyte count, haematocrit, 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-haemoglobin, 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.
Organ weights were determined for 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, epididymis, uterus, prostate, stomach (fundus and pre-pyloric region), jejunum, colon, gall bladder, lymph nodes (superficial, cervical 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 diarrhoea, 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 initial status.

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

Haematology, clinical chemistry and 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, haematocrit, 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 2,000 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 above, those at 2,000 ppm were distinctly above the adrenal weights in control and 80 ppm groups.

Macroscopic examination: All animals of the 2,000 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 haemorrhages. 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 2,000 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, haemorrhages 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 2,000 ppm. No clear effects could be observed at lower dose levels.

B.6.3.5. Oral 90-day studies with Fenoxaprop-ethyl

B.6.3.5.1. Rat

Reference:	Repeated-dose (3 months) oral toxicity study of the active substance Hoe 33171 (Code: Hoe 33171 0H AT204) administered in the feed to rats
Author(s). year:	[redacted] 1981
Report/Doc. number:	A35788 / Hoechst Report No. 695/81 Supplement to Report No. 695/81, [redacted] 1986, Doc No. A32697 Addendum to Report No. 695/81, [redacted] 1986, Doc No. A32985
Guideline(s):	No guideline is mentioned in the study report. However, the study design is close to OECD guideline 408.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Groups of 30 male and 30 female rats 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 per sex in the control and treatment groups over a 4-week observation period. Diets were prepared at 14-day intervals. The stability and homogeneity of the test substance in the diet were controlled by analytical examinations.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity: 96% according to certificate of analysis No. 01514

Test animals: Wistar rat, strain WISKf(SPF 71), Hoechst
5weeks old, mean bw 128g (♂) and 121 g (♀).
Number of animals: 30 rats per sex per dose
+ 10 animals per sex per dose for reversibility study

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.
Haematological 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: haemoglobin, erythrocytes, haematocrit, MCV, MCH, MCHC, reticulocytes, Heinz bodies, leukocytes, thrombocytes, coagulation time and differential blood count.
Clinical chemistry was performed in 10 non-fasted rats per sex per group prior to the beginning of the study and at week 6, while the final values at week 13 were determined from 20 rats per sex per 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 were 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, oesophagus, stomach (fundus and pre-pyloric region), intestine (duodenum, jejunum, ileum, caecum, colon, rectum), urinary bladder, prostate, epididymides, uterus, pancreas, abdominal aorta, diaphragm, eyes with optic nerves, skeletal muscle, marrow of the femur, 1st lumbar vertebra, lymph nodes (hilum and iliacus), skin with mammary gland, tumours (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.

Haematology: 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 6.3.5-1 Relevant haematology and clinical chemistry findings after 3 months (final values), 3 months feeding study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	20	80	320	0	20	80	320
Haematology								
Haemoglobin (g/L)	166	158 -4.8%	157 -5.4%	**154*** **-7.2%**	156	156	152 -2.6%	149 -4.5%
Erythrocytes (10^{12}/L)	8.35	8.14 -2.5%	8.07 -3.4%	**7.75*** **-7.2%**	7.70	7.88 +2.3%	7.50 -2.6%	7.44 -3.4%
Clinical chemistry								
Cholesterol (mmol/L)	2.07	1.86 -10.1%	**1.63*** **-21.3%**	**1.68*** **-18.8%**	1.76	1.65 -6.3%	1.62 -8.0%	**1.51*** **-14.2%**
Total lipids (g/L)	3.55	3.19 -10.1%	3.41 -3.9%	3.28 -7.6%	5.02	**4.27*** **-14.9%**	3.67* -26.9%	3.61* -28.1%
ALP (U/L)	254	248 -2.4%	251 -1.2%	**302*** **+18.9%**	184	174 -5.4%	171 -7.1%	178 -3.3%

* (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 marginally elevated in males at 320 ppm but not in females. 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 6.3.5-2 Relevant Organ weight findings after 3 months, 3 months feeding study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	20	80	320	0	20	80	320
Liver weight								
absolute (g)[1]	*12.91*	*12.33* +4.5%	*12.84* -0.5%	*14.81* +15.5%	*7.28*	*7.03* -3.4%	*7.15* -1.8%	*7.39* +1.5%
relative (% bw)	3.080	3.033 -1.5%	3.083	**3.558*** **+15.5%**	3.190	3.221 +1.0%	3.151 -1.2%	3.257 +2.1%
Kidney weight								
absolute (g)[1]	*2.42*	*2.37* -2.1%	*2.45* +1.2%	*2.65* +9.5%	*1.49*	*1.46* -2.0%	*1.55* +4.0%	*1.57* +5.4%
relative (% bw)	0.579	0.583 +0.7%	0.589 +1.7%	**0.641*** **+10.7%**	0.653	0.666 +2.0%	0.683 +4.6%	**0.694*** **+6.3%**
Adrenals weight								
absolute (g)[1]	*0.0552*	*0.0531* -3.8%	*0.0573* +3.8%	*0.0596* +8.0%	*0.0629*	*0.0669* +6.4%	*0.0722* +14.8%	*0.0749* +19.1%
relative (% bw)	0.0133	0.0131 -1.5%	0.0138 +3.8%	0.0143 +7.5%	0.0277	0.0305 +10.1%	**0.0319*** **+15.2%**	**0.0331*** **+19.5%**
Thyroid weight								
absolute (g)[1]	*0.0197*	*0.0211* +7.1%	*0.0223* +13.2%	*0.0238* +20.8%	*0.0145*	*0.0153* +5.5%	*0.0163* +12.4%	*0.0160* +10.3%
relative (% bw)	0.0047	0.0052 +10.6%	0.0054 +14.9%	**0.0057*** **+21.3%**	0.0064	0.0071 +10.9%	0.0072 +12.5%	0.0071 +10.9%

* (p< 0.05); significantly different from control

[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).

B.6.3.5.2. Mouse

Reference:	Hoe 33171, substance technical. Subchronic oral toxicity (13-week range finding feeding study) in the NMRI mice
Author(s). year:	[redacted] 1993a
Report/Doc. number:	A50244 / Hoechst Report No. 93.0157
Guideline(s):	EPA guideline 82-1 (1984), MAFF Guidelines (1985), OECD guideline 408 (1981)
Deviations to OECD Guideline 408 (1998):	Limited histopathology, clinical chemistry and organ weight analysis.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
20 mice per sex and dose group received a diet containing 0, 320, 640 or 1,280 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. Diets were prepared before and 3 times during the study period, with the stability of the test substance guaranteed for 30 days.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H ZD96 0005
Purity: 96.8% according to the certificate of analysis No. 04663 (1991)

Test animals: NMRI mice, strain NMRKf, [redacted]
Approx. 4 weeks old, mean bw of 24.3 g (♂) and 21.7 g (♀).
Number of animals: 20 rats per sex per dose

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 haematology the following parameters were assessed: erythrocytes, haemoglobin, haematocrit, 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, bone marrow (femur with knee-joint), aorta, parotid gland, submandibular gland, cervical/iliac lymph nodes, oesophagus and trachea, epididymides, dia-

phragm, 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 1,280 ppm 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 6.3.5-3 Body weights and body weights minus liver weights after 3 months, 3 months feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Terminal body weight (g)	35.9	37.2 +3.6%	39.7* +10.6%	38.9* +8.4%	28.7	29.0 +1.0%	30.7* +7.0%	31.5* +9.8%
Terminal body weight (g) minus liver weight	34.5	34.6	36.1 +4.6%	33.7 -2.3%	27.6	27.3 -1.1%	28.3 +2.5%	28.2 +2.2%

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

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

Haematology: Some haematological findings were observed which did not follow a clear dose-relationship. A treatment related effect (impaired liver erythropoiesis) could not be excluded in view of the severe liver toxicity seen in this study. Reticulocytes and MCV were increased in males at 1,280 ppm and females at 320 ppm and above. In females, erythrocytes (320 ppm and above) and thrombocytes (1,280 ppm) were decreased, while leucocytes were increased (640 and 1,280 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 1,280 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 1,280 ppm and in females at 320, 640 and 1,280 ppm), ASAT (decreased in males at 320 ppm and increased in females at 1,280 ppm), ALAT (increased in males at 640 ppm, 1,280 ppm not evaluable, and increased in females at 1,280 ppm) and ALP (increased in males at 640 and 1,280 ppm and in females at 1,280 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 6.3.5-4 Relevant haematology and clinical chemistry findings after 3 months, 3 months feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Haematology								

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Reticulocytes (U)	0.029	0.033 +13.8%	0.032 +10.3%	**0.042*** **+44.8%**	0.023	0.030* +30.4%	**0.033*** **+43.5%**	**0.032*** **+39.1%**
Erythrocytes (10^{12}/L)	9.68	9.67	9.81 +1.3%	9.53 -1.5%	9.79	**9.37*** **-4.3%**	**9.39*** **-4.1%**	**9.40*** **-4.0%**
MCV (10^{-15}l)	48	49 +2.1%	49 +2.1%	**50*** **+4.2%**	49	**50*** **+2.0%**	**51*** **+4.1%**	**51*** **+4.1%**
Thrombocytes (10^{9}/L)	777	859 +10.6%	771 -0.8%	751 -3.3%	746	811 +8.7%	745	**669*** **-10.3%**
Leucocytes (10^{9}/L)	6.6	8.0 +21.2%	8.8 +33.3%	6.6	6.0	6.3 +5.0%	**8.6*** **+43.3%**	8.0* +33.3%
Clinical chemistry								
Bilirubin (µmol/L)	21.6	**9.9*** **-54.2%**	**7.0*** **-67.6%**	**8.6*** **-60.2%**	11.7	**7.9*** **-32.5%**	9.9 -15.4%	**7.8*** **-33.3%**
Triglycerides (mmol/L)	0.93	1.09 +17.2%	**1.27*** **+36.6%**	**1.28*** **+37.6%**	0.85	[1]	[1]	[1]
Total protein (g/L)	49	50 +2.0%	**54*** **+10.2%**	**56*** **+14.3%**	[1]	[1]	[1]	[1]
Albumin (g/L)	25.3	24.4 -3.6%	28.2 +11.5%	**30.2*** **+19.4%**	24.6	**28.6*** **+16.3%**	**28.4*** **+15.4%**	**30.2*** **+22.8%**
ASAT (U/L)	276	**115*** **-58.3%**	184 -33.3%	328 +18.8%	91	108 +18.7%	105 +15.4%	**223*** **+145.1%**
ALAT (U/L)	70	45 -35.7%	**307*** **+338.6%**	[1]	38	41 +7.9%	71 +86.8%	**286*** **+652.6%**
ALP (U/L)	112	153 +36.6%	**655*** **+484.8%**	**833*** **+643.8%**	118	146 +23.7%	221 +87.3%	**711*** **+502.5%**

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

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 1,280 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 1,280 ppm; decreased relative brain weight in males and females at 640 and 1,280 ppm; decreased relative ovaries weight at 1,280 ppm).

Table 6.3.5-5 Organ weight findings after 3 months, 3 months feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Liver weight								
absolute (g)	1.394	**2.559*** **+83.6%**	**3.636*** **+160.8%**	**5.166*** **+270.6%**	1.143	**1.727*** **+51.1%**	**2.364*** **+106.8%**	**3.332*** **+191.5%**
relative (% bw)	3.885	**6.887*** **+77.3%**	**9.158*** **+135.7%**	**13.265*** **+241.4%**	3.985	**5.958*** **+49.5%**	**7.684*** **+92.8%**	**10.604*** **+166.1%**
Kidneys weight								
absolute (g)	0.470	0.493 +4.9%	**0.552*** **+17.4%**	**0.537*** **+14.3%**	0.327	**0.367*** **+12.2%**	**0.393*** **+20.2%**	**0.400*** **+22.3%**
relative (% bw)	1.308	1.325 +1.3%	1.389 +6.2%	1.381 +5.6%	1.138	**1.268*** **+11.4%**	**1.279*** **+12.4%**	**1.272*** **+11.8%**
Spleen weight								
absolute (g)	0.133	0.146 +9.8%	0.147 +10.5%	**0.163*** **+22.6%**	0.127	0.126 -0.8%	0.126 -0.8%	0.138 +8.7%
relative (% bw)	0.371	0.392 +5.7%	0.369 -0.5%	**0.421*** **+13.5%**	0.443	0.435 -1.8%	0.409 -7.7%	0.438 -1.1%

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Adrenals weight								
absolute (g)	0.0054	**0.0077*** **+42.6%**	**0.0083*** **+53.7%**	**0.0095*** **+75.9%**	0.0128	0.0117 -8.6%	0.0121 -5.5%	0.0129 +0.8%
relative (% bw)	0.0150	**0.0207*** **+38.0%**	**0.0208*** **+38.7%**	**0.0247*** **+64.7%**	0.0447	0.0405 -9.4%	0.0395 -11.6%	0.0409 -8.5%

* (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 1,280 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 6.3.5-6 Relevant histopathological findings after 3 months, 3 months feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	320	640	1280	0	320	640	1280
Liver								
- centrilobular hypertrophy	-	20/20	20/20	1/20	-	20/20	5/20	-
- diffuse hypertrophy	-	-	-	19/20	-	-	15/20	20/20
- single cell necrosis	3/20	16/20	20/20	20/20	4/20	6/20	18/20	20/20
- mitoses increased	-	-	19/20	20/20	-	3/20	10/20	18/20
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 6.3.5-7 Special biochemical investigations from liver samples after 3 months, 3 months feeding study in mice with fenoxaprop-ethyl

	Dose group level (ppm)

	Males				Females			
	0	**320**	**640**	**1,280**	**0**	**320**	**640**	**1,280**
Catalase (R/mg)	9.29	**46.26*** **+398.0%**	**40.60*** **+337.0%**	**48.94*** **+426.8%**	8.06	**30.73*** **+281.3%**	**45.57*** **+465.4%**	**42.52*** **+427.5%**
Malic enzyme (U/kg)	781	**1023*** **+31.0%**	**1153*** **+47.6%**	**1160*** **+48.5%**	878	971 +10.6%	**1267*** **+44.3%**	**1483*** **+68.9%**
Lactate dehydrogenase (U/g)	119	119	**137*** **+15.1%**	**174*** **+46.2%**	106	**132*** **+24.5%**	**158*** **+49.1%**	**175*** **+65.1%**
Glycerophosphate dehydrogenase (U/g)	10.9	10.6 -2.8%	**13.7*** **-25.7%**	**18.4*** **+68.8%**	9.2	**13.2*** **+43.5%**	**14.5*** **+57.6%**	**22.1*** **+140.2%**
Glutathione (mg/g)	0.20	**0.24*** **+20.0%**	**0.28*** **+40.0%**	**0.31*** **+55.0%**	0.24	**0.17*** **+29.2%**	**0.18*** **-25.0%**	**0.29*** **+20.8%**
Pentylresorufin O-depentylase (U/kg)	55.2	**38.9*** **-29.5%**	**43.3*** **-21.6%**	**72.3*** **+31.0%**	123.2	**90.2*** **-26.8%**	**66.0*** **-46.4%**	**69.0*** **-44.0%**

* ($p < 0.05$); 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 macrocytic 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.

B.6.3.5.3. Dog

Reference:	Repeated-dose (3-month) oral toxicity study of Hoe 33171 0H AT204 in dogs
Author(s). year:	[redacted] 1981a
Report/Doc. number:	A24131 / Hoechst Report No. 674/81 Supplement to Doc. No. A324131, Brunk, 1986, A32690
Guideline(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 409.
Deviation:	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 the study.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
6 male and female Beagle dogs per dose were fed diets containing 0, 16, 80 or 400 ppm Fenoxaprop-ethyl for 3 months (test substance intake was not reported, but provided in the Addendum Vol.3 rev. 2 in August 2007). Calculation of dose rates were based on food consumption of 1.0/0.8 kg daily for male/females, and the fact that no effect on food consumption was observed and the offered daily feed ration was completely eaten for all animals. Considering the terminal bodyweight as worst case, dose rates were calculated to be 1.2, 5.4 and 28.2 mg/kg/d, and, 1.0, 4.9 and 25.6 mg/kg/d for male and female animals, respectively. 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.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity: 96% according to certificate of analysis No. 01514

Test animals: Beagle dogs, strain BEAK, [redacted]
11 months old, bw of 10.9-14.9 kg (♂, mean 12.9) and 10.0-15.2 kg (♀, mean 11.7).
Number of animals: 6 dogs per sex per dose

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 (flexor, patellar, anal, cutaneous, corneal, pupillary and blink reflexes, and of placing, righting reflexes), 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, haematocrit, 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, methaemoglobin (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, colour, 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.
Organs weights were recorded for 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), oesophagus, trachea, aorta (thoracic), diaphragm, skeletal muscle (psoas) and skin with mammary gland.
Statistical evaluation was performed on haematological and clinical chemistry values and the relative organ weights, except the following: differential blood count, Heinz bodies, methaemoglobin, 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.

Behaviour and neurological condition: Unremarkable behaviour and no changes in reflex excitability and postural reactions were observed.

Haematology, 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 statistically significant change observed was an increase in relative pituitary weight in males receiving 400 ppm. The relevance of this finding is not clear. Biologically significant but not dose-related

changes were observed most profoundly for the following: absolute and relative liver weight, absolute kidney weight, absolute and relative ovary weights as well as relative thyroid weights in all dose groups in females, and absolute pituitary weights in males.

Table 6.3.5-8 Organ weights after 13 weeks, 3 months feeding study in dogs with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	16	80	400	0	16	80	400
Liver weight								
absolute (g)[1]	*538*	*547* *+1.7*	*512* *-4.8*	*522* *-3.0*	*389*	*510* *+31.1*	*504* *+29.6*	*459* *+18.0*
Relative (%bw)	3.703	3.989 +7.7%	3.473 -6.2%	3.671	3.345	4.028 +20.4%	3.876 +15.9%	3.691 +10.3%
Kidney weight								
absolute (g)[1]	*62.5*	*60.7* *-2.9%*	*62.2* *-0.5%*	*65* *+4.0%*	*47.5*	*56.5* *+18.9%*	*55* *+15.8%*	*52.2* *+9.9%*
Relative (%bw)	0.432	0.445 +3.0%	0.422 -2.3%	0.458 +6.0%	0.408	0.445	0.424 +3.9%	0.420 +2.9%
Spleen								
absolute (g)[1]	*56*	*43.5* *-22.3%*	*52.2* *-6.8%*	*32.5* *-42.0%*	*47.5*	*40.5* *-14.7%*	*47* *-1.1%*	*35.7* *-24.8%*
Relative (%bw)	0.393	0.314 -20.1%	0.353 -10.2%	0.228 -42.0%	0.408	0.319 -21.8%	0.368 -9.8%	0.285 -30.1%
Testis / Ovaries								
absolute (g)[1]	*21*	*24* *+14.3%*	*21.2*	*21*	*915*	*1419* *+55.1%*	*1552* *+69.6%*	*1203* *+31.5%*
Relative (%bw)	0.1450	0.1760 +21.4%	0.1440	0.1480	0.0079	0.0113 +43.0%	0.0119 +50.6%	0.0098 +24.1%
Adrenals								
absolute (g)[1]	*1175*	*1216* *+3.5%*	*1276* *+8.6%*	*1028* *-12.5%*	*1190*	*1250* *+5.0%*	*1105* *-7.1%*	*1136* *-4.5%*
Relative (%bw)	0.0081	0.0089 +9.9%	0.0087 +7.4%	0.0072 -11.1%	0.0102	0.0098 -3.9%	0.0085 -16.7%	0.0092 -9.8%
Thyroid								
absolute (g)[1]	*652*	*693* *+6.3%*	*689* *+5.7%*	*778* *+19.3%*	*781*	*669* *-14.3%*	*754* *-3.5%*	*652* *-16.5%*
Relative (%bw)	0.0045	0.0051 +13.3%	0.0047 +4.4%	0.0055 +22.2%	0.0067	0.0053 -20.9%	0.0058 -13.4%	0.0053 -20.9%
Pituitary weight								
absolute (g)[1]	*60*	*92* *+53.3%*	*82* *+36.7%*	*105* *+75.0%*	*81*	*83* *+2.5%*	*79* *-2.5%*	*87* *+7.4%*
relative (% bw)	0.0004	0.0007 +75.0%	0.0006 +50.0%	**0.0007*** **+75.0%**	0.0007	0.0007	0.0006 -14.3%	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 of 4 males from the main group and in 1 of 2 males after recovery, and at 400 ppm in 3 of 4 males and 3 of 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, equivalent to 1.2 and 1.0 mg/kg bw/d for males and females.

B.6.3.6. 1-year dog study with fenoxaprop-ethyl

Reference:	Toxicological testing of Hoe 33171 – active ingredient technical by repeated oral administration to beagle dogs for one year
Author(s). year:	[redacted].; 1984
Report/Doc. number:	A29692 / Hoechst Report No. 84.0437
Guideline(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 452 (1981).
Deviation:	Animals were 14 months of age. Urine volume and some clinical chemistry values (gamma glutamyl transpeptidase, ornithine decarboxylase, and albumin concentration) were not performed. At histopathology, spinal cord (cervical, thoracic, lumbar) and parathyroids were not assessed.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
6 male and 6 female dogs per dose group received diets containing 0, 3, 15 or 75 ppm Fenoxaprop-ethyl for 1 year (test substance intake was not reported, but provided in the Addendum Vol.3 rev. 2 in August 2007). Calculation of dose rates were based on food consumption of 1.0/0.8 kg daily for male/females, and the fact that no effect on food consumption was observed and the offered daily feed ration was completely eaten for all animals. Considering the mean bodyweight (between initial and terminal bodyweight), dose rates were calculated to be 0.2, 1.0 and 5.0 mg/kg/d, and, 0.2, 0.8 and 4.4 mg/kg/d for male and female animals, respectively. 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.

Test material:	fenoxaprop-ethyl, batch Hoe 33171 0H ZC94 0001
Purity:	94 % according to certificate of analysis dated 27 April 1982
Test animals:	Beagle dogs, strain BEAK, [redacted] 14 months old, mean bw of 14.1 kg (♂) and 12.5 kg (♀).
Number of animals:	6 dogs per sex per dose

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 (flexor, patellar, anal, cutaneous, corneal, pupillary and blink reflexes, visual and tactile placing, righting reactions), 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, haematocrit, 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, 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, colour, 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 pre-pyloric region), duodenum, jejunum, ileum, cecum, colon, rectum, gall bladder, tonsils, salivary glands (parotid and submandibular), lymph nodes (cervical and iliac), oesophagus, 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, haematocrit, 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, cholesterol, 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, statistically significant increases in body weights were observed in one male at each 15 ppm and 75 ppm. However, these increases did not exceed 10% and thus, were not considered of biological significance. Strong reductions in bodyweight gain were observed in males, while females had higher bodyweight gains at the high dose only. In both cases however the effects were not dose-related.
No substance-related changes were noted regarding behaviour, ophthalmoscopy, hearing, teeth and visible mucous membranes.

Table 6.3.6-1 Bodyweight data, Repeated oral administration to beagle dogs for one year

	Dose group level in ppm (mg/kg bw/d)							
	Males				Females			
	0	3 (0.2)	15 (1)	75 (5)	0	3 (0.16)	15 (0.8)	75 (4)
Body weight (kg)	15.1±0.9	14.9±1.1 -1.3%	15.8±0.8 +4.6%	15.8±0.9 +4.6%	13.8±1.5	14.3±0.5 +3.6%	15.1±1.4 +9.4%	14.6±1.2 +5.8%
Body weight gains (kg)[b]	1.98	0.95 -52%	0.74 -62.6%	1.33 -32.8%	1.8	1.98 +10%	1.65 -8.3%	2.32 +28.9%

Neurological examination: no adverse changes in reflex excitability and postural reactions were detected.

Haematology, clinical chemistry and urinalysis: At the beginning and throughout the study various statistical significances 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. However, dose-related changes were observed for females, where a decrease of triglycerides and an increase in total lipids was observed.

Table 6.3.6-2 Relevant clinical parameter, Repeated oral administration to beagle dogs for one year

	Males				Females			
	Control	3	15	75	Control	3	15	75
Cholesterin (mmol/L)	4.03	3.95 -2.0%	4.04 +0.3%	3.78 -6.2%	4.13	4.89 +18.4%	6.79 +64.4%	5.15 +24.7%
Triglycerides (mmol/L)	0.95	0.4 -57.9%	0.25 -73.7%	0.31 -67.4%	0.6	0.53 -11.7%	0.48 -20.0%	0.46 -23.3%
Total Lipids (g/L)	6.41	6.07 -5.3%	6.96 +8.6%	5.77 -10.0%	6.22	6.54 +5.1%	7.18 +15.4%	7.38 +18.7%

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. However, biologically relevant and dose-related changes were detected in the relative adrenal weight (decrease) and in the absolute and relative uterus weight (increase) in females, and the relative prostate weight (decrease) in males.

Table 6.3.6-3 Organ weights after 1 years, Repeated oral administration to beagle dogs for one year

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Brain weight	79.5	87.2 +9.7%	87.4 +9.9%	87.0 +9.4%	79.8	78.8	80.7	80.8
Liver weight absolute (g)[1]	468	501 +7.1%	495 +5.8%	525 +12.2%	469	405 -13.6%	504 +7.5%	490
Relative (%bw)	3.11	3.35 +7.7%	3.13	3.32 +6.8%	3.40	2.83 -16.8%	3.40	3.37
Spleen absolute (g)[1]	54.8	67.7 +23.5	61.2 +11.7	36.0 -34.3%	45.7	65.8 +44.0%	48.0 +5.0%	72.2 +58.0%
Relative (%bw)	0.364	0.459 +26.1%	0.388 +6.6%	0.228 -37.4%	0.330	0.459 +39.1%	0.321 -2.7%	0.496 +50.3%
Thymus absolute (g)[1]	7.3	5.0 -31.5%	4.4 -39.7%	4.5 -38.4%	6.2	5.8 -6.5%	9.2 +48.4%	7.2 +16.1%
Relative (%bw)	0.048	0.033 -31.3%	0.028	0.029 -39.6%	0.044	0.041	0.060 +36.4%	0.049 +11.4%
Pancreas absolute (g)[1]	31.7	30.2 -4.7%	34.6 +9.1%	39.7 +25.2%	31.3	29.5 -5.8%	36.2 +15.7%	29.2 -6.7%
Relative (%bw)	0.210	0.203 -3.3%	0.218 +3.8%	0.251 +19.5%	0.229	0.205 -10.5%	0.241 +5.2%	0.201 -12.2%
Adrenals absolute (g)[1]	1171	1183 +1.0%	1380 +17.8%	1251 +6.8%	1372	1337 -2.6%	1231 -10.3%	1163 -15.2%
relative (% bw)	0.0078	0.0080	0.0087 +11.5%	0.0079	0.0101	0.0093 -7.9%	0.0082 -18.8%	0.0080 -20.8%
Relative (%brain weight)								
Thyroid absolute (g)[1]	581	801 +37.9%	788 +35.6%	834 +43.5%	777	650 -16.3%	823 +5.9%	790 +1.7%
relative (% bw)	0.0039	0.0054 +38.5%	0.0050 +28.2%	0.0053 +35.9%	0.0057	0.0045	0.0055	0.0054
Pituitary absolute (g)[1]	87	86	87	100 +14.9%	89	88	88	84 -5.6%
relative (% bw)	0.0006	0.0006	0.0006	0.0006	0.0007	0.0006	0.0006	0.0006
Prostate / Uterus absolute (g)[1]	18.7	17.0 -9.1%	17.0 -9.1%	16.2 -13.4%	7.5	9.3 +24.0%	17.2 +129.3%	17.8 +137.3%
relative (% bw)	0.123	0.115 -6.5%	0.108 -12.2%	0.103 -16.3%	0.055	0.066 +20.0%	0.117 +112.7%	0.126 +129.1%
Ovaries absolute (g)[1]					1079	1063 -1.5%	1596 +47.9%	1710 +58.5%
relative (% bw)					0.0078	0.0074 -5.1%	0.0109 +39.7%	0.0120 +53.8%

No statistical significances were detected

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:

Biologically relevant organ weight changes were observed starting from the mid dose, however due to the high variability no statistical significances were detected. The NOAEL is thus considered to be 75 ppm, equivalent to 5 and 4 mg/kg bw/day in males and females, respectively.

The applicant submitted a position paper in response to RMS' comment on the abovementioned effects, which is summarized in the following section.

B.6.3.6.1. Position Paper

Reference:	**Fenoxaprop-P-ethyl, AE F046360 – Response to a request of the RMS Austria within the EU-re-approval process**
Author(s). year:	Bomann W., 2017
Report/Doc. number:	
Acceptability:	Yes

RMS Austria had the following comment: '*Due to effects observed in the thyroid weight in males, and, the weights of ovaries and uterus in females in the 2-year and 1-year dog studies, the setting of NOAEL values should be reconsidered. Attached please find the relevant tables from studies A31854 and A29692.*

We would appreciate historical control data and further information about the stated shortcomings – could you please elaborate more on inadequate exsanguinations, and how the oestrus phase might have an effect on the weights of ovaries and uterus?

In addition to the highly altered lipid metabolism seen in most of the studies, these are also effects that concern ED-related organs.

Therefore argumentation on ED properties of this substance would be helpful later for the peer-review.'

A question was also raised on available ToxCast and Tox21 Activity Data.

These questions and comments are addressed in this paper. For clarity, only the section regarding the 1-year dog study is summarized here.

Organ weight effects in the 1-year dog study

This 1-year dog toxicity study was conducted with the same doses and approximately at the same time period as the 2-year study (November 1982-November 1983). The following table gives an overview of the body weights, body weight gains, and the organ weights of the thyroids, ovaries, uterus and pituitary.

Table 6.3.6-4 Body weights and selected endocrine organ weights in the 1-year dog study, (Brunk, R.; Weigand, W.; Kramer, M.; 1984; 29692)

Organ[a] weights (% changes vs. control in brackets)	**Dose group level in ppm (mg/kg bw/d)**							
	Males				**Females**			
	0	**3 (0.2)**	**15 (1)**	**75 (5)**	**0**	**3 (0.16)**	**15 (0.8)**	**75 (4)**
Body weight (kg)	15.1±0.9	14.9±1.1 (-1.3%)	15.8±0.8 (+4.6%)	15.8±0.9 (+4.6%)	13.8±1.5	14.3±0.5 (+3.6%)	15.1±1.4 (+9.4%)	14.6±1.2 (+5.8%)
Body weight gains (kg)[b]	1.98	0.95 (-52%)	0.74 (-62.6%)	1.33 (-32.8%)	1.8	1.98 (+10%)	1.65 (-8.3%)	2.32 (+28.9%)
Thyroid weight absolute (mg)	581±63	801±88 (+37.9%)	788±76 (+35.6%)	834±257 (+43.5%)	777±92	650±92 (-16.3%)	823±142 (+5.9%)	790±208 (+1.7%)

Organ[a] weights (% changes vs. control in brackets)	Dose group level in ppm (mg/kg bw/d)							
	Males				Females			
	0	3 (0.2)	15 (1)	75 (5)	0	3 (0.16)	15 (0.8)	75 (4)
Thyroid weight relative (% BW)	0.0039±0.0005	0.0054±0.0005 (+38.5%)	0.0050±0.0005 (+28.2%)	0.0053±0.0017 (+35.9%)	0.0057±0.0006	0.0045±0.0005 (-21.1%)	0.0055±0.0009 (-3.5%)	0.0054±0.0011 (-5.3%)
Pituitary weight absolute (mg)	87±15	86±12 (-1.2%)	87±6 (0%)	100±16 (+14.9%)	89±11	88±29 (-1.1%)	88±9 (-1.1%)	84±13 (-5.6%)
Pituitary weight relative (% BW)	0.0006±0.0001	0.0006±0.0001	0.0006±0.0000	0.0006±0.0001	0.0007±0.0001	0.0006±0.0002	0.0006±0001	0.0006±0.0001
Ovary weight absolute (mg)					1079±138	1063±231 (-1.5%)	1596±482 (+47.9%)	1710±928 (+58.5%)
Ovary weight relative (% BW)					0.0078±0.0008	0.0074±0.0017 (-5.1%)	0.0109±0.0040 (+39.7%)	0.0120±0.0072 (+53.8%)
Uterus weight absolute (g)					7.5±1.4	9.3±6.1 (+24.0%)	17.2±8.2 (+129.3%)	17.8±17.8 (+137.3%)
Uterus weight relative (% BW)					0.055±0.013	0.066±0.044 (+20.0%)	0.117±0.117 (+112.7%)	0.126±0.069 (+129.1%)

[a] Mean ± SD
[b] No SD for body weight gain given in the report
BW = body weight
Dose in mg/kg bw/day calculated based on the values given in the report for the highest dose

In male dogs comparable body weights but variably reduced body weight gains (due to different start weights) were seen, whereas there was an increase of body weights and body weight gains at the two highest doses in female dogs. The different effects on body weights and body weight gains seem to be the reason for the observed different organ weight effects, especially for the increased uterus and ovary weights. For the thyroid weights no clear dose response is apparent and furthermore, a different pattern between males and females was seen which makes a treatment effect rather unlikely. For the pituitary weights no treatment effect occurred. None of the changes of the discussed parameters were statistically significant. Therefore, no clear treatment effects on endocrine organs can be derived from the data of this study, but rather a high variability (high standard deviations) and probably an additional impact of the body weights on the organ weights.
Overall, therefore the current NOAEL of 75 ppm (equivalent to 5 and 4 mg/kg bw/day in males and females, respectively) as established by the study director in this study is justified.

Comparison of organ weight data with historical control data (HCD)

The organ weights were furthermore within published historical background ranges from Beagle dogs. Historical organ weight data from the publication of Jackson, B. et al, 1964, where observed organ weight data from 1-year Beagle dog studies from 1958 to 1961, were used. In this publication, no body weight data were provided, the age of the dogs given was from 8 to 38 months.
Although the HCD are from a different time period, big differences are not expected, since no breeding changes in Beagle dogs occurred over the extended time period of when the fenoxaprop dog studies were conducted and since the organ weights in adult dogs should be comparable in untreated Beagles. Therefore, they are appropriate for this comparison. The relevant endocrine organ weights of the one- and two-year dog study are presented (only means without SD) in comparison with the HCD ranges of this publication in the following tables.

Table 6.3.6-5 Historical control ranges of Beagle dogs (Jackson *et al.*, 1964), Repeated oral administration to beagle dogs for one year

Study/Organ weights of males	Dose level in ppm				HCD Beagle dogs (Jackson *et al*, 1964)
	0	3	15	75	
males					
Body weight (kg)	15.1	14.9	15.8	15.8	na
Thyroid weight ab-	581	801	788	834	500-1600

solute (mg)					
Thyroid weight relative (% of BW)	0.0039	0.0054	0.0050	0.0053	0.005-0.014
females					
Body weight (kg)	13.8	14.3	15.1	14.6	Na
Thyroid weight absolute (mg)	777	650	823	790	400-1300
Thyroid weight relative (% of BW)	0.0057	0.0045	0.0055	0.0054	0.004-0.013
Ovary weight absolute (mg)	1079	1063	1596	1710	600-2300
Ovary weight relative (% of BW)	0.0078	0.0074	0.0109	0.0120	0.005-0.019
Uterus weight absolute (g)	7.5	9.3	17.2	17.8	3.1-25
Uterus weight relative (% BW)	0.055	0.066	0.117	0.126	0.033-0.276

RMS' conclusion

RMS does not agree to the above conclusions of the applicant, due to following reasons:

- Changes in bodyweight were less than 10% and not dose-related. Effects on bodyweight gain were observed in males of all dose groups and in females at low dose and high dose. In females, however, the changes were not dose-related and in both sexes not statistically significant. However, the decrease in bodyweight gain did not affect the bodyweight. Therefore the effect of bodyweight changes is considered not sufficient to explain the alteration of organ weights (i.e. ovary, uterus and prostate).
- The applicant provided publicly available historical control data, which were obtained from control groups of toxicological studies conducted with dogs from at least 23 years before this study was performed. The data do not fulfil the criteria as pointed out in Commission Regulation (EU) No 283/2013, in which it is stated that historical control data should be provided from not later than 5 years and conducted in the same laboratory. Therefore they cannot be considered valid and acceptable.

However, RMS agrees to the conclusions of the high variability in organ weights and that no histopathological changes were observed in any of the organs affected - no microscopic changes were described and seem to have occurred in the adrenals, prostate, ovaries and uterus. Lipid alterations were seen only in female dogs but not in male dogs. Also the standard deviations were high, indicating a high variability. None of the observed organ weight alterations nor changes in the lipid metabolism were statistically significant.
Summing all these points together, RMS proposed the NOAEL as mentioned above.

B.6.3.7. Comparison of short-term toxicity studies with fenoxaprop-P-ethyl and fenoxaprop-ethyl

Oral studies

Rats: Similar results were obtained after administration of Hoe 046360 (fenoxaprop-P ethyl) and Hoe 033171 (fenoxaprop-ethyl) in 4 and 13 week toxicity studies. At very high doses (5000 ppm and above) severe toxicity was found leading to premature sacrifice of the animals. Reduction of body weights was observed at dose levels of 640 ppm and above. The target organs identified were the liver and the kidneys as demonstrated by blood and urine parameters predominantely indicating changes in lipid metabolism and liver toxicity, increased organ weights, macroscopically enlarged organs (Hoe 046360 only), and histopathology findings (enlarged hepatocytes).
The oral short-term toxicity NOAELs derived from the rat studies are in the same order of magnitude for both test substances, being 10 ppm for Fenoxaprop-P-ethyl and 20 ppm for Fenoxaprop-ethyl.

Mice: As in the rat studies, both test substances had a similar outcome in 4 and 13 week toxicity studies. However, the studies were not directly comparable in all aspects as different dose ranges were used, especially the 13

week study with Hoe 033171 used high dose levels (320, 640 and 1280 ppm) for special investigations of hepatic effects. In contrast to the rat studies, body weights were increased after high dose levels of Hoe 046360 and 033171 which was discussed to be a secondary effect due to markedly increased liver weights at these dose levels. The target organs identified were the liver and the kidney for both test substances and also the spleen and the adrenals in the 13 week study with Hoe 033171. Clinical chemistry evaluation revealed clear effects on lipid metabolism, liver enzymes and protein levels for both substances. Liver and kidney weights were increased which was confirmed by macroscopic enlargement of these organs. At histopathology, hepatocellular hypertrophy, single cell necrosis, increased mitotic activity and tubular necrosis were observed in the studies with Hoe 046360 and 033171. In the high dose 13 week study with Hoe 033171, special investigations were performed to prove peroxisome proliferation of hepatocytes by electron microscopy. Also, adrenal and spleen weights were increased in this study with only the spleen showing correlating histopathological findings (increased erythropoesis).
No NOAEL could be derived from the 13 week study with Hoe 033171 due to the high dose levels used. However, also considering the 4 week studies, the effect levels were generally comparable between the two test substances. The oral short-term toxicity NOAEL derived from the studies conducted with Fenoxaprop-P-ethyl is considered to be 10 ppm.

Dogs: 1 and 3 months studies were conducted with both test substances while a 1 year study was only performed with Hoe 033171. The 1 month studies were dose finding studies using only few animals which limited the validity of these data. In the 3 months study with Fenoxaprop-P-ethyl, the only effects observed were a decrease of body weight and increased ASAT, LDH and protein levels at the highest dose tested (2000 ppm). These results are in contrast to the 1 month study with Hoe 033171, where excessive toxicity was observed at 2000 ppm leading to premature sacrifice of this dose group. However, in a comparison of toxicological profiles of Hoe 033171 and Hoe 046360 (Leist K.-H. and Ebert E., 1989, Doc. A40415), the level of test substance intake in mg/kg bw/d is presented and showed substantial difference of the amount of ingested test substance (2000 ppm equivalent to 142 mg/kg bw/d in the 1 month toxicity study with Hoe 033171; 2000 ppm equivalent to 81 mg/kg bw/d in the 3 month toxicity study with Hoe 046360). In the 3 month study with Hoe 033171, the only treatment-related finding was interstitial pyelonephritis in both sexes at 80 and 400 ppm. No effects could be identified in the 1 year study with Hoe 033171, where doses of only 3 - 75 ppm were administered to the dogs.
Taken together, the results of the dog studies with Fenoxaprop-P-ethyl and Fenoxaprop-ethyl showed no consistent pattern of effects. However, the real uptake of test substance was not directly comparable between the studies. The NOAEL derived from the the 3 month study with Fenoxaprop-P-ethyl was 400 ppm while the NOAELs of the 3 month and 1 year study with Fenoxaprop-ethyl were 16 ppm and >75 ppm, respectively.

Other routes

Inhalation and dermal toxicity studies with a repeated dosing study design were only submitted for Fenoxaprop-P-ethyl, therefore no comparison of data can be presented.

B.6.4. GENOTOXICITY

Data on the genotoxicity of fenoxaprop-P-ethyl and fenoxaprop-ethyl were previously submitted and evaluated in the context of the original EU review of this active substance, resulting in the first approval of fenoxaprop-P. All data were considered acceptable and fenoxaprop-P was concluded to be non-genotoxic based on weight of evidence analysis across the package of studies.
Five new in-vitro studies were undertaken for fenoxaprop-P-ethyl and are included in this renewal application.

Summary of genotoxicity studies with Fenoxaprop-P-ethyl
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 study guidelines. None of the 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*. A summary of all the essential data is presented in the following table (newly submitted data marked).

Summary of genotoxicity testing with fenoxaprop-P-ethyl

Study, reference	Dose range	Results
***In vitro*-studies**		
Reverse mutation assay (S. typhimurium and E. coli strains) *Müller W., 1994* A53077, CA 5.4.1/01	0; 4; 20; 100; 500; 2,500 and 5,000 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix)
S. typhimurium reverse mutation assay, *Sokolowski, A., 2015* 1698300, CA 5.4.1/13	0; 3; 10; 33; 100; 333; 1,000; 2,500 and 5,000 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix)
S. typhimurium reverse mutation assay *Thompson, P.W., 2005* 132 FPE, CA 5.4.1/14	0; 50; 150; 500 and 1,500 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix)
Reverse mutation assay using bacteria (S. typhimurium and E. coli) *Donath, C., 2011* 396 FPE, CA 5.4.1/15	0; 10.0*; 31.6; 100; 316*; 1,000; 2,500; 5,000 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix)
Forward mutation assay in S. pombe *Edwards C.N., 1986a* A34056, CA 5.4.1/03	0; 2.5; 5; 10; 20 and 40 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
Gene mutation assay in Chinese hamster V79 cells *Seeberg A.H., 1986* A34057, CA 5.4.1/05	0; 6.25; 12.5; 25; 50 and 100 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
L5178Y TK +/- Mouse Lymphoma assay *Flanders, L., 2006* 175 FPE, CA 5.4.1/16	I: 0-450 µg/ml (+/- S9) II: 0-300 µg/ml (-S9), 0-225 µg/ml (+S9) III: 0-275 µg/ml (-S9), 0-287.5 µg/ml (+S9)	Negative (+/- S9-mix)
Chromosome aberration test in human lymphocytes *Mosesso P., 1987* A35218, CA 5.4.1/06	0; 50; 79 and 125 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
Chromosome aberration test in human lymphocytes *in vitro* *Wright, N.P., 2006* 178 FPE, CA 5.4.1/17	I: 0-678.75 (-S9), 0-1,357.5 µg/ml (+S9) II: 0-452.9 (-S9), 0-1,810 µg/ml (+S9) III: 3 groups, 0-905/1,131.25 µg/ml (+/-S9)	Negative (+/- S9-mix)
Mitotic gene conversion in S. cerevisiae *Edwards C.N., 1986b* A34058, CA 5.4.1/08	0; 1.25; 2.5; 5; 10 and 20 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
In vitro UDS test in primary rat hepatocytes *Cifone M.A., 1986* A34916, CA 5.4.1/11	0; 2.51; 5.02; 10; 25.1; 50.2; 100; 201 and 301 µg/ml (dissolved in DMSO)	Negative (supplementary information)
In vitro UDS test in mammalian cells *Müller W., 1995* A54045, CA 5.4.1/12	0; 0.1; 0.3; 1; 3; 10; 30 and 100 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
***In vivo* studies**		

Study, reference	Dose range	Results
Oral micronucleus test in NMRI mice [redacted], *1986* A34297, CA 5.4.2/01	0; 1,000; 2,000 and 4,000 mg/kg bw (dissolved in sesame oil)	Negative

* additional concentrations in the second experiment (pre-incubation method)

Summary of genotoxicity studies with Fenoxaprop-ethyl

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 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 tests 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*. A summary of all the essential data is presented in the following table.

Summary of genotoxicity studies with fenoxaprop-ethyl

Study, reference	Dose range	Results
***In vitro*-studies**		
Reverse mutation assay (S. typhimurium and E. coli strains) *Jung et al., 1982* A24677, CA 5.4.1/02	0, 4, 20, 100, 500, 2500 and 5000 µg/plate (dissolved in DMSO)	Negative (+/- S9-mix) (supplementary information)
Forward mutation assay in S. pombe *Mellano D., Mondino A., 1982a* A24239, CA 5.4.1/04	0, 125, 250, 500 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
Chromosome aberration test in human lymphocytes *Mellano D., Mondino A., 1982b* A26227, CA 5.4.1/07	0, 1, 10, 100 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
Mutagenic activity in S. cerevisiae *Mellano D., Mondino A., 1982c* A24238, CA 5.4.1/09	0, 125, 250, 500 and 1000 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
In vitro UDS test in mammalian cells *Mellano D., Mondino A., 1982d* A24582, CA 5.4.1/10	0, 5, 50 and 500 µg/ml (dissolved in DMSO)	Negative (+/- S9-mix)
***In vivo*-studies**		
Oral micronucleus test in NMRI mice [redacted] *1986* A34294, CA 5.4.2/02	0, 750, 1500 and 3000 mg/kg bw (dissolved in sesame oil)	Negative

B.6.4.1. *In vitro* studies with fenoxaprop-P-ethyl

B.6.4.1.1. Ames test

Reference:	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
Author(s). year:	Müller W. *et al.*, 1994
Report/Doc. number:	A53077 / Hoechst Report No. 94.0627
Guideline(s):	OECD guideline 471 and 472 (1983); EPA guideline 798.5265 and 798.5100 (1985); EEC Directive 92/69, L383 A, Annex B13 and Annex B14
Deviations to OECD GD 471 (1997):	Minor deviation: 2-Aminoanthracene used as sole positive control with metabolic activation.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:

The test substance was dissolved in DMSO and tested in the following concentrations

0 (solvent control); 4; 20; 100; 500; 2,500 and 5,000 µg/plate

in both S. typhimurium and E. coli. Mutagenicity was tested in the in the absence and presence of S9-mix from Arochlor 1254- induced liver fractions from male Sprague-Dawley rats. Toxicity and dose range finding tests were performed with all bacterial strains using three plates per dose. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity. The following substances were used as positive controls: 1) without metabolic activation: sodium azide (TA 100, TA 1535); 9-aminoacridine (TA 1537); 2-nitrofluorene (TA 98); N-methyl-N-nitro-N-nitrosoguanidine (WP2uvrA); 2) with metabolic activation: 2-aminoanthracene (all strains).

Test material:	fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002
Purity:	88.7% (+7.4% L-isomer)
Test strains:	Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537) Escherichia coli (WP2uvrA)
Number of plates:	3 per dose

Evaluation criteria: A test substance is classified mutagenic if either of the following conditions under 1) and 2) is achieved and if the test results are reproducible: 1) A test substance produces at least a 2-fold increase in the mean number of revertants per plate of at least one of the tester strains over the mean number of revertants per plate of the appropriate vehicle control at complete bacterial background lawn. 2) A test substance induces a dose-related increase in the mean number of revertants per plate of at least one of the tester strains over the mean number of revertants per plate of the appropriate vehicle control in at least two to three concentrations of the test article at complete bacterial background lawn.

Findings:
Solubility: Visible precipitation of the test substance on the plates was observed at 2,500 µg/plate and above.

Toxicity: The test compound proved to be toxic to most of the bacterial strains at doses of 2,500 µg/plate and above. Thinning of the bacterial lawn and a reduction in the number of colonies were observed at these doses.

Mutagenicity test: The test substance did not cause a significant increase in the number of revertant colonies in any of the tester strains, neither in the absence nor in the presence of S-9 mix. No dose dependent effect was obtained. The results were confirmed in a second independent experiment.

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in Salmonella typhimurium and Escherichia coli with and without S-9 mix at concentrations up to 5,000 µg/plate.

B.6.4.1.2. Newly submitted study: Ames test (study 1)

Reference:	Fenoxaprop-P-ethyl (AE 046360): Salmonella typhimurium reverse mutation assay
Author(s). year:	Sokolowski A., 2015
Report/Doc. number:	Harlan Study No. 1698300 / M-528795-01-1
Guideline(s):	OECD guideline 471 (1997), Commission Regulation No. 440/2008 B13/B14 (2008), EPA guideline 870.5100
Deviations:	No.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
The test substance was dissolved in DMSO and tested in a concentration range of 3-5,000µg/plate in S. typhimurium in the pre-experiment, conducted as plate incorporation assay. Based on the observed precipitation, the following 8 concentrations were selected for experiment II (pre-incubation assay)

0 (solvent or positive control); 3; 10; 33; 100; 333; 1,000; 2,500 and 5,000 µg/plate

and tested in S. typhimurium. Mutagenicity was tested in the in the absence and presence of S9-mix from phenobarbital/ß-napthoflavone-induced liver fractions from rats. The tests were performed with all bacterial strains using three plates per dose. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity.

Test material: fenoxaprop-P-ethyl, batch AE F046360-01-19
Purity: 94.1%

Test strain: Salmonella typhimurium (TA 98, TA 100, TA 102, TA 1535, TA 1537)
Number of plates: 3 per dose

The following substances were used as positive controls:
1) without metabolic activation: sodium azide, NaN3 (TA 100, TA 1535); 4-nitro-o-phenylene-diamine, 4-NOPD (TA 1537, TA 97); methyl methane sulfonate, MMS (TA 102);
2) with metabolic activation: 2-aminoanthracene (all strains).

Evaluation criteria: A test item is considered mutagenic if a biologically relevant increase in the number of revertants exceeding the threshold of twice (strains TA 98, TA 100 and TA 102) or thrice (strains TA 1535 and TA 1537) the colony count of the corresponding solvent control is observed. A dose dependent increase is considered biologically relevant if the threshold is exceeded at more than one concentration unless it is reproduced in an independent second experiment, or, exceedance at only one concentration is reproduced in an independent second experiment. However, whenever the colony counts remain within the historical range of negative and solvent controls such an increase is not considered biologically relevant.

Findings:
Solubility: Precipitation of the test item in the overlay agar on the incubated agar plates was observed in experiment I from 333 to 5000 µg/plate without S9 mix and in experiment II with and without S9 mix. In experiment I with S9 mix precipitation was observed from 1,000 to 5,000 µg/plates. The undissolved particles had no influence on the data recording.

Toxicity: The plates incubated with the test item showed normal background growth up to 5,000 µg/plate with and without S9 mix in all strains used. Only in strain TA 100 reduced background growth was observed in experiment II from 1,000 to 5,000 µg/plate in the presence of S9 mix. No toxic effects, evident as a reduction in the number of revertants (below the indication factor of 0.5), occurred in nearly all the test strains. Only in strain TA 100 toxic effects were observed with S9 mix at 2,500 and 5,000 µg/plate in experiment I and from 1,000 to 5,000 µg/plate in experiment II.

Mutagenicity: No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with Fenoxaprop-P-ethyl (AE F046360) at any concentration level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency of higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.

Table 6.4.1-1 Summary of results - Experiment I, fenoxaprop-P-ethyl (AE 046360): Salmonella typhimurium reverse mutation assay

Concentration in µg	Revertant colony counts (mean ±SD) without metabolic activation				
	TA 1535	TA 1537	TA 98	TA 100	TA 102
DMSO	12 ± 2	12 ± 1	25 ± 4	158 ± 8	404 ± 76
Untreated	12 ± 3	11 ± 1	25 ± 5	170 ± 17	420 ± 104
3	11 ± 2	9 ± 5	24 ± 5	184 ± 21	455 ± 19
10	12 ± 2	10 ± 4	24 ± 3	166 ± 18	500 ± 18
33	11 ± 2	15 ± 1	25 ± 3	162 ± 12	513 ± 8
100	13 ± 1	11 ± 1	22 ± 4	169 ± 16	506 ± 10
333[P]	14 ± 1	11 ± 1	23 ± 3	155 ± 9	457 ± 25
1,000[P M]	9 ± 3	8 ± 3	19 ± 6	181 ± 4	440 ± 21
2,500[P M]	10 ± 1	9 ± 2	16 ± 6	179 ± 4	442 ± 15
5,000[P M]	13 ± 2	8 ± 1	18 ± 1	164 ± 5	436 ± 15
NaN3 10	1169 ± 105			2056 ± 31	
4-NOPD 10			352 ± 33		
4-NOPD 50		92 ± 2			
MMS 2.0 µL					5659 ± 957
Concentration in µg	**Revertant colony counts (mean ±SD) with metabolic activation**				
	TA 1535	**TA 1537**	**TA 98**	**TA 100**	**TA 102**

DMSO	11 ± 3	13 ± 1	33 ± 6	173 ± 8	590 ± 39
Untreated	13 ± 3	15 ± 2	31 ± 16	174 ± 8	651 ± 44
3	9 ± 1	12 ± 4	30 ± 6	146 ± 26	587 ± 5
10	8 ± 1	13 ± 4	32 ± 7	154 ± 21	613 ± 11
33	11 ± 3	14 ± 1	28 ± 2	154 ± 10	619 ± 24
100	11 ± 5	10 ± 3	26 ± 3	157 ± 10	655 ± 47
333	11 ± 3	13 ± 3	34 ± 7	144 ± 9	545 ± 3
1,000[P]	8 ± 2	14 ± 1	30 ± 9	142 ± 14	570 ± 38
2,500[P M]	9 ± 2	8 ± 1	21 ± 3	57 ± 10	535 ± 14
5,000[P M]	12 ± 1	7 ± 1	23 ± 3	46 ± 1	529 ± 22
2-AA 2.5	495 ± 6	152 ± 10	4944 ± 216	3873 ± 46	
2-AA 10.0					1573 ± 228

[P] precipitate in all strains
[M] manual count

Table 6.4.1-2 Summary of results – Experiment II, fenoxaprop-P-ethyl (AE 046360): Salmonella typhimurium reverse mutation assay

Concentration in µg	**Revertant colony counts (mean ±SD); without metabolic activation**				
	TA 1535	**TA 1537**	**TA 98**	**TA 100**	**TA 102**
DMSO	8 ± 2	7 ± 1	25 ± 1	141 ± 19	419 ± 27
Untreated	6 ± 1	7 ± 3	19 ± 1	155 ± 18	417 ± 25
3	13 ± 5	5 ± 3	23 ± 4	127 ± 15	430 ± 16
10	13 ± 1	6 ± 2	23 ± 4	119 ± 6	456 ± 19
33	8 ± 1	9 ± 3	20 ± 3	127 ± 11	443 ± 12
100	9 ± 1	8 ± 2	18 ± 3	126 ± 12	454 ± 6
333	13 ± 1[P]	8 ± 2[P]	17 ± 6[P]	127 ± 18[P]	496 ±90[P]
1,000	9 ± 2[P M]	6 ± 2[P M]	12 ± 2[P M]	134 ± 8[P M]	534 ± 90[P M]
2,500	8 ± 1[P M]	6 ± 2[P M]	16 ± 2[P M]	126 ± 13[P M]	495 ± 37[P M]
5,000	8 ± 2[P M]	6 ± 1[P M]	15 ± 4[P M]	134 ± 7[P M]	396 ± 59[P M]
NaN3 10	976 ± 25			1917 ± 29	
4-NOPD 10			316 ± 27		
4-NOPD 50		84 ± 7			
MMS 2.0 µL					4241 ± 185
Concentration in µg	**Revertant colony counts (mean ±SD); with metabolic activation**				
	TA 1535	**TA 1535**	**TA 1535**	**TA 1535**	**TA 1535**
DMSO	16 ±2	9 ± 2	23 ± 11	108 ± 23	577 ± 41
Untreated	10 ± 3	15 ± 1	25 ± 5	136 ± 30	582 ± 37
3	12 ± 3	9 ± 1	38 ± 2	89 ± 6	553 ± 12
10	12 ± 3	11 ± 5	27 ± 3	94 ± 6	564 ± 27
33	10 ± 2	11 ± 3	30 ± 4	105 ± 11	558 ± 50
100	10 ± 3	9 ± 3	34 ± 4	116 ± 4	554 ± 55
333	14 ± 2[P]	9 ± 3[P]	27 ± 5[P]	87 ± 1[P]	516 ± 59[P]
1,000	10 ± 3[P M]	9 ± 2[P M]	25 ± 5[P M]	37 ± 5[P M R]	523 ± 12[P M]
2,500	9 ± 2[P M]	7 ± 2[P M]	19 ± 3[P M]	16 ± 7[P M R]	518 ± 8[P M]
5,000	9 ± 2[P M]	8 ± 3[P M]	19 ± 4[P M]	0 ± 0[P M R]	519 ± 30[P M]
2-AA 2.5	401 ± 26	141 ± 7	3650 ± 285	3341 ± 319	
2-AA 10.0					1398 ± 175

[P] precipitate
[M] manual count
[R] reduced background growth

Appropriate reference mutagens were used as positive controls. They showed a distinct increase in induced revertant colonies. In experiment II, the data in the untreated control of strain TA 1535 without S9 mix did not quite reached the lower limit of our historical control data. Since this deviation is rather small, this effect is considered to be based upon biologically irrelevant fluctuations in the number of colonies and had no detrimental impact on the outcome of the study. The following table summarizes historical control data of the laboratory, approx. 450 (TA102: 200) conducted experiments from Jan 2013-Dec 2013.

Table 6.4.1-3 Historical control data, fenoxaprop-P-ethyl (AE 046360): Salmonella typhimurium reverse mutation assay

	Without S9 mix	**With S9 mix**

		Mean	SD	Min	Max	Mean	SD	Min	Max
TA 1535	Solvent control	16	2.84	7	27	18	4.50	7	36
	Untreated control	15	3.35	7	27	19	4.99	9	34
	Positive control	2248	468.15	803	3722	418	119.81	182	683
TA 1537	Solvent control	10	2.19	6	23	18	4.37	8	32
	Untreated control	10	2.52	5	22	19	4.64	8	30
	Positive control	74	10.30	50	159	300	126.74	77	651
TA 98	Solvent control	26	4.27	16	46	38	6.29	21	59
	Untreated control	28	5.15	16	54	41	6.40	21	55
	Positive control	326	56.74	211	560	2306	944.29	330	4691
TA 100	Solvent control	107	20.07	74	184	132	22.97	83	205
	Untreated control	113	21.29	82	204	142	21.11	82	210
	Positive control	1987	376.71	478	2594	2864	946.03	530	4983
TA 102	Solvent control	398	58.44	302	518	479	80.78	298	637
	Untreated control	400	66.28	299	548	492	74.82	333	668
	Positive control	4113	1128.01	1341	6469	2080	727.44	1073	4244

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in Salmonella typhimurium with and without S-9 mix at concentrations up to 5,000 µg/plate.

B.6.4.1.3. Newly submitted study: Ames test (study 2)

Reference:	Fenoxaprop-p-ethyl technical: Reverse mutation assay "Ames Test" using Salmonella thypimurium.
Author(s). year:	Thompson P. W., 2005
Report/Doc. number:	132 FPE / M-548064-01-1
Guideline(s):	OECD guideline 471, Method B13/B14 of Commission Directive 2000/32/EC, EPA OPPTS 870.5100 (1998).
Deviations:	No
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
The test substance was dissolved in DMSO and tested in a concentration range of 0.15-5,000 µg/plate in S. typhimurium TA 100 in the preliminary toxicity test (10 concentrations). Based on the observed precipitation, the following 5 concentrations were selected for the mutation test and the repeat experiment (experiment 1 + 2)

0 (solvent or positive control); 50; 150; 500 and 1,500 µg/plate

and tested in the 5 strains of S. typhimurium. Mutagenicity was tested in the in the absence and presence of S9-mix from phenobarbital/ß-napthoflavone-induced liver fractions obtained from Sprague-Dawley rats. The tests were performed with all bacterial strains using three plates per dose. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity. The following substances were used as positive controls: 1) without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine, ENNG (TA 100, TA 1535); 9-aminoacridine, 9AA (TA 1537); 4-Nitroquinoline-1-oxide, 4NQO (TA 98); Mitomycin C, MMC (TA 102); 2) with metabolic activation: 2-aminoanthracene, 2AA (TA 100, TA 1535, TA 1537); Benzo(a)pyrene, BP (TA 98); 1,8-Dihydroxyanthraquinone, DAN (TA 102).

Test material: fenoxaprop-P-ethyl CHA 480, batch 660-PSH-45
Purity: 95.6%

Test strain: Salmonella typhimurium (TA 98, TA 100, TA 102, TA 1535, TA 1537)
Number of plates: 3 per dose

Evaluation criteria: The criteria for determination of positive result were (1) dose-related increase in revertant frequency over the dose range tested and/or (2) reproducible increase at one or more concentrations in at least one bacterial strain with or without metabolic activation. Biological relevance of the results was considered first and statistical significance was not the only determining factor for a positive response.

The test material was considered non-mutagenic (negative) if the above criteria were not met.

Findings:

Preliminary toxicity test: The test material precipitated at 1,500 µg/plate and above. It did not exhibit any toxicity to S. typhimurium TA 100. The number of revertant colonies is given in Table 6.4.1-4.

Table 6.4.1-4 Number of revertant colonies in preliminary toxicity test after treatment with fenoxaprop-P-ethyl

With or without metabolic activation	Nominal Dose (µg/plate)										
	0	0.15	0.5	1.5	5	15	50	150	500	1,500	5,000
-	169	117	113	143	126	135	135	135	139	118 [P]	116 [P]
+	116	93	84	91	76	91	104	117	124	74 [P]	85 [P]

[P] Precipitate

Mutation test: The test material caused no visible reduction in the growth of bacterial background lawn at any dose level. The test material was, therefore, tested up to the maximum recommended dose level of 5,000 µg/plate. A white coloured precipitate was observed at 1,500 µg/plate and above, which did not prevent the scoring of revertant colonies.

No significant increases in the frequency of revertant colonies were recorded for any of the strains of Salmonella, at any dose level either with or without metabolic activation.

All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity S9-mix and the sensitivity of the bacterial strains.

Table 6.4.1-5 Summary of Results – Experiment 1, fenoxaprop-p-ethyl technical: Reverse mutation assay "Ames Test" using Salmonella thypimurium

Concentration in µg	**Revertant colony counts (mean ±SD); without metabolic activation**				
	Base pair substitution type			Frameshift type	
	TA 100	**TA 1535**	**TA 102**	**TA 98**	**TA 1537**
0	98 ± 11.1	23 ± 2.1	329 ± 41.0	26 ± 4.7	13 ± 3.5
50	119 ± 1.2	22 ± 8.0	334 ± 15.6	22 ± 8.4	12 ± 4.2
150	102 ± 4.9	27 ± 4.6	336 ± 13.7	21 ± 2.5	15 ± 0.6
500	105 ± 15.9	22 ± 5.7	303 ± 12.1	18 ± 2.1	13 ± 1.5
1500 [P]	104 ± 10.5	22 ± 4.6	318 ± 19.6	24 ± 1.0	18 ± 1.7
5000 [P]	99 ± 23.7	15 ± 2.6	285 ± 38.0	27 ± 1.5	15 ± 2.6
Positive controls	ENNG 3µg	ENNG 5µg	MMC 0.5µg	4NQO 0.2µg	9AA 80µg
	466 ± 23.6	271 ± 49.9	1035 ± 234.6	108 ± 1.0	1311 ± 307.7
Concentration in µg	**Revertant colony counts (mean ±SD); with metabolic activation**				
0	86 ± 9.1	12 ± 3.6	374 ± 28.7	30 ± 6.7	14 ± 3.1
50	80 ± 14.0	8 ± 0.6	363 ± 4.6	33 ± 9.1	12 ± 5.1
150	87 ± 7.0	9 ± 0.6	344 ± 34.2	25 ± 2.5	14 ± 7.0
500	80 ± 9.1	14 ± 3.6	371 ± 22.8	31 ± 5.1	12 ± 3.8
1500 [P]	73 ± 4.9	13 ± 1.5	358 ± 30.5	32 ± 4.0	10 ± 4.5
5000 [P]	74 ± 2.1	14 ± 2.1	296 ± 26.2	29 ± 3.5	15 ± 0.6
Positive controls	2AA 1µg	2AA 2µg	DAN 10µg	BP 5µg	2AA 2µg
	1052 ± 148.2	234 ± 4.6	911 ± 268.2	233 ± 21.6	337 ± 12.6

Table 6.4.1-6 Summary of Results – Experiment 2, fenoxaprop-p-ethyl technical: Reverse mutation assay "Ames Test" using Salmonella thypimurium

Concentration in µg	**Revertant colony counts (mean ±SD); without metabolic activation**				
	Base pair substitution type			Frameshift type	
	TA 100	**TA 1535**	**TA 102**	**TA 98**	**TA 1537**
0	80 ± 2.0	26 ± 1.5	313 ± 36.1	22 ± 8.3	18 ± 3.8
50	88 ± 16.2	25 ± 1.2	322 ± 19.9	21 ± 4.7	16 ± 5.5
150	98 ± 15.8	33 ± 12.7	339 ± 12.7	22 ± 1.0	14 ± 4.6

500	92 ± 13.5	27 ± 11.4	327 ± 7.6	21 ± 7.8	17 ± 8.7
1500 [P]	98 ± 4.7	29 ± 5.8	279 ± 48.4	22 ± 7.0	19 ± 5.1
5000 [P]	100 ± 11.1	32 ± 4.5	229 ± 12.9	21 ± 2.1	18 ± 3.2
Positive controls	ENNG 3µg	ENNG 5µg	MMC 0.5µg	4NQO 0.2µg	9AA 80µg
	390 ± 100.4	188 ± 27.9	1258 ± 47.7	123 ± 12.5	257 ± 114.00
Concentration in µg	**Revertant colony counts (mean ±SD); with metabolic activation**				
0	87 ± 5.7	11 ± 2.1	369 ± 28.5	25 ± 3.5	15 ± 5.5
50	84 ± 20.8	13 ± 6.4	365 ± 26.6	22 ± 4.0	14 ± 6.7
150	77 ± 10.0	12 ± 6.1	365 ± 19.3	27 ± 4.0	14 ± 6.7
500	73 ± 12.5	14 ± 7.1	377 ± 22.0	26 ± 5.0	13 ± 5.3
1500 [P]	71 ± 2.3	12 ± 2.1	379 ± 10.4	19 ± 3.2	7 ± 1.0
5000 [P]	79 ± 6.8	15 ± 3.6	360 ± 36.7	25 ± 4.5	20 ± 3.5
Positive controls	2AA 1µg	2AA 2µg	DAN 10µg	BP 5µg	2AA 2µg
	833 ± 66.1	209 ± 3.5	759 ± 89.0	209 ± 25.9	274 ± 58.4

[P] precipitate

The following table summarizes historical control data from 2004 (data from 2003 were also available in the study report).

Table 6.4.1-7 Historical Control Data from 2004, fenoxaprop-p-ethyl technical: Reverse mutation assay "Ames Test" using Salmonella thypimurium

	Combined Vehicle and Untreated Controls									
	TA 100		TA 1535		TA 102		TA 98		TA 1537	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Mean	94	98	24	14	333	367	21	31	12	18
SD	16.5	14.8	7.0	4.8	34.9	24.5	5.1	6.5	3.4	4.0
Min	61	60	9	7	192	263	10	11	5	6
Max	163	157	40	39	397	406	49	57	26	35
n	993	798	911	713	291	183	917	740	889	708
	Positive Control Values									
Mean	557	1124	440	265	1250	893	175	219	999	366
SD	163.5	417.4	275.3	80.5	239.3	124.8	52.5	68.9	511.6	130.1
Min	189	348	93	162	728	660	95	114	130	137
Max	1215	2942	1634	1026	1960	1288	435	495	4964	832
n	180	178	176	175	103	103	179	178	176	175

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in Salmonella typhimurium with and without S-9 mix at concentrations up to 5,000 µg/plate.

B.6.4.1.4. Newly submitted study: Ames test (study 3)

Reference:	**Reverse Mutation Assay using Bacteria (Salmonella thypimurium and Escherichia Coli) with Fenoxaprop-P-ethyl technical**
Author(s). year:	Donath C., 2011
Report/Doc. number:	396 FPE / M-548280-01-1
Guideline(s):	OECD guideline 471 (1997); Commission Regulation (EC) No. 440/2008 B.13/14 (2008); EPA OPPTS 870.5100 (1998)
Deviations:	No.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:

The test substance was dissolved in DMSO and tested in a concentration range of 3.16 -5,000 µg/plate in S. typhimurium TA 98 and TA 100 in the pre-experiment (8 concentrations). Based on the results of the pre-experiment, the following concentrations were selected

Experiment I (Plate-incorporation test): 31.6; 100; 1,000; 2,500; 5,000 µg/plate

Experiment II (Pre-incubation test): 10.0; 31.6; 100; 316; 1,000; 2,500; 5,000 µg/plate

and tested in the strains of S. typhimurium and E.coli. Mutagenicity was tested in the in the absence and presence of S9-mix from phenobarbital/ß-napthoflavone-induced liver fractions obtained from Wistar rats. The tests were performed with all bacterial strains using three plates per dose. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity.

Test material: fenoxaprop-P-ethyl technical, batch 090630-18
Purity: 99.2%

Test strains: Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537)
E.coli WP2 uvrA

The following substances were used as positive controls:
1) without metabolic activation: sodium azide, NaN3 (TA 100, TA 1535); 4-nitro-o-phenylene-diamine, 4-NOPD (TA 98, TA 1537); methylmethanesulfonate, MMS (E. coli WP2 uvrA)
2) with metabolic activation: 2-aminoanthracene, 2-AA (TA 98, TA 100, TA 1535, TA 1537, E. coli WP2 uvrA).

Evaluation criteria: The criteria for determination of (1) cytotoxicity were clearing or diminution of the background lawn or a reduction in the number of revertants down to a mutation factor of approximately ≤0.5 in relation to the solvent control and, determination of (2) mutagenicity were done by calculation of mutation factor (mean value revertant counts / mean value solvent control), where a test item is considered mutagenic if
- a clear and dose-related increase in the number of revertants and/or
- biologically relevant positive response for at least one of the dose groups occur in at least one tester strain with or without metabolic activation (number of reversions in strains TA 98, TA 100 and E.coli WP2 uvrA is at least twice as high, in strains TA 1535 and TA 1537 at least three times higher as compared to the reversion rate of the solvent control).
The test material was considered non-mutagenic (negative) if the above criteria were not met.

Findings:
In experiment I, precipitation of the test item was observed at a concentration of 316 µg/plate and higher (without metabolic activation) and at a concentration of 5,000 µg/plate (with metabolic activation). In experiment II, this occurred at a concentration of 100 µg/plate and higher (without metabolic activation), and, at a concentration of 5,000 µg/plate (with metabolic activation). The precipitation did not affect the counting of revertant colony numbers and thus did not affect the evaluation and interpretation of the results.

Toxicity: No toxic effects of the test item were noted in any of the five tester strains used up to the highest dose group evaluated with and without metabolic activation in experiment I.
Toxic effects were noted in four tester strains evaluated in experiment II in the following strains and concentrations:

- TA 98: 5,000 µg/plate without metabolic activation
- TA 100 and TA 1535: 1,000 µg/plate and higher, without metabolic activation
- TA 1537: 2,500 µg/plate and higher, with and without metabolic activation)

Mutagenicity: In experiment I, reduction in the number of revertants down to a mutation factor of 0.5 found in tester strain TA 1535 at a concentration of 2,500 µg/plate (without metabolic activation was regarded as not biologically relevant due to a lack of a dose-response relationship.

Table 6.4.1-8 Summary of Results – Experiment I, Reverse Mutation Assay using Bacteria (Salmonella thypimurium and Escherichia Coli) with fenoxaprop-P-ethyl technical

Concentration in µg	Revertant colony counts (mean ±SD); without metabolic activation				
	TA 98	TA 100	TA 1535	TA 1537	WP2 uvrA

A. dest	26 ± 6.2	138 ± 24.8	11 ± 2.3	12 ± 4.5	51 ± 0.6
DMSO	28 ± 4.0	115 ± 10.5	15 ± 7.2	15 ± 2.5	41 ± 4.4
31.6	27 ± 9.0	121 ± 10.6	12 ± 3.2	11 ± 4.0	45 ± 3.8
100	22 ± 10.0	113 ± 17.2	12 ± 4.6	15 ± 1.0	42 ± 4.6
316	23 ± 3.1	129 ±6.7	9 ± 4.6	17 ± 1.0	43 ± 4.0
1,000	24 ± 6.6	120 ± 9.0	11 ± 0.6	14 ± 3.8	45 ± 4.6
2,500	27 ± 6.7	122 ± 3.6	7 ± 0.6	16 ± 2.1	45 ± 3.6
5,000	26 ± 5.8	136 ± 13.8	13 ± 1.7	14 ± 2.9	45 ± 5.5
Positive controls	4-NOPD 10µg	NaN3	NaN3	4-NOPD 40µg	MMS 1µl
	345 ± 30.1	995 ± 57.9	1053 ± 31.7	138 ± 29.1	436 ± 47.9
Concentration in µg	**Revertant colony counts (mean ±SD); with metabolic activation**				
A. dest	31 ± 1.2	115 ± 3.5	12 ± 4.0	9 ± 0.6	66 ± 6.0
DMSO	31 ± 7.0	102 ± 2.9	8 ± 0.6	12 ± 2.3	48 ± 2.6
31.6	30 ± 6.1	100 ± 4.9	11 ± 1.7	13 ± 1.2	51 ± 4.4
100	29 ± 10.5	102 ± 16.6	8 ± 0.6	14 ± 2.3	43 ± 3.5
316	28 ± 2.5	104 ± 9.7	9 ± 4.5	11 ± 3.2	52 ± 1.7
1,000	26 ± 5.5	90 ± 14.7	8 ± 2.6	12 ± 4.4	51 ± 3.2
2,500	26 ± 5.5	77 ± 9.8	7 ± 4.0	8 ± 4.6	51 ± 7.1
5,000	25 ± 7.8	71 ± 15.6	8 ± 4.6	12 ± 3.5	51 ± 6.9
Positive controls	2-AA 2.5µg	2-AA 2.5µg	2-AA 2.5µg	2-AA 2.5	2-AA 10µg
	2856 ± 92.1	1288 ± 35.8	135 ± 10.1	375 ± 15.0	287 ± 17.4

In experiment II, no biologically relevant increases in revertant colony numbers of any of the five tester strains were observed following treatment with fenoxaprop-P-ethyl technical at any concentration level, neither with nor without metabolic activation in experiment I and II.

Table 6.4.1-9 Summary of Results – Experiment II, Reverse Mutation Assay using Bacteria (Salmonella thypimurium and Escherichia Coli) with fenoxaprop-P-ethyl technical

Concentration in µg	**Revertant colony counts (mean ±SD); without metabolic activation**				
	TA 98	**TA 100**	**TA 1535**	**TA 1537**	**WP2 uvrA**
A. dest	18 ± 4.5	108 ± 13.0	8 ± 3.1	6 ± 3.6	44 ± 3.1
DMSO	24 ± 3.6	112 ± 13.7	10 ± 0.6	7 ± 0.6	44 ± 3.0
10.0	20 ± 5.3	89 ± 6.7	10 ± 2.6	9 ± 3.2	33 ± 2.3
31.6	21 ± 3.5	103 ± 6.7	10 ± 5.3	9 ± 2.5	37 ± 6.7
100	19 ± 4.0	87 ± 10.1	11 ± 4.9	11 ± 2.3	40 ± 9.1
316	26 ± 2.1	103 ± 11.9	7 ± 2.1	10 ± 2.9	44 ± 6.4
1,000	23 ± 4.2	94 ± 16.2	6 ± 2.3	7 ± 1.0	45 ± 7.0
2,500	23 ± 7.0	84 ± 4.6	5 ± 1.7	5 ± 0.0	35 ± 5.5
5,000	22 ± 5.0	90 ± 7.9	5 ± 3.6	8 ± 3.0	40 ± 1.5
Positive controls	4-NOPD 10µg	NaN3	NaN3	4-NOPD 40µg	MMS 1µl
	536 ± 56.6	1246 ± 64.7	1162 ± 65.3	161 ± 26.9	634 ± 85.7
Concentration in µg	**Revertant colony counts (mean ±SD); with metabolic activation**				
A. dest	38 ± 4.5	111 ± 22.1	12 ± 2.5	7 ± 2.6	46 ± 9.1
DMSO	29 ± 9.6	106 ± 9.5	9 ± 1.2	7 ± 1.2	51 ± 10.1
10.0	23 ±4.9	82 ± 25.0	9 ± 2.6	6 ± 2.5	43 ± 1.5
31.6	25 ± 4.0	100 ± 17.6	11 ± 3.5	8 ± 3.2	46 ± 3.1
100	25 ± 4.4	86 ± 11.7	7 ± 2.5	9 ± 2.1	46 ± 6.7
316	25 ± 4.7	115 ± 6.5	9 ± 2.6	10 ± 4.6	52 ± 10.7
1,000	27 ± 5.5	102 ± 3.5	6 ± 5.8	8 ± 2.3	57 ± 3.6
2,500	23 ± 3.8	69 ± 1.5	3 ± 2.0	3 ± 2.5	40 ± 18.2
5,000	22 ± 3.8	70 ± 2.6	2 ± 2.5	4 ± 2.5	47 ± 7.2
Positive con-	2-AA 2.5µg	2-AA 2.5µg	2-AA 2.5µg	2-AA 2.5	2-AA 10µg

trols	2972 ± 340.5	1564 ± 36.6	59 ± 1.2	196 ± 11.6	266 ± 22.1

The following table summarizes historical control data of negative and positive controls of the laboratory from 2007-2009.

Table 6.4.1-10 Historical Control Data, Reverse Mutation Assay using Bacteria (Salmonella thypimurium and Escherichia Coli) with fenoxaprop-P-ethyl technical

	Combined Vehicle and Untreated Controls									
	TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Mean	24.0	32.1	113.9	114.5	13.3	10.4	11.0	12.1	55.6	60.3
SD	4.3	6.1	16.2	16.7	4.7	3.0	3.9	4.2	10.6	9.5
Min	18	18	77	78	5	5	5	5	35	38
Max	46	57	163	165	29	27	30	36	83	92
n	909	910	921	921	863	863	859	859	275	275
	Positive Control Values									
Mean	522.5	2378.0	1002.8	2083.8	1099.2	148.3	140.4	278.4	531.6	195.5
SD	145.1	536.1	240.2	528.0	246.7	63.0	34.3	81.8	123.6	61.7
Min	250	260	240	500	389	31	43	58	193	89
Max	1508	3599	2307	3341	1827	387	453	502	1238	583
n	871	872	888	892	825	825	821	821	259	259

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in Salmonella typhimurium and E.coli WP2 uvrA with and without S-9 mix at concentrations up to 5,000 µg/plate.

B.6.4.1.5. Forward mutation test (S. pombe)

Reference:	Forward mutation in Schizosaccharomyces pombe P1. Test substance: Hoe 046360 Substance technical (Code: Hoe 046360 0H ZC96 0002)
Author(s). year:	Edwards C.N., 1986a
Report/Doc. number:	A34056 / Life Science Research Roma Toxicology Centre Report No. 157011-M-01986
Guideline(s):	No guideline available.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-P-ethyl was tested in a forward mutation assay in the yeast strain Schizosaccharomyces pombe P1. The haploid yeast strain S. pombe P1 carries a mutation in a gene involved in the adenine biosynthesis pathway. As a result, it forms bright red colonies. A mutation occurring in any of the preceding five genes prevents the accumulation of the red pigment and the double mutant thus produces white colonies which can be readily scored. The test is performed with and without metabolic activation system.
The test substance Fenoxaprop-p-ethyl (Hoe 046360 0H ZC96 0002) with a purity of 95.6 % (according to the certificate of analysis No. 02912, 1985) was dissolved in DMSO and tested at dose levels of

0 (distilled water and solvent controls); 2.5; 5; 10; 20 and 40 µg/ml

with and without metabolic activation.
Two independent experiments were performed under the same conditions. For metabolic activation, S9-mix from the livers of male Sprague-Dawley rats which were treated with phenobarbitone and betanaphthoflavone were used. The dose levels were defined after a solubility test and a toxicity test. Positive controls were included in every experiment: 1) without metabolic activation: methylmethane-sulphonate; 2) with metabolic activation: cyclophosphamide.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ less than 1.0% L-isomer)

Test strain: Schizosaccharomyces pombe P1

Evaluation criteria: The test substance is considered mutagenic if it induces statistically significant, three-fold increases in mutation frequency at two consecutive dose-levels or at the last non-toxic dose level or at the maximum dose-level tested. The increases must be reproduced in an independent experiment, and solvent control results are used as the reference value.

Findings:
Solubility: At concentrations of 40 µg/ml and above, cloudy suspensions or white precipitates were produced, while at 20 µg/ml a clear solution was obtained.

Toxicity: The test substance did not cause marked toxicity, neither in the presence nor in the absence of S9-mix.

Mutagenicity test: There was no statistically significant increase in mutation frequency at any dose-level, with or without metabolic activation, in two independent experiments. No marked toxicity was observed at any dose-level. Positive responses were achieved with the positive control substances.

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in the yeast strain *Schizosaccharomyces pombe* P1 with and without S9-mix at concentrations up to 40 µg/ml.

B.6.4.1.6. Gene mutation test (CH V79)

Reference:	Gene mutation in Chinese hamster V79 cells. Test substance: Hoe 046360 Substance Technical. Final report
Author(s). year:	Seeberg A.H., 1986
Report/Doc. number:	A34057 / Life Science Research Roma Toxicology Centre Report No. 157013-M-02186
Guideline(s):	OECD guideline 476
Deviations to OECD Guideline 476 (2016):	Number of cells used for main test does not cover spontaneous mutation frequency. No historical control data for negative and positive control substances reported. However, as responses were clear these are considered as minor deviations.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-P-ethyl (Hoe 046360 0H ZC96 0002) with a purity of 95.6 % (according to certificate of analysis 02912, 1985) was tested for mutagenicity in Chinese hamster V79 fibroblast colonies, which are HPRT-deficient and resistant to a toxic purine analogue (6-thioguanine). Mutagenicity was tested in two independent assays with triplicates at concentrations of

0 (solvent control DMSO), 6.25, 12.5, 25, 50 and 100 µg/ml

in the absence and presence of metabolic activation.
S9-mix was derived from phenobarbital and beta-naphthoflavone-induced liver fractions from male Sprague-Dawley rats. Positive control treatments were included in every experiment: ethylmethansulphonate was used in the absence of S9-mix while dimethylnitrosamine was used in the presence of S9-mix. Solubility and toxicity tests were performed before the main study.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ less than 1.0% L-isomer)

Test system: Chinese hamster V79 fibroblasts

Evaluation criteria: A test substance is classified mutagenic if 1) there is a five-fold (or more) increase in mutation frequency compared with the solvent controls, over two consecutive doses of the test substance, or at the last non-toxic dose; 2) the increases are reproduced in an independent experiment; 3) analysis of variance shows a statistically significant effect of the test substance.

Findings:

Solubility: A slightly opaque suspension was achieved at a concentration of 100 µg/ml which indicated that some of the test substance remained undissolved and that the maximum solubility of the test substance was exceeded. On the basis of this finding 100 µg/ml was chosen as the maximum concentration for the toxicity test.

Toxicity: There was no marked toxicity either in the absence or the presence of S9-mix. Therefore 100 µg/ml was selected as the maximum concentration for the main test.

Mutagenicity test: There was no effect of the test substance on pH and osmolality of the treatment solutions. For the cultures treated without S9-mix only very weak toxicity was observed in the first experiment. In the second experiment, however, survival was reduced up to 25 %. In the presence of S9-mix no marked toxicity was observed in either experiment. Regarding mutation frequency, no five-fold increases were observed at any treatment level without S9-mix. In the presence of metabolic activation, one five-fold increase was observed in the second experiment (bold marking in Table 6.4.1-11). This increase was not dose-related and could not be reproduced at the second expression day or at any other dose level. It did not appear to result from the test substance but rather reflected the low spontaneous mutation rate observed at this expression day. The positive controls gave marked responses in both experiments indicating the correct functioning of the test system.

Table 6.4.1-11 Plating efficiency and Mutation counts in experiment II, Gene mutation in Chinese hamster V79 cells with fenoxaprop-P-ethyl

Dose (µg/ml)	Expression Days	S9	RPE	Total Mutation counts	Mean	±SD
0	6	+	100	4	0.4	0.7
	9		100	11	1.1	2.2
6.25	6	+	88	4	0.8	0.8
	9		85	10	2.0	2.4
12.5	6	+	91	1	0.2	0.4
	9		86	1	0.2	0.4
25.0	6	+	96	8	1.6	1.1
	9		85	2	0.4	0.5
50.0	6	+	79	10	**2.0**	**0.7**
	9		96	1	0.2	0.4
100	6	+	77	4	0.8	0.4
	9		88	7	1.4	1.5
Positive Control (DMSO)						
0.00	6	+	100	4	0.4	0.7
	9		100	11	1.1	2.2
5.00	6	+	75	98	19.6	3.9
	9		91	119	23.8	5.4
10.0	6	+	66	155	31.0	6.9
	9		76	169	32.8	6.8

RPE … relative plating efficiency

Conclusion:
Fenoxaprop-P-ethyl was not mutagenic in Chinese hamster V79 cells with and without S-9 mix at concentrations up to 100 µg/ml.

B.6.4.1.7. Newly submitted study: Gene mutation test (MLA)

Reference:	Fenoxaprop-P-ethyl Technical: L5178 TK +/- Mouse Lymphoma assay
Author(s). year:	Flanders L., 2006
Report/Doc. number:	175 FPE / M-548098-01-1
Guideline(s):	OECD guideline 476; EC Method B17 Commission Directive 2000/32/EC; EPA OPPTS 870.5300 (1998)
Deviations to OECD Guideline 490 (2016):	- Number of cells used (10^6) for main test does not cover spontaneous mutation frequency ($6x10^6$ cells recommended). - Dose levels were not corrected for the revised purity value. However, as responses were clear, these are considered as minor deviations.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
The test item fenoxaprop-P-ethyl technical was assessed for its potential to induce mutations at the mouse lymphoma thymidine kinase locus in the cell line L5178Y.

Test material:	fenoxaprop-P-ethyl technical CHA 480, batch 660-PSH-45, dissolved in DMSO
Purity:	96.6% (amended to 95.6% by GLP C of A received 24 April 2006), dose calculation was not adjusted for purity
Test system:	L5178Y TK+/- 3.7.2c mouse lymphoma cell line
Replicate	Twice per dose

A preliminary toxicity test was conducted with fenoxaprop-P-ethyl at up to ten dose levels, followed by three main experiments. Experiment I without and with metabolic activation and experiment II with metabolic activation were performed as a 4 h short-term exposure assay. Experiment II without metabolic activation was performed as a 24 h long-term exposure assay. Upon request of the sponsor, experiment III without and with metabolic activation was performed as a 4 h short-term assay. S9-mix was derived from phenobarbital and beta-naphthoflavone-induced liver fractions from male Sprague-Dawley rats.
The positive controls used for experiments without metabolic activation were EMS (ethylmethanesulfonate) and for experiments with metabolic activation CP (cyclophosphamide).
10^6 cells were treated with the test item in the concentrations for exposure times as follows:
Experiment I
4-hour with and without metabolic activation:
0*, 28.13*, 56.25*, 112.5*, 168.75*, 225*, 300*, 375, 450 µg/ml
positive control EMS 400* µg/ml (-S9), CP 1.25* µg/ml (+S9)

Experiment II
24-hour without metabolic activation:
0*, 7.03, 14.06*, 28.13*, 56.25*, 84.38*, 112.5*, 168.75*, 225 µg/ml EMS 150* µg/ml
4-hour with metabolic activation:
0*, 100, 150*, 175*, 200*, 225*, 250*, 275*, 300 µg/ml, CP 1.25* µg/ml

Experiment III
4-hour without metabolic activation:
0*, 50, 75, 100*, 125*, 150*, 175*, 200*, 225*, 250*, 275* µg/ml, EMS 400* µg/ml
4-hour with metabolic activation:
0*, 125*, 175*, 200*, 225*, 250*, 262.5*, 275*, 287.5* µg/ml, CP 1.25* µg/ml

*plated for viability and TFT resistance

Evaluation criteria: The test item is considered clearly positive if
- the induced mutant frequency (MF) meets or exceeds the Global Evaluation factor (GEF) of 126 mutants per 10^6 cells. The GEF is defined as the mean of the negative/vehicle mutant frequency plus one standard deviation; data are gathered from ten laboratories. For the microwell method the GEF was defined to be 126.
- a dose-dependent increase in mutant frequency is detected.

Findings:
Summary of results for all three experiments are given in Table 6.4.1-12 to Table 6.4.1-15.

Toxicity: In all three exposure groups in the preliminary test, a marked dose-related reduction was observed in the Relative Suspension Growth (%RSG) of cells treated with the test material when compared to the vehicle controls.

In all three experiments, there was evidence of toxicity following exposure to the test material in both the absence and presence of metabolic activation. In Experiment I, there was evidence of a reduction in viability (%V) in the absence of S9, indicating residual toxicity beyond the 48-hour expression period.
Optimum levels of toxicity (80-90%) were not achieved in either the absence or presence of metabolic activation. However, in Experiment II and III near optimum levels of toxicity were achieved in both the absence (27% RSG and 24-27% RTG, resp.) and in presence (27% RSG and 30-37% RTG, resp.) of metabolic activation.
Fenoxaprop-P-ethyl was shown to have a very steep toxicity curve in Experiment I and III. In Experiment I, it was also seen to be marginally more toxic in the absence of S9 when compared to the results of the preliminary toxicity test.
The values observed at the following concentrations were excluded from the statistical analysis

- Experiment I: 168.75 µg/ml in the absence of metabolic activation and at 300 µg/ml in the presence of metabolic activation due to an exceedance of the upper acceptable limit of 90%
- Experiment III: upper dose levels in the presence of metabolic activation (275 µg/ml and 287.5 µg/ml) due to excessive toxicity

Precipitation: In the preliminary test, the test material precipitated at 905 µg/ml and above. No precipitate was observed at the end of the exposure period in all three main experiments.

Mutagenicity: In all three experiments, no statistically significant or dose related increases in the mutant frequency x 10^{-6} per viable cell in either the presence or absence of metabolic activation were observed. In Experiment I, an increase in mutant frequency was observed at 168.75 µg/ml in the absence of S9 and at 275 µg/ml in the presence of S9. However, these values were excluded from the statistical analysis (see above), and due to heterogeneity in replicates were considered to be of no biological relevance. In Experiment III, in the absence of S9, the single dose level 200 µg/ml in the 48-hour expression group was marked as significant, but the increase did not exceed the GEF value and was not considered as part of a clear dose related response. In the presence of metabolic activation, a weak significant response was given for linear trend in both the 48- and 72-hours expression periods. These were considered to have no toxicological significance. The only marked increase in MF was observed in the presence of metabolic activation at a dose level (275 µg/ml) with an unacceptable level of toxicity (4% RTG).

Clastogenicity: No significant alterations in colony size were observed after treatment with fenoxaprop-P-ethyl.

Table 6.4.1-12 Summary of Results: Experiment I, fenoxaprop-P-ethyl technical: L5178 TK+/- Mouse Lymphoma assay

Treatment (µg/ml)	4-Hours -S9			Treatment (µg/ml)	4-Hours +S9		
	%RSG	RTG	MF§		%RSG	RTG	MF§
0	100	1.00	125.22	0	100	1.00	117.34
28.13	89	1.02	124.72	28.13	113	1.15	117.24
56.25	102	1.01	94.32	56.25	102	1.12	145.16
112.5	78	0.89	115.32	112.5	98	1.31	82.46
168.75 [x]	7	0.05	160.00	168.75	48	0.53	145.30
225 [x]	8	0.08	140.91	225	67	1.01	95.45
300 [x]	2	0.01	106.98	300 [x]	3	0.04	128.86
375 [ø]	1			375 [ø]	1		
450 [ø]				450 [ø]	1		
Linear Trend			NS	Linear Trend			NS
EMS				CP			
400	73	0.39	1470.30	1.25	91	0.63	596.12

[x] treatment excluded from test statistics due to toxicity
[ø] not plated due to toxicity or surplus to requirements

MF§ …5-TFT resistant mutants/10^6 viable cells 2 days after treatment

Table 6.4.1-13 Summary of Results: Experiment II, fenoxaprop-P-ethyl technical: L5178 TK+/- Mouse Lymphoma assay

Treatment (µg/ml)	4-Hours -S9			Treatment (µg/ml)	4-Hours +S9		
	%RSG	RTG	MF§		%RSG	RTG	MF§
0	100	1.00	166.34	0	100	1.00	117.34
7.03 Ø	89	1.02	124.72	100 Ø	96		
14.06	135	1.53	138.40	150	82	0.84	147.90
28.13	123	1.34	124.90	175	87	0.84	152.24
56.25	87	0.95	112.32	200	67	0.74	132.22
84.38	43	0.47	135.82	225	61	0.62	147.09
112.5	27	0.30	127.62	250	27	0.29	152.31
168.75 $^{\$\$,X}$	6	(0.04)	(284.26)	275 X	12	0.09	174.35
225 Ø	1			300 Ø	2		
Linear Trend			NS	Linear Trend			NS
Positive control: EMS				Positive control: CP			
150	76	0.70	992.21	1.25	69	0.67	441.67

$^{\$\$}$ treatment excluded due to excessive heterogenicity
X treatment excluded from test statistics due to toxicity
Ø not plated due to toxicity or surplus to requirements
MF§ …5-TFT resistant mutants/10^6 viable cells 2 days after treatment

Table 6.4.1-14 Summary of Results: Experiment III (48-hour expression period), fenoxaprop-P-ethyl technical: L5178 TK+/- Mouse Lymphoma assay

Treatment (µg/ml)	4-Hours -S9			Treatment (µg/ml)	4-Hours +S9		
	%RSG	RTG	MF§		%RSG	RTG	MF§
0	100	1.00	95.85	0	100	1.00	107.02
50 Ø	97			125	85	0.77	168.19
75 Ø	99			175	74	0.87	121.10
100	97	1.04	128.29	200	49	0.56	117.62
125	92	1.08	112.65	225	61	0.64	154.41
150	84	0.94	137.25	250	32	0.32	137.16
175	60	0.72	125.96	262.5	34	0.30	168.38
200	39	0.38	176.99*	275 X	5	0.04	290.71!
225	49	0.57	118.23	287.5 X	18	0.13	190.07
250	43	0.50	113.59				
275	27	0.27	118.37				
Linear Trend			NS	Linear Trend			*
EMS				CP			
400	85	0.61	997.49	1.25	70	0.43	695.58

X treatment excluded from test statistics due to toxicity
! based on one replicate only
MF§ …5-TFT resistant mutants/10^6 viable cells 2 days after treatment

Table 6.4.1-15 Summary of Results: Experiment III (72-hour expression period), fenoxaprop-P-ethyl technical: L5178 TK+/- Mouse Lymphoma assay

Treatment (µg/ml)	4-Hours -S9			Treatment (µg/ml)	4-Hours +S9		
	%RSG	RTG	MF§		%RSG	RTG	MF§
0	100	1.00	122.09	0	100	1.00	90.66
50 Ø	102			125	88	0.83	132.90
75 Ø	93			175	75	0.85	104.81

100	96	0.88	134.18	200	51	0.58	105.20
125	90	0.95	120.14	225	61	0.58	127.43
150	87	0.76	140.17	250	34	0.42	118.53
175	65	0.56	114.48	262.5	37	0.37	145.83
200	38	0.40	130.47	275 [x]	5	0.03	163.80
225	48	0.45	100.89	287.5 [x]	20	0.15	161.30
250	43	0.47	96.21				
275	47	0.24	105.85				
Linear Trend			NS	Linear Trend			*
EMS				CP			
400	78	0.52	1029.57	1.25	70	0.50	488.78

[x] treatment excluded from test statistics due to toxicity
[ø] not plated due to toxicity or surplus to requirements
MF[§] …5-TFT resistant mutants/10^6 viable cells 2 days after treatment
SG = Suspension growth, (24-hr cell count/2) x (48-hr cell count/2) [x 72-hr cell count/2]
Day 0 factor = dose 0-hr cell count / vehicle control 0-hr cell count
%RSG = [(dose SG x dose d0 factor) / vehicle control SG] x100
PE = plating efficiency, -ln P(0) x 100 / number of cells/well; where P(0) = number of negative cells / total wells plated
RCE = PE/mean solvent control PE x100%
RTG = RCE x RSG /100%
MF = {[-ln (P(0) selective medium/cells per well in selective medium]/surviving fraction in non-selective medium

The following table summarizes historical control data for mutation frequencies.

Table 6.4.1-16 Historical Vehicle and Positive Control Mutation Frequencies, fenoxaprop-P-ethyl technical: L5178 TK+/- Mouse Lymphoma assay

	Negative Control		**Positive Control**	
	-S9	+S9	-S9	+S9
Mean	94.40	105.84	959.74	739.60
SD	29.0	34.9	300.9	223.3
Min	52.65	63.64	542.2	498.27
Max	164.98	181.99	1449.2	1502.75
n	20	19	20	19

Conclusion:
Fenoxaprop-P-ethyl did not induce any toxicologically significant increases in the mutant frequency at the TK +/- locus in L5178Y cells and is therefore considered to be non-mutagenic under the conditions of the test.

B.6.4.1.8. Chromosomal aberration test (HLA)

Reference:	Chromosome aberrations in human lymphocytes cultured *in vitro*. Test substance: Hoe 046360 – Substance technical
Author(s). year:	Mosesso P., 1987
Report/Doc. number:	A35218 / Life Science Research Roma Toxicology Centre Report No. 157012-M-02086
Guideline(s):	OECD guideline 473; EEC Directive 92/69, Annex V, Part B
Deviations to OECD Guideline 473 (2016):	- No historical control data for negative and positive control substances reported. - Number of scored metaphases lower than recommended by GD. However, as the response was clear these are considered as minor deviations.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-P-ethyl was tested in an *in vitro* mammalian chromosome aberration test in human lymphocytes. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % according to the certificate of analysis No. 02912, 1985. Solutions of mitomycin-C and cyclophosphamide were prepared in distilled water and served as positive controls, while the vehicle DMSO served as solvent control. A single experiment with duplicate cultures was performed with the lymphocyte cultures from a healthy 23-year old volunteer donor. S9-mix was de-

rived from phenobarbital and beta-naphthoflavone-induced liver fractions from male Sprague-Dawley rats. In the absence of S9-mix, cells were treated for an entire cell cycle and were harvested after 24 hours. In the presence of S9-mix, the treatment time was 2 hours but two harvesting times (12 and 24 hours) were used. A solubility test was performed before the main study. During the main study, the mitotic index was scored for the following range of dose levels

5; 7.9; 12.5; 20; 31; 50*; 79*; 125* µg/ml)

of which *three were selected for scoring also chromosomal aberrations.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ less than 0.1% L-isomer)

Test system: Human lymphocytes

Evaluation criteria: For a substance to be considered clastogenic, statistically significant increases in aberration-bearing cells must be observed at two consecutive dose-levels, or at the highest practicable dose-level. The increases must be reproduced in replicate cell cultures.

Findings:
Solubility: At 125 µg/ml and above opalescent solutions or precipitates were produced while a clear solution was obtained at 100 µg/ml. On the basis of these results, a maximum dose level of 125 µg/ml was selected for treatment.

Main test: There was no effect of the test substance on pH and osmolality of the treatment solutions. In the absence of S9-mix, there was a dose-related depression of the mitotic index. In the presence of S9-mix, a slight reduction in the mitotic index was observed at the high-dose level, although there was no clear pattern of toxicity over the range of dose levels employed. On the basis of toxicity the following three levels were selected for the scoring of aberrations: 50, 79 and 125 µg/ml. One hundred metaphases were scored for chromosomal aberrations from each culture. The test substance did not induce any marked increases in chromosomal aberrations at any test point. Marked increases in the frequency of aberrant cells (mainly chromatid interchange aberrations) were seen in the cultures treated with the positive control substances.

Conclusion:
Fenoxaprop-P-ethyl was not clastogenic in human lymphocytes with and without S9-mix at concentrations up to 125 µg/ml.

B.6.4.1.9. Newly submitted study: Chromosomal aberration test (HLA)

Reference:	Fenoxaprop-P-ethyl Technical: Chromosome aberration test in human lymphocytes *in vitro*
Author(s). year:	Wright N.P., Jenkinson P.; 1994
Report/Doc. number:	178FPE / M-548121-01-1
Guideline(s):	OECD guideline 473 (1997); Method B10 of Commission Directive 2000/32/EC; EPA OPPTS 870.5300 (1998)
Deviations to OECD Guideline 473 (2016):	- Dose levels were not corrected for the revised purity value. - Number of cells not mentioned in study report. - Number of scored metaphases lower than recommended by GD. However, as response was clear these are considered as minor deviations.
GLP:	Yes.
Acceptability:	Yes.

Materials and Methods:
Fenoxaprop-P-ethyl was dissolved in dimethyl sulphoxide (DMSO) and tested in an *in vitro* mammalian chromosome aberration test in human lymphocytes. Solutions of mitomycin-C (MMC) dissolved in Minimal Essential Medium and cyclophosphamide (CP) dissolved in DMSO served as positive controls, while the vehicle DMSO served as solvent control. A single experiment with duplicate cultures was performed with the lymphocyte cultures from different donors. S9-mix was derived from phenobarbital and beta-naphthoflavone-induced liver fractions from male Sprague-Dawley rats. Both in the absence and in the presence of S9-mix, the cells were treated for 4 hours and harvested after further 20 hour incubation (24-hour time point).

Test material:	fenoxaprop-P-ethyl technical CHA 480, batch 660-PSH-45, dissolved in DMSO
Purity:	96.6% (amended to 95.6% by GLP C of A received 24 April 2006),
Test system:	Human lymphocytes from freshly heparinised whole blood
Replicate	Twice per dose

A preliminary toxicity test was performed for 3 exposure treatments using single cultures and concentrations up to 10mM (3,620 µg/ml), where cells were exposed for 4 hours with and without metabolic activation, along with a continuous exposure of 24 hours without metabolic activation. Precipitate observations were made for the three exposure conditions in parallel flasks, containing culture medium without whole blood.
Two experiments were conducted, with the following range of dose levels used, and appropriate *dose levels selected for metaphase analysis:

Experiment 1: 4(20)-hour exposure both groups,
without S9: 0*, 28.28, 56.56, 113.13, 226.25*, 452.5*, 678.75* µg/ml, MMC 0.4* µg/ml
with S9 (2%): 0*; 56.56; 113.13; 226.25*; 452.5*; 905; 1,357.5 µg/ml, CP 5* µg/ml

Experiment 2:
24-hour without S9: 0*, 28.28, 56.56, 113.13*, 226.25*, 339.38, 452.5 µg/ml, MMC 0.2* µg/ml
4(20)-hour with S9 (1%): 0*; 226.25; 452.5; 678.75*; 905; 1,357.5; 1,810* µg/ml, CP 5* µg/ml

A third experiment was conducted to assess the reproducibility of the response observed in Experiment I, and to investigate any potential for the test material to affect cell cycle progression (AGT, average generation time, determination). 3 groups with the following concentrations were used:

4(20)-hour without S9 4(44)-hour without S9	0*; 113.13; 226.25; 452.5*; 565.63; 678.75; 791.88; 905 µg/ml; MMC 0.4* µg/ml
4(20)-hour with S9 (1%) 4(44)-hour with S9 (1%) 4(20)-hour with S9 (2%) 4(44)-hour with S9 (2%)	0*; 226.25; 452.5*; 452.5; 565.63; 678.75; 791.88; 905*; 1,131.25; CP 7.5* µg/ml

Evaluation criteria: For a substance to be considered clastogenic, statistically significant increases in aberration-bearing cells must be observed at two consecutive dose-levels, or at the highest practicable dose-level. The increases must be reproduced in replicate cell cultures.

Findings:
All vehicle (solvent) controls had frequencies of cells with aberrations within the range expected for normal human lymphocytes. All the positive control materials in Experiment 1 and 2 induced statistically significant increases in the frequency of cells with aberrations at the 24 hours harvest time, indicating acceptable performance of the test and of the activity of the metabolising system. In Experiment 3, the positive control material in the absence of S9 induced a statistically significant increase in the frequency of cells with aberrations at the 48 hours harvest time. In the presence of S9, small increases in the frequency of cells with aberrations were seen but the increase was only statistically significant in the 1% S9 group. The positive control cultures from the 24 hours harvest time-point for the 2% S9 exposures group were evaluated and shown to have demonstrated the normal positive response (17.4% cells with aberrations). The metabolic activation system was therefore shown to be functional and the test method itself was operating as expected. It is clear that the clastogenic effects of CP do not persist at high levels at the 48-hour time point.

Solubility: In the preliminary toxicity test, precipitation was observed in the parallel blood-free cultures at the end of the exposure, at and above 113.13µg/ml in exposure groups without metabolic activation and at and above 1,810 µg/ml in the group with metabolic activation. Similar observations were made in experiment 1 and 2. No information on precipitation was given for experiment 3.

In the Preliminary Toxicity test: Metaphase cells of an acceptable quality to score were at concentrations up to 452.5 µg/ml in the 4(20)-hour exposures in the absence of S9 and up to 905 µg/ml in the presence of metabolic activation (S9). In the 24 hours continuous exposure group there were scorable metaphases up to 226.25 µg/ml. Under the three treatment conditions with and without S9, metaphase cells were observed in cultures exposed to 3,620 µg/ml. The study authors considered that this may have occurred as a result of the test material precipitat-

ing out of solution (forming aggregates in some cases) and thereby reducing its availability for uptake into the cells. Fenoxaprop-P-ethyl induced clear evidence of toxicity in all of the exposure groups that extended into the precipitating dose range.
The selection of the maximum dose level for the subsequent experiments was based on reduction in mitotic index compared to concurrent vehicle control cultures.

Table 6.4.1-17 Preliminary toxicity test: Mean mitotic index, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Dose (µg/ml)	4(20)h -S9		4(20)h +S9 (2%)		24h –S9	
	Mitotic Index	% of control	Mitotic Index	% of control	Mitotic Index	% of control
0	5.80	100	6.95	100	5.95	100
14.14	-	-	-	-	-	-
28.28	-	-	-	-	-	-
56.56	-	-	-	-	3.50	59
113.13	6.30C	109	-	-	3.20	54
226.25	8.15C	141	6.15	88	1.85C	31
452.5	4.60C	79	5.60	81	NmC	Nm
905	NmP	Nm	0.75	11	NmC	Nm
1810	NmP	Nm	NmP	Nm	NmP	Nm
3620	-P	-	-P	-	-A	-

- … not assessed for mitotic index
Nm … no scorable metaphases
C, A, P … (cloudy or aggregated) precipitate observed at end of exposure period in blood free cultures

The test material induced statistically significant increases in the frequency of cells with aberrations, in Experiment 1 and 2, both of which used dose ranges that included a dose level that induced approximately 50% or greater mitotic inhibition.
In Experiment 1, the frequencies of cells with aberrations that demonstrated a statistically significant increase were 4.5% at 678.75 µg/ml for the without S9 group (MI = 39%) and 6.5% at 905 µg/ml in the presence of S9 (MI = 23%).

Table 6.4.1-18 Frequency of aberrant cells in Experiment 1, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Concentration (µg/ml)	S9 mix (1%)	Number of scored cells	Harvesting Time	Frequency of aberrant cells (%)	
				Incl. gaps	Excl. gaps
Vehicle control	-	200	24h	0 (0.0)	0 (0.0)
226.25	-	200	24h	7 (3.5)	1 (0.5)
452.5	-	200	24h	2 (1.0)	2 (1.0)
678.75	-	200	24h	13 (6.5)	**9** (4.5)**
Positive control (MMC)	-	100[a]	24h	61 (61.0)	**58*** (58.0)**
Vehicle control	+	200	24h	3 (1.5)	2 (1.0)

226.25	+	200	24h	4 (2.0)	0 (0.0)
452.5	+	200	24h	4 (2.0)	2 (1.0)
905	+	200	24h	19 (9.5)	**13** (6.5)**
Positive control (CP)	+	100[a]	24h	46 (46.0)	**40*** (40.0)**

[a] slide evaluation terminated at 50 cells (each replicate) because approximately 50% cells with aberrations had been observed
** p<0.01, *** p<0.001

Table 6.4.1-19 Mean Frequency of Polyploid cells (%) in Experiment 1, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Dose Level (µg/ml)	4 Hours treatment, harvest time 24 Hours	
	without S9	with 2% S9
0	0.0	0.0
226.25	0.0	0.0
452.5	0.0	0.5
678.75	0.5	NA
905	NA	0.5
MMC 0.4	0.0	NA
CP 5	NA	0.0

NA = not applicable

In Experiment 2, the frequency of cells with aberrations were 2.5% at both the 905 and 1,810 µg/ml in the with-S9 group only (MI = 57% and 44%, respectively). These observed increases were small, most were within the historical range for this laboratory (Table 6.4.1-24 and Table 6.4.1-25), and in some case were apparently at high levels of mitotic inhibition (approaching 80%). Therefore the increases were considered to have no clastogenic significance.

Table 6.4.1-20 Frequency of aberrant cells in Experiment 2, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Concentration (µg/ml)	S9 mix (1%)	Number of scored cells	Harvesting Time	Frequency of aberrant cells (%)	
				Incl. gaps	Excl. gaps
Vehicle control	-	200	24h	3 (1.5)	2 (1.0)
56.56	-	200	24h	2 (1.0)	2 (1.0)
113.13	-	200	24h	3 (1.5)	2 (1.0)
226.25	-	200	24h	4 (2.0)	4 (2.0)
Positive control (MMC)	-	100[a]	24h	59 (59.0)	**51*** (51.0)**
Vehicle control	+	200	24h	2 (1.0)	0 (0.0)
678.75	+	200	24h	7 (3.5)	2 (1.0)
905	+	200	24h	8 (4.0)	**5* (2.5)**
1,810	+	200	24h	6 (3.0)	**5* (2.5)**
Positive control (CP)	+	200	24h	48 (24.0)	**35*** (17.5)**

* p <0.05

Table 6.4.1-21 Mean Frequency of Polyploid cells (%) in Experiment 2, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Dose Level (µg/ml)	4 Hours treatment, harvest time 24 Hours	
	without S9	with 2% S9
0	0.0	0.0
56.56	0.5	NA
113.13	0.0	NA
226.25	0.0	NA
678.75	NA	0.0
905	NA	1.5
1,810	NA	0.0
MMC 0.2	0.0	NA
CP 5	NA	0.0

NA = not applicable

In Experiment 3, the AGT data clearly showed that exposure to the test material increased the duration of the cell cycle by between 2.5 and 8.1 hours and that in treatments in the presence of S9 this correlated with an increase in the mitotic index. The proportion of cells in first metaphase increased with dose of the test material both in the presence of absence of S9. Therefore, cultures that exhibited mitotic indices that were at or close to 50% of vehicle control values were selected from the 48-hours harvest time of each of the three exposure groups and evaluated for chromosome aberrations, together with the vehicle and positive controls. The doses selected were 452.5 µg/ml for the exposure group without S9, and, 905 µg/ml for the groups with S9 at 1% and 2% concentration. The positive control cultures for the with-S9 exposure groups showed only weak responses, although in the 1% S9 group the increase in aberrant cells was significant ($p<0.01$). There are no historical positive control data for the 48-hours harvest time-point. Therefore it was considered that the weak responses were acceptable and the biological system was working as the 24-hours harvest group showed an acceptable positive control response. No statistically significant increases in the number of cells with aberrations were observed in any of the three test material exposure groups.

Table 6.4.1-22 Frequency of aberrant cells in Experiment 3, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Concentration (µg/ml)	S9 mix	Number of scored cells	Harvesting Time	Frequency of aberrant cells (%)	
				Incl. gaps	Excl. gaps
Vehicle control	-	200	48h	5 (2.5)	4 (2.0)
452.5	-	200	48h	8 (4.0)	4 (2.0)
Positive control (MMC)	-	200	48h	45 (22.5)	**40*** (20.0)**
Vehicle control	+ 1%	200	48h	0 (0.0)	0 (0.0)
905	+ 1%	200	48h	8 (4.0)	4 (2.0)
Positive control (CP)	+ 1%	200	48h	9 (4.5)	**8** (4.0)**
Vehicle control	+ 2%	200		4 (2.0)	2 (1.0)
905	+ 2%	200	48h	9 (4.5)	8 (4.0)
Positive control (CP)	+ 2%	149	24h	29 (19.5)	**26*** (17.4)**
Positive control[t] (CP)	+ 2%	200	48h	10 (5.0)	8 (4.0)

** $p<0.01$
*** $p<0.001$
[t] no historical control data available for positive control cultures at 48h harvesting

Table 6.4.1-23 Mean Frequency of Polyploid cells (%) in Experiment 3, fenoxaprop-P-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro*

Dose Level (µg/ml)	4 Hours treatment, harvest time 48 Hours		
	without S9	with 1% S9	with 2% S9
0	0.0	0.0	0.0
452.5	0.0	NA	
905	NA	1.0	905
MMC 0.4	0.0	NA	
CP 7.5	NA	0.0	0.0

NA = not applicable

The following tables summarize the historical control data for vehicle and positive control cultures.

Table 6.4.1-24 Historical control data for vehicle control cultures

	Pulse exposure –S9		Pulse exposure + 1% S9		24-hour –S9		Pulse exposure + 2% S9	
	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids
Min.	0	0	0	0	0	0	0	0
Max.	3	1	4	1.5	4.5	1	2.5	1.5
Mean	0.95	0.13	1.09	0.13	1.18	0.12	0.86	0.19
SD	0.74	0.28	1.02	0.28	0.99	0.24	0.68	0.37
n	47	47	47	47	43	43	40	40

Table 6.4.1-25 Historical control data for positive control cultures

	Pulse exposure –S9		Pulse exposure + 1% S9		24-hour –S9		Pulse exposure + 2% S9	
	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids	% cells with aberrations (-gaps)	% cells with polyploids
Min.	5.5	0	7.5	0	11	0	10.8	0
Max.	68	0.5	42	1	71	0.5	59	0.5
Mean	38.12	0.02	19.71	0.07	37.84	0.01	28.84	0.03
SD	14.70	0.10	8.14	0.21	14.94	0.08	12.54	0.11
n	47	47	47	47	43	43	40	40

Conclusion:
Despite being evaluated in three independent experiments including both 4 hour and 24 hour exposures in the absence of metabolic activation, two different concentrations of S9 (1% and 2%), and two different harvest times (24 and 48 hours), the test material did not induce clearly toxicologically significant increases in the frequency of cells with structural or numerical aberrations. Therefore it was considered that it was not possible to conclude that the test material was unequivocally clastogenic to human lymphocytes *in vitro*.
The test material was considered to be equivocal regarding chromosome aberration to human lymphocytes *in vitro*.

B.6.4.1.10. Gene mutation test (S. cerevisiae)

Reference:	Mitotic gene conversion in S. cerevisiae D4. Test substance: Hoe 046360
Author(s). year:	Edwards C.N., 1986b
Report/Doc. number:	A34058 / Life Science Research Roma Toxicology Centre Report No. 157010-M-01886
Guideline(s):	EEC Directive 79/831, Annex V, Part V
Deviations to OECD GD 480 (1986):	More cells used and shorter incubation time than recommended in the GD. However, as response was clear, these are considered as minor deviations.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-P-ethyl was tested for the ability to induce mitotic gene conversion in the eukaryotic organism Saccharomyces cerevisiae D4, as measured by the induction of prototroph colonies. The test substance (Hoe 046360

0H ZC96 0002) had a purity of 95.6 % according to the certificate of analysis No. 02912, 1985, and was dissolved in DMSO immediately before use. Two independent tests were performed using dose levels of

0; 1.25; 2.5; 5; 10 and 20 µg/ml

with and without S9-mix prepared from phenobarbital and beta-naphthoflavone-induced liver fractions from male Sprague-Dawley rats. Untreated and solvent vehicle controls served as negative controls, while methylmethanesulphonate and cyclophosphamide were used as positive controls for the absence and the presence of metabolic activation, respectively. Solubility and toxicity tests were performed before the main assay.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ less than 0.1% L-isomer)

Test system: Saccharomyces cerevisiae D4

Evaluation criteria: The test substance will be considered to induce mitotic gene conversation if: 1) three-fold increases are observed at two consecutive dose levels. A three-fold increase at a single dose level is sufficient if it is the highest dose level not causing unacceptable toxicity or the highest dose level tested. 2) These increases must be observed in both experiments.

Findings:
Solubility: At concentrations of 20 µg/ml and above cloudy suspensions or white precipitates were produced, while at 10 µg/ml a clear solution was obtained. On the basis of these results, a maximum dose level of 20 µg/ml was selected for use in the toxicity test.

Toxicity: The test substance did not induce marked toxicity at all the dose levels tested (0, 0.2, 0.632, 2, 6.32 and 20 µg/ml) with and without metabolic activation.

Main test: In none of the two independent tests induction of mitotic gene conversion by the test substance was observed. Positive responses were obtained in both tests with the positive control substances.

Conclusion:
Fenoxaprop-P-ethyl did not induce mitotic gene conversion in Saccharomyces cerevisiae D4 in the presence or absence of S9-mix at concentrations up to 20 µg/ml.

B.6.4.1.11. Unscheduled DNA synthesis (primary rat hepatocytes)

Reference:	Evaluation of Hoe 046360 – substance technical in the rat primary hepatocyte unscheduled DNA synthesis assay.
Author(s). year:	Cifone M.A., 1986
Report/Doc. number:	A34916 / Hazelton Biotechnologies Company Project No. 20991
Guideline(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 473.
Deviations:	The first experiment was not evaluated due to unacceptable positive controls.
GLP:	Yes.
Acceptability:	Supplementary information only, due to the missing results of the first experiment.

Materials and Methods:
Fenoxaprop-P-ethyl was tested in primary cell cultures of rat hepatocytes for unscheduled DNA synthesis at a range of fifteen concentrations from 0.025 to 1,000 µg/ml of which the following were chosen for evaluation:

2.51; 5.02; 10; 25.1; 50.2; 100; 201 and 301 µg/ml.

No metabolic activation system was required because of the metabolic capacity of primary hepatocytes. The hepatocytes were obtained from an adult male Fischer 344 rat by perfusion of the liver. The purity of the test substance (Hoe 046360 0H ZC96 0002) was 95.6 % according to certificate of analysis 02912, 1985. Negative controls were performed on cells exposed only to the test material solvent DMSO. 2-acetyl-aminofluorene was used as positive control compound. Two trials were performed. Toxicity and solubility were evaluated in course of the main assay.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ less than 0.1% L-isomer)

Test system: Hepatocytes from Fischer 344 rat

Evaluation criteria: The test material is considered active if 1) there is an increase in the mean net nuclear grain count to at least six grains per nucleus after subtraction of the concurrent negative control value, and/or 2) there is an increase in the percent of nuclei having six or more net grains to at least 10 % of the analysed population after subtraction of the concurrent negative control value, and/or 3) the percent of nuclei with twenty or more grains reaches or exceeds 2 % of the analysed population.

Findings:
Solubility: The test substance appeared soluble in the assay medium up to 25.1 µg/ml but higher concentrations contained a precipitate.

Viability of hepatocytes and toxicity: The hepatocytes were collected at a viability of 83.7 %, and 71.1 % of the viable cells attached to the culture dishes during the 1.5-hour settling period. The treatments were initiated 2 hours later with cell monolayers that were 89.2 % viable. After an additional 21 hours in culture which included the treatment period, the average viable cell count in the solvent control cultures was 83.4 % of the viable count at the beginning of the treatment. This stability in cell number and the normal morphological appearance of the cells indicated that the hepatocyte cultures were in good metabolic condition. Concentrations of 1,000 and 502 µg/ml were lethal to the cell cultures while 301 µg/ml was moderately toxic (41.8 % survival). At 201 and 100 µg/ml the toxicities were moderate to low (56.9 % and 89.2 % survival, respectively). When the concentration was reduced to 50.2 µg/ml, cell number and appearance were similar to the solvent controls. Eight treatments from 2.51 to 301 µg/ml were therefore selected for the analysis of nuclear labelling. The positive was not detectably toxic.

UDS induction: Two trials of the UDS assay were performed but trial 1 was terminated because of unacceptable positive controls. Only the results of trial 2 are presented in the study report. The minimum criteria for UDS in this assay were: a mean net nuclear grain count exceeding 6.39 %; or at least 10.7 % of the nuclei containing six or more grains; or at least 2 % of the nuclei containing twenty or more grains. None of the treatments with the test substance caused nuclear labelling significantly different from the solvent control. In contrast, the 2-acetylaminofluorene treatment induced large increases in nuclear labelling that greatly exceeded all three criteria used to indicate UDS. Heavily-labelled nuclei represent cells undergoing DNA replication as opposed to DNA repair. The number of these cells undergoing DNA-replication present in this study was low (0.01 %) and did not interfere with the assay.

Conclusion:
Fenoxaprop-P-ethyl did not induce UDS in primary rat hepatocytes at concentrations up to 301 µg/ml.

B.6.4.1.12. Unscheduled DNA synthesis (A549 cells)

Reference:	Hoe 046360, substance technical. Detection in the unscheduled DNA synthesis test in mammalian cells *in vitro*
Author(s). year:	Müller W., 1995
Report/Doc. number:	A54045 / Hoechst Report No. 95.0206
Guideline(s):	OECD guideline 482 (1986); EPA guideline 798.5550; EEC Directive 88/302, L 133
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
In this *in vitro* UDS assay a mammalian cell line (A549) was used to test the potential of Fenoxaprop-P-ethyl to induce UDS in concentrations of

0.1, 0.3, 1, 3, 10, 30 and 100 µg/ml

in two independent experiments. The purity of the test substance (Hoe 046360 00 ZC97 0002) was 88.7 %. Cells were treated with and without S9-mix which was derived from the livers of Aroclor 1254 treated male Sprague Dawley rats. Negative controls were either untreated cells or cells treated with the vehicle DMSO. 4-nitroquinoline-N-oxide (without metabolic activation) and benzo(a)pyrene (with metabolic activation) served as positive controls. In order to set appropriate dose levels for the UDS assay a preliminary experiment for cytotoxicity and solubility was performed.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002
Purity: 88.7% (+7.4% L-isomer)

Test system: A549, mammalian lung epithelial carcinoma cell line

Evaluation criteria: The test substance is classified as genotoxic if it induces a reproducible statistically significant increase in [^{3}H] thymidine incorporation compared with the solvent control value in one of the test points, or if it induces a reproducible statistically significant dose-related increase in the incorporation of [^{3}H] thymidine into treated cells.

Findings:
Solubility: The test compound was soluble in the medium up to the concentration of 100 µg/ml which was then used as the maximum dose in the UDS assay. At higher concentrations precipitates were found.

Toxicity: No relevant cytotoxic effects were seen at any test substance with or without metabolic activation.

UDS induction: No relevant reproducible increase in the rate of UDS was observed at any concentration of the test substance. A statistically significant induction of UDS was noted with the positive control substance.

Conclusion:
Fenoxaprop-P-ethyl did not induce UDS in a mammalian cell line with and without metabolic activation at concentrations up to 100 µg/ml.

B.6.4.2. *In vivo* study in somatic cells with fenoxaprop-P-ethyl

Reference:	Hoe46360, substance technical. Micronucleus test in male and female NMRI mice after oral administration
Author(s). year:	[redacted]; 1986
Report/Doc. number:	A34297 / Hoechst Report No. 86.0921
Guideline(s):	EPA guideline: *in vivo* mammalian bone marrow cytogenetic tests: micronucleus assay. HG-Chromo-Micronuc, August 1982
Deviations to OECD Guideline 474 (2016):	- Individual bodyweights as well as standard deviation of mean bw not stated. - Historical negative control distribution mentioned but values not given in the report. - Clinical observations of individual animals not stated. - No blood sample taken and plasma levels not analysed (exposure to bone marrow). - Number of scored cells per animal were lower (10^3) than recommended in the guideline. - Criteria for positive or negative response not stated.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Groups of 5 male and female mice per dose level received fenoxaprop-P-ethyl by oral gavage at the following doses:

0; 1,000; 2,000 or 4,000 mg/kg bw

The dose levels for the micronucleus assay were selected on the basis of a preliminary study to determine the acute toxicity and the maximal applicable dose.

Test material: fenoxaprop-P-ethyl, batch Hoe 046360 0H ZC96 0002
Purity: 95.6% (+ <0.1% L-isomer)

Test animal: NMRI mouse, strain: NMRKf, [redacted]
7-8 weeks old, mean bw of 29.2 g (♂) and 25.6 g (♀)
Number of animals: 5 per sex per dose

Treatment was performed once with the test substance except for the top dose level which was administered in two equal parts within two hours. The animals were killed 24, 48 or 72 hours after administration of the test compound. The test substance (Hoe 046360 0H ZC96 0002) had a purity of 95.6 % (according to certificate of analysis No. 02912, 1985) and was dissolved in sesame oil. Cyclophosphamide at a dose level of 50 mg/kg bw served as positive control and was administered once orally to the mice. Animals receiving cyclophosphamide

were sacrificed 24 hours after treatment. After sacrifice of the animals, bone marrow was removed and 1000 polychromatic erythrocytes were counted for each animal. The number of cells with micronuclei was recorded but not the number of individual micronuclei. As a control measure, 1000 mature erythrocytes were also counted and examined for micronuclei. In addition, the ratio of polychromatic to normochromatic erythrocytes was determined.

Findings:

Preliminary toxicity test: Groups of 3 mice/sex/dose were treated with 4000, 4500 or 5000 mg/kg bw. In all treatment groups clinical signs like reduced spontaneous activity, narrowed or closed palpebral fissures or impaired general health condition were observed. Lethality occurred in 2/3 females of the 4500 mg/kg group and in 1/3 males and 1/3 females of the 5,000 mg/kg group. On the basis of this study, 4,000 mg/kg bw were chosen as the maximum tolerable dose.

Toxicity and clinical signs: All animals survived the application of the test substance. The following signs of toxicity were observed in the 4,000 mg/kg bw dose group: narrow palpebral fissures and reduced spontaneous activity. In between 48 hours after application all animals were free of clinical signs of toxicity. The dissection of the animals revealed rest of the test substance in the stomach or/and tightly filled stomach. Some of the male animals of the 72 hours killing time had lobular pattern of the liver.

Evaluation of micronuclei: The incidences of micronucleated polychromatic erythrocytes in the dose groups of the test substance did not differ significantly from those of the negative controls. However at the low dose group at the 72 hours killing time (male animals) the mean value of the polychromatic cells with micronuclei was slightly increased and outside the normal range of erythrocytes with micronuclei. As can be decided from the individual data this effect was caused due to an unexpected high number of cells with micronuclei in one animal. This observation was found only in one animal at the lowest dose and therefore considered as not test substance related. The ratio of polychromatic erythrocytes to normocytes remained unaffected by the test substance and was statistically not different from control values. Exposure to bone marrow has been shown in previous ADME studies (see section B.6.1). Cyclophosphamid induced a marked and statistically significant increase in of the number of polychromatic erythrocytes with micronuclei in both males and females indicating the sensitivity of the test substance.

Table 6.4.2-1 Findings in bone marrow erhytrocytes after 72h, fenoxaprop-P-ethyl - micronucleus test in male and female NMRI mice after oral administration

Dose (mg/kg)	Sample time (h)	P/N	±SD	Poly (%)	±SD	MI	Normo (%)	±SD	MI
Males									
Control	72	1.03	0.14	0.20	0.17	1.0	0.18	0.15	1.0
1000[a]		1.26	0.28	0.52	0.43	2.6	0.16	0.09	0.9
2000		1.18	0.27	0.26	0.15	1.3	0.14	0.11	0.8
4000		1.15	0.18	0.26	0.09	1.3	0.22	0.24	1.2
Females									
Control	72	1.31	0.22	0.08	0.13	1.0	0.06	0.05	1.0
1000[b]		1.35	0.40	0.20	0.16	2.5	0.02	0.04	0.3
2000[c]		1.37	0.37	0.20	0.25	2.5	0.18	0.13	3.0
4000		1.13	0.22	0.20	0.00	2.5	0.26	0.05	4.3

MI … mutagenic index
Poly … polychromatic. Normo… normochromatic erythrocytes with micronuclei
P/N… poly- to normochromatic erythrocytes ratio
[a] values from one animal outside range; without:0.35±0.24% polychromatic and 0.125±0.05% normochromatic erythrocytes 1.34±0.26% P/N) with micronuclei, resulting in MI of 1.75% and 0.69%
[b] values from one animal outside range; without: 0.15±0.13% polychr. and 0.03±0.05% normochromatic eryhthrocytes with micronuclei (1.26±0.41% P/N), resulting in MI of 1.88% and 0.42%
[c] values from one animal outside range; without: 0.1±0.14% polychr. and 0.23±0.1% normochromatic eryhthrocytes with micronuclei (1.69±0.11% P/N), resulting in MI of 1.25% and 3.83%

Conclusion:

Fenoxaprop-P-ethyl was not mutagenic in the micronucleus test with NMRI mice at doses up to 4000 mg/kg bw Although bone marrow exposure could not be concluded in this study, it is known from ADME studies (see section B.6.1.1.1) that fenoxaprop-P-ethyl reaches blood and thus the bone marrow.

B.6.4.3. *In vitro* studies with fenoxaprop-ethyl

B.6.4.3.1. Ames test

Reference:	Study of the mutagenic potential of the compound Hoe 33171 0H AS201 in strains of Salmonella typhimurium (Ames test) and Escherichia coli
Author(s). year:	Jung *et al.*, 1982
Report/Doc. number:	A24677 / Hoechst Report 432/82
Guideline(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 471 and 472.
GLP:	Yes.
Deviations:	A repeat experiment was only performed with S. typhimurium strain 1535.
Acceptability:	Supplementary information only.

Material and Methods:
Fenoxaprop-ethyl (Hoe 33171 0H AS201) with a purity of 94 % (according to certificate of analysis No. 01888) was tested for mutagenicity in Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and Escherichia coli (WP2uvrA). The test substance was dissolved in DMSO and tested in concentrations of

0 (solvent control); 4; 20; 100; 500; 2,500 and 5,000 µg/plate

in both Salmonella typhimurium and Escherichia coli. Mutagenicity was tested in the absence and presence of S9-mix from Arochlor 1254-induced liver fractions from male Sprague-Dawley rats. Preliminary toxicity tests were performed with all bacterial strains. A reduced rate of spontaneously occurring colonies as well as visible thinning of the bacterial lawn were used as indicator for toxicity. The following substances were used as positive controls: 1) without metabolic activation: sodium azide (TA 100, TA 1535); 9-aminoacridine (TA 1537); 2-nitrofluorene (TA 98, TA 1538); N-methyl-N-nitro-N-nitrosoguanidine (WP2uvrA); 2) with metabolic activation: 2-benzo[a]pyrene (all strains); 2-aminoanthracene (all strains). The mutagenicity test was performed using 3 plates per strain per dose group. No information is presented about statistical evaluation of results.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AS201
Purity: 94.0%

Test strains: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Escherichia coli WP2uvrA

Findings:
Solubility: Visible precipitation or formation of crystals on the plates was observed at 500 µg/plate and above.

Toxicity: Thinning of the bacterial lawn and a reduction in the number of colonies were observed only on few occasions at 2500 or 5000 µg/plate.

Mutagenicity test: The test substance did not cause a significant increase in the number of revertant colonies with any of the tester strains, neither in the absence nor in the presence of S9-mix. However, a small increase in the number of colonies was obtained with TA 1535 in the presence of S9 mix. Therefore the test was repeated with TA 1535 in a second independent experiment. No dose dependent effect was obtained this time.

Conclusion:
Fenoxaprop-ethyl was not mutagenic in Salmonella typhimurium and Escherichia coli with and without S9-mix at concentrations up to 5000 µg/plate.

B.6.4.3.2. Forward mutation test (S. pombe)

Reference:	Study of mutagenic activity "*in vitro*" of the compound Hoe 33171 0H AS 201 with Schizosaccharomyces pombe
Author(s). year:	Mellano D., Mondino A., 1982a
Report/Doc. number:	A24239 / Istituto di ricerche biomediche "Antoine Marxer" S.p.A., Experiment No. M 417
Guideline(s):	No guideline available.
GLP:	Yes.
Deviations:	No repeat experiment performed.
Acceptability:	Therefore, the study is of limited validity.

Material and Methods:
Fenoxaprop-ethyl was tested in a forward mutation assay in the yeast strain Schizosaccharomyces pombe. The haploid yeast strain S. pombe carries a mutation in a gene involved in the adenine biosynthesis pathway. As a result, it forms bright red colonies. A mutation occurring in any of the preceding five genes prevents the accumulation of the red pigment and the double mutant thus produces white colonies which can be readily scored. The test is performed with and without metabolic activation system.
The test substance Fenoxaprop-ethyl (Hoe 33171 0H AS 201) was dissolved in DMSO and tested at concentrations of

0; 125; 250; 500 and 1,000 µg/ml

with and without metabolic activation. For metabolic activation, S9-mix from the livers of male Sprague-Dawley rats which were treated with Aroclor 1254 were used. The purity of the test substance was 94.0 % according to the certificate of analysis No. 01888, 1982. The positive controls used were methylmethane-sulphonate (without metabolic activation) and dimethylnitrosamine (with metabolic activation). No information is provided about determination of solubility and toxicity. Comparison of the spontaneous mutant frequency in the negative control groups with that of the treatment groups and of the positive control groups was conducted by chi-square method.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AS201
Purity: 94.0%

Test strain: Schizosaccharomyces pombe

Findings:
Solubility: There is no information on solubility of the test substance.

Toxicity: At the highest dose level of 1000 µg/ml, survival rates in the cultures were 51 % and 88 % in the absence and in the presence of metabolic activation, respectively.

Mutagenicity test: In the single experiment, statistical analysis of the results revealed no significant difference at any dose-level and with or without metabolic activation. Clear significant positive responses were achieved with the positive control substances.

Conclusion:
Fenoxaprop-ethyl was not mutagenic in the yeast strain Schizosaccharomyces pombe with and without S9-mix at concentrations up to 1000 µg/ml.

B.6.4.3.3. Chromosomal aberration test (HLA)

Reference:	Study of the capacity of the test article Hoe 33171 0H AS 201 to induce chromosome aberrations in human lymphocytes cultured *in vitro*
Author(s). year:	Mellano D., Mondino A., 1982b
Report/Doc. number:	A26227 / Istituto di ricerche biomediche "Antoine Marxer" S.p.A., Experiment No. M 419
Guideline(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 473.
GLP:	Yes.
Deviations:	No information on solubility, cytotoxicity, and changes in pH or osmolality presented in the study report. No duplicate cultures were used.
Acceptability:	Therefore, the study is of limited validity.

Material and Methods:

Fenoxaprop-ethyl was tested in an *in vitro* mammalian chromosome aberration test in human lymphocytes. The purity of the test substance (Hoe 33171 0H AS 201) was 94.0 % according to the certificate of analysis No. 01888, 1982. Fenoxaprop-ethyl was dissolved in DMSO and tested at concentrations of

0; 1; 10; 100 and 1,000 µg/ml.

There is no information if solubility or toxicity tests were performed in advance of the main study. Positive controls were mitomycin C (without metabolic activation) and cyclophosphamide (with metabolic activation). S9-mix was prepared from the livers of male Sprague-Dawley rats treated with Aroclor 1254. The human lymphocytes were derived from a healthy male volunteer. After 3 hours of exposure to the test substance, the test medium was replaced with fresh culture medium and cells were incubated for another 23 hours. For each treatment group about 100 metaphases were examined. The Chi square method was used to compare the incidences of aberrations.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AS201
Purity: 94.0%

Test system: Human lymphocytes

Findings:
The test substance was found to be toxic at 1,000 µg/ml with metabolic activation so that this treatment group could not be evaluated. There was no increase in chromosomal aberrations observed in the cells treated with the test substance. The reference mutagens produced statistically significant increases in the percentage of chromosome aberration incidence both including and excluding gaps.

Conclusion:
Fenoxaprop-ethyl was not clastogenic in human lymphocytes, in the absence of metabolic activation up to the concentration of 1000 µg/ml and in the presence of metabolic activation up to 100 µg/ml.

B.6.4.3.4. Gene mutation test (S. pombe)

Reference:	Study of mutagenic activity of the compound Hoe 33171 0H AS 201 with Saccharomyces pombe – Gene conversion-DNA repair test
Author(s). year:	Mellano D., Mondino A., 1982c
Report/Doc. number:	A24238 / Istituto di ricerche biomediche “Antoine Marxer” S.p.A., Experiment No. M 416
Guideline(s):	No guideline is mentioned in the study report. However, the study was performed to meet EEC Directive 79/831, Annex V, Part B.
GLP:	Yes.
Deviations:	There is no information on solubility or cytotoxicity presented in the study report. No repeat experiment was performed.
Acceptability:	Therefore, the study is of limited validity.

Material and Methods:
Fenoxaprop-ethyl was screened for the induction of gene conversion at the “Ade 2” and “Trp 5” loci on different chromosomes of Saccharomyces cerevisiae at concentrations of

0, 125, 250, 500 and 1,000 µg/ml.

The purity of the test substance (Hoe 33171 0H AS 201) was 94.0 % according to the certificate of analysis No. 01888, 1982. Cyclophosphamide and methylmethanesulphonate served as positive controls for treatment with and without metabolic activation, while the vehicle DMSO was used for negative controls. S9-mix was prepared from the livers of male Sprague-Dawley rats which received a single dose of Aroclor 1254. There is no information on solubility or cytotoxicity presented in the study report and only a single mutagenicity experiment was performed.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AS201
Purity: 94.0%

Test strain: Saccharomyces pombe

Evaluation criteria: The spontaneous mutant frequency in the negative controls were compared with that of the test article incubations and with positive controls. Statistical significances were calculated using the chi-square method.

Findings:
Mutagenicity test: No statistically significant differences were observed between controls and test article incubations. The reference mutagens induced a significant increase in convertant frequency with respect to controls.

Conclusion:
Fenoxaprop-ethyl did not induce mitotic gene conversion in Saccharomyces cerevisiae in the presence or absence of S-9 mix at concentrations up to 1,000 µg/ml.

B.6.4.3.5. Unscheduled DNA synthesis test (HeLa cells)

Reference:	Study of the capacity of the test article Hoe 33171 0H AS 201 to induce "unscheduled DNA synthesis" in cultured HeLa cells
Author(s). year:	Mellano D., Mondino A., 1982d
Report/Doc. number:	A24582 / Istituto di ricerche biomediche "Antoine Marxer" S.p.A., Experiment No. M 418
Guideline(s):	No guideline is mentioned in the study report. However, the study was performed to meet OECD guideline 473.
GLP:	Yes.
Deviations:	No repeat experiment was performed in this study. Information on solubility and investigation of toxicity is missing.
Acceptability:	Therefore, the study is of limited validity.

Material and Methods:
Fenoxaprop-ethyl was tested in the mammalian cell line HeLa for unscheduled DNA synthesis at concentrations of

0, 5, 50 and 500 µg/ml

without and with metabolic activation. The S9-mix was derived from the livers of adult male Sprague-Dawley rats treated with Aroclor 1254. The purity of the test substance (Hoe 33171 0H AS 201) was 94.0 % according to certificate of analysis 01888, 1982. The vehicle DMSO served as negative control substance, while cyclophosphamide and methylmethanesulfonate were used as positive controls for treatment with and without metabolic activation. Only one trial was performed. No preliminary assay on solubility and toxicity of the test substance was conducted. UDS activity was detected by incorporation of tritiated thymidine in the presence of hydroxyurea.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AS201
Purity: 94.0%

Test system: Mammalian cell line HeLa

Evaluation criteria: The genotoxic activity can be identified if the detected radioactivity in the cultures treated with test substance is statistically greater than that of the controls and if a statistically significant positive response is induced by the positive controls.

Findings:
Solubility: There is no information on solubility of the test substance.

Toxicity: The test substance was found to be toxic at 500 µg/ml in the test without metabolic activation.

UDS induction: No increase of radioactivity was observed in the cultures treated with the test substance compared to the control cultures. In contrast, the reference mutagens induced increases in radioactive labelling.

Conclusion:
Fenoxaprop-ethyl did not induce UDS in HeLa cells with and without S9-mix at concentrations up to 500 µg/ml.

B.6.4.4. *In vivo* study with fenoxaprop-ethyl

Reference:	Mouse micronucleus test with Hoe 033171, substance technical grade
Author(s). year:	[redacted] 1986
Report/Doc. number:	A34294 / RCC Project No. 066813
Guideline(s):	EPA guideline 84-1 and 84-2 (1983); OECD guideline 474, EEC Directive 84/449 No. B 12
Deviations to OECD Guideline 474 (2016):	- Number of scored cells per animal were lower (10^3) than recommended in the guideline. - No historical control data (negative and positive) reported.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
6 mice per sex per group received single doses of

0; 750; 1,500 or 3,000 mg/kg bw

fenoxaprop-ethyl by oral gavage. The maximum tolerated dose was based on acute oral toxicity data which indicated that the highest dose of 3000 mg/kg corresponded to approximately 50 – 80 % of the acute oral LD50 data on mice.
Fenoxaprop-ethyl (Hoe 033171 0H ZD97 0001) had a purity of 96.1 % (according to reanalysis, 1986) and was dissolved in sesame oil. The animals of the positive control groups received 50 mg/kg bw of cyclophosphamide.
24, 48 and 72 hours after treatment, 6 mice/sex/dose group were sacrificed for examination. The first five animals of each sex were evaluated while the remaining animal was evaluated only if macroscopic examination of the slide revealed technical imperfections or if a test animal died prematurely. Bone marrow was removed, and 1000 polychromatic erythrocytes were scored under the microscope for the incidence of micronuclei. The calculated ratio of polychromatic to normochromatic erythrocytes based on 1000 erythrocytes scored per slide measured the toxic effect of the test substance.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H ZD97 0001
Purity: 96.1%

Test animal: NMRI mouse, [redacted]
11 weeks old, bw of 29-40 g (♂) and 24-33 g (♀)

Evaluation criteria: Frequencies of micronuclei were evaluated statistically. If the test substance produced no statistically significant positive response at any of the test points, it was considered to be non-mutagenic in this system.

Findings:
Toxicity and clinical signs: No death occurred during the treatment period and no treatment-related clinical findings were observed.
Evaluation of micronuclei: No significant test substance related increases of micronucleated polychromatic erythrocytes were observed in either males or females of the treated groups when compared with corresponding negative control groups at the three examination times. The ratio of polychromatic to normochromatic erythrocytes was not affected by the test substance. In contrast, cyclophosphamide induced a statistically significant increase in the number of micronuclei in polychromatic erythrocytes at 24 and 48 hours post-application and decreased the ratio of polychromatic to normochromatic erythrocytes at 48 and 72 hours post-application.

Conclusion:
Fenoxaprop-ethyl was not mutagenic in the micronucleus test with NMRI mice at doses up to 3,000 mg/kg bw.

B.6.4.5. *In vivo* studies in germ cells
The *in vitro* as well as the *in vivo* studies are showing negative results and therefore it is not considered necessary to perform an *in vivo* study in germ cells.

B.6.5. LONG-TERM TOXICITY AND CARCINOGENESIS

The long term toxicity and carcinogenicity studies were performed with fenoxaprop-ethyl from which the information on long term toxicity and carcinogenicity was bridged to fenoxaprop-P-ethyl.
Therefore, an important aspect of the toxicological studies, including acute and subchronic toxicity, embryotoxicity and mutagenicity, was to establish whether there were differences between the toxicological profiles of 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 the studies with fenoxaprop-ethyl. A comparison was provided by Leist and Ebert (A40415, 1989).
This comparative toxicological evaluation summarizes the results of the toxicological studies performed with both compounds to assess whether they differ in their toxicological profiles or not. Both compounds 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 and LC_{50} concentration higher than 604 mg/m^3 of fenoxaprop-ethyl and 511 mg/m^3 of fenoxaprop-P-ethyl, which were the highest technically feasible concentrations. The LD_{50} values and the clinical signs of intoxication of both compounds corresponded closely, particularly in the rat. Neither of the compounds showed mutagenic potential in a variety of tests with different end-points. Repeated-dose (4-week) and subchronic (3-month) feeding studies in rat, mouse and dog indicated that the toxicological profiles of both compounds were identical indicating that also in the longer-term studies similar profiles can be expected. Also testing for prenatal development in rats and rabbits indicated that both compounds 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 is concluded that the toxicological profile of fenoxaprop-P-ethyl is identical to that of fenoxaprop-ethyl. There was nothing within the available datasets to indicate any differences of toxicological significance between fenoxaprop-P-ethyl and fenoxaprop-ethyl. Thus from a toxicological point of view, it is considered justified to base the evaluation of chronic toxicity and oncogenicity and the calculation of the ADI for fenoxaprop-P-ethyl on the long-term studies with fenoxaprop-ethyl.

Summary of long-term toxicity and carcinogenicity 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 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. In the high dose study, Fenoxaprop-ethyl caused carcinogenicity in the liver of rats. 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. 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. 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, slight decreases in bodyweight were observed at the high dose in both sexes, in males additionally at the mid dose, however did not follow a dose relation. Dose-related reductions in organ weights of thyroid (relative to bw) in males and ovaries in females (absolute and relative to bw) were observed. The study authors stated that these effects were a result of inadequate exsanguinations. The applicant submitted a position paper with detailed reasoning and historical control data, which did not fulfil the criteria set out in Regulation (EC) No 283/2013. However, statistically significant changes in the organ weights of thyroid and ovaries were observed at the high dose

only (75 ppm), and no histopathological changes occurred. As also a high variability in organ weights was noted, these effects were not considered as relevant. Therefore 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).

Results summary of chronic toxicity and carcinogenicity studies with fenoxaprop-ethyl

Study, reference	Dose levels	NOAEL	LOAEL	Effects observed at the LOAEL
28 months chronic toxicity and carcinogenicity study in rats [redacted] *1985a* A31880, CA 5.5/30 Combined chronic toxicity and carcinogenicity study in rats. Part II [redacted]. *1985b, 1987* A31878, CA 5.5/6	0, 5, 30 and 180 ppm fenoxaprop-ethyl (0-0.3-1.6-9.4 mg/kg bw/d for males and 0-0.3-2.0-11.9 mg/kg bw/d for females)	30 ppm ♂: 9.4 ♀: 2.0 mg/kg bw/d	180 ppm ♂: 9.4 ♀: 11.9 mg/kg bw/d	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 month: increased adrenals weight: distension of the sinuses of the zona reticularis and of medulla of adrenal, 24 and 28 months: decreased liver weight, no carcinogenicity observed. No significant differences between treated and control animals.
Chronic study in rats -interim kill after 6 months [redacted]., *1983a* A30803, CA 5.5/1	0, 5, 30 and 180 ppm fenoxaprop-ethyl in diet (0-0.3-2.0-11.9 mg/kg bw/d for males and 0-0.4-2.5-14.6 mg/kg bw/d for females)	30 ppm ♂: 2.01 ♀: 2.45 mg/kg bw/d	180 ppm ♂: 11.88 ♀: 14.58 mg/kg bw/d	Lipid changes (cholesterol reduced), liver weight increase
Chronic study in rats -interim kill after 12 months [redacted] *1983b* A29693, CA 5.5/2 Supplement: Determination of hepatic enzyme levels [redacted] *1984* A29694, CA 5.5/3	0, 5, 30 and 180 ppm fenoxaprop-ethyl in diet (0-0.3-1.7-10.2 mg/kg bw/d for males and 0-0.4-2.1-13.3 mg/kg bw/d for females)	30 ppm ♂: 1.7 ♀: 2.1 mg/kg bw/d	180 ppm ♂: 10.2 ♀: 13.3 mg/kg bw/d	In the adrenals frequent occurrences of more pronounced sinus dilatation in the zona reticularis and the medulla, but without tissue lesions
		>180 ppm	>180 ppm	The biochemical examinations showed that feeding of Hoe 33171 in concentrations of 5, 30 or 180 ppm over a 12-months period did not lead to an induction of foreign substance metabolism or to peroxisome proliferation. Moreover, histological examination of the livers showed that no organ changes resulted from feeding of Hoe 33171.
24 months study in rats [redacted] *1984a* A30807, CA 5.5/4 Supplement: Determination of residues in organs and tissues [redacted] *1985* A30804, CA 5.5/5	0, 5, 30 and 180 ppm fenoxaprop-ethyl in diet (0-0.3-1.6-9.4 mg/kg bw/d for males and 0-0.3-2.0-11.9 mg/kg bw/d for females)	30 ppm ♂: 1.58 ♀: 2.0 mg/kg bw/d	180 ppm ♂: 9.43 ♀: 11.87 mg/kg bw/d	Liver weight increase
				The residue examinations showed that feeding of 5, 30 or 180 ppm Hoe 33171 resulted in dose-related residues in organs and tissues of rats. However, there was no accumulation of residues over a period of time. No differences were observed between males and females.

Study, reference	Dose levels	NOAEL	LOAEL	Effects observed at the LOAEL
24 months carcinogenicity study in NMRI mice [redacted] *1985c* A30816, CA 5.5/7	0, 2.5, 10 and 40 ppm fenoxaprop-ethyl (0-0.34-1.38-5.48 mg/kg bw/d for males, 0-0.40-1.61-6.54 mg/kg bw/d for females)	40 ppm ♂: 5.48 ♀: 6.54 mg/kg bw/d	-	-
Chronic study in mice -interim kill after 12 months [redacted] *1983c* A29695, CA 5.5/8 Supplement: Determination of hepatic enzyme levels [redacted] *1984b* A29696, CA 5.5/9	0, 2.5, 10 and 40 ppm fenoxaprop-ethyl in diet (0-0.35-1.30-5.54 mg/kg bw/d for males, 0-0.43-1.63-6.59 mg/kg bw/d for females)	10 ppm ♂: 1.30 ♀: 1.63 mg/kg bw/d	40 ppm ♂: 5.54 ♀: 6.59 mg/kg bw/d	Kidney weight increases (absolute and relative) in both sexes, without histological correlate
		>40 ppm	>40 ppm	No induction of foreign substance metabolism or peroxisomal proliferation. Moreover, histological examination of the livers showed that no organic changes were due to feeding of Hoe 33171.
24 months carcinogenicity study in NMRI mice [redacted] *1996* A57500, CA 5.5/13 Supplement: Histophotographs [redacted] *1996* A58176, CA 5.5/14	0, 40, 115 and 320 ppm fenoxaprop-ethyl (0-5.67-16.59-44.63 mg/kg bw/d for males, 0-6.83-19.44-53.68 mg/kg bw/d for females)	40 ppm ♂: 5.67 ♀: 6.83 mg/kg bw/d	115 ppm ♂: 16.59 ♀: 19.44 mg/kg bw/d	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
Repeated 2 year oral study in beagle dogs [redacted] *1985* A31854, CA 5.3.2/11 Supplement [redacted] *1987* A37042, CA 5.3.2/12	0, 3, 15 and 75 ppm fenoxaprop-ethyl in diet (0-0.2-1.1-5.2 mg/kg bw/d for males, 0-0.18-0.9-4.6 mg/kg bw/d for females)	15 ppm ♂: 1.1 ♀: 0.9 mg/kg bw/d	75 ppm ♂: 5.2 ♀: 4.6 mg/kg bw/d	75ppm: ⇩ bodyweight in ♀ ⇩ haematological parameters ⇧ clinical chemistry ⇧ thyroid weight (relative to bw) in ♂ ⇧ ovaries weight (abs.+rel. to bw) in ♀

B.6.5.1. Studies with fenoxaprop-P-ethyl

No long term toxicity or carcinogenicity study has been performed with Fenoxaprop-P-ethyl.

B.6.5.2. Oral studies in rats with fenoxaprop-ethyl

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.

B.6.5.2.1. 24-months study

Reference:	Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Combined chronic toxicity and carcinogenicity study in rats (24 and 28 months feeding study)
Author(s). year:	[redacted]., 1985a
Report/Doc. number:	A31880 / Hoechst Report No. 85.0688
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	The following deviations concern all individual studies indicated in Table 6.5.2-1 - Animal maintenance: humidity around 10-20% higher than recommended - No ophthalmological examinations performed - Chronic toxicity phase: No measurements for haematology, clinical chemistry and urinalysis at 3 months conducted. - Haematological analysis of coagulation time: not specified which parameter was used. - Urinalysis: volume not assessed. - Organ weights (in chronic toxicity phase) and pathology of epididymides, uterus and parathyroids not assessed. - Pathology: lacrimal gland, coagulating gland, vagina and Harderian gland as well as the required three section levels of brain not assessed. - Test Report: Physical nature and physicochemical properties not reported.
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
116 male and 116 female rats per dose group were treated with 0, 5, 30 or 180 ppm Fenoxaprop-ethyl for different periods of time. The test concentrations were derived from the results of a subchronic toxicity study, where data indicated that chronic application of 180 ppm Hoe 33171 would produce a toxic effect.

Test material and Purity:	Hoe 33171 0H AT206 for the first month of the study; purity 95.8 % (according to certificate of analysis No. 01805) Hoe 33171 0H AS201 for the rest/major part of the study; purity 94.0% (according to certificate of analysis No. 01888)
Test animal:	Wistar rats, Hoe:WISKf(SPF71), source [redacted] 4 weeks old, mean bw of 133 g (♂) and 118 g (♀)
Number of animals:	116 per sex per dose group

Table 6.5.2-1 Study design and number of animals, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats

	Number of animals/group	Reference	Report No.
Chronic toxicity			
6-month interim sacrifice	10 males / 10 females	[redacted]., 1983a	24/83
12-month interim sacrifice Determination of hepatic enzyme levels	10 males / 10 females	[redacted]., 1983b [redacted] 1984	83.0613 84.0639
24 months treatment period BSP/PSP function tests	26 males / 26 females	[redacted] 1984a	84.0632
Residue examination	10 males / 10 females	[redacted] 1985	84.0205
Carcinogenicity			
28 months treatment period	60 males / 60 females	[redacted] 1985b	85.0682

The actual intake of Fenoxaprop-ethyl was calculated separately for each period of treatment time.

Table 6.5.2-2 Test substance intake in mg/kg bw/d, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats

Dietary level	Test substance intake in mg/kg bw/d

	Males				Females			
	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. 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).
Haematology (at 6, 12 and 24 months), non-starved animals: erythrocytes, haemoglobin, haematocrit, 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 analysed were ALP, LDH, glycerophosphate dehydrogenase and malate enzyme together with microsomal lipid peroxidation.
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, oesophagus, 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 in each specific study report):
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.

Haematology: 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 peroxisome 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 no 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 peroxisome 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.

B.6.5.2.1.1. 6 months interim kill

Reference:	Chronic feeding study in rats (interim killing after 6 months)
Author(s). year:	[redacted] 1983a
Report/Doc. number:	Hoechst Report No. 24/83 / A30803
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	Please refer to [redacted] *et al. 1985* (at the beginning of this section, B.6.5.2.1).
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
Please refer to [redacted] *et al.*, 1985a (at the beginning of this section, B.6.5.2.1).

Findings (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 haemorrhage of the urinary bladder. The cause of the haemorrhage 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 6.5.2-3 Body weight data, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Initial body weight (g)	133	134 +0.8%	130 -2.3%	134 -0.8%	121	120 -0.8%	114 -5.8%	115 -5.0%
Terminal body weight (g)	433	430 -0.7%	455 +5.1%	**475*** **+9.7%**	258	254 -1.6%	243 -5.8%	245 -5.0%
Bodyweight gain (g)	300	296	325 +8.3%	341 +13.7%	137	134	129 -5.8%	130 -5.1%

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

Food consumption: There was no effect observed.

Haematology: 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 6.5.2-4 Relevant haematology and clinical chemistry findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 6 months interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Haematology								
Leucocyte count (10^9/L)	5.3	5.2 -1.9%	6.7 +26.4%	6.8 +28.3%	4.1	4.3 -4.9%	4.5 -9.8%	**5.5*** **+34.1%**
Clinical chemistry								
Cholesterol (mmol/L)	2.14	1.86 -13.1%	**1.66*** **-22.4%**	**1.46*** **-31.8%**	2.10	1.79 -14.8%	**1.59*** **-24.3%**	1.78 -15.2%
Total lipids (g/L)	3.47	**2.49*** **-28.2%**	2.81 -19.0%	3.07 -11.5%	3.18	**2.59*** **-18.6%**	3.04 -4.4%	3.55 +11.6%

* ($p<0.05$); 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 6.5.2-5 Absolute[1] and relative organ weights, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Kidneys weight								
absolute (g)[1]	*2.47*	*2.35* -4.9%	*2.64* +6.9%	*2.93* +18.6%	*1.53*	*1.63* +6.5%	*1.55* +1.3%	*1.72* +12.4%
relative (% bw)	0.571	0.551 -3.5%	0.585 +2.5%	0.612 +7.2%	0.594	0.639 +7.6%	0.636 +7.1%	**0.707*** **+19.0%**
Liver weight								
absolute (g)[1]	*12.42*	*12.35* -0.6%	*12.55* +1.0%	*13.89* +11.8%	*8.09*	*7.55* -6.7%	*7.72* -4.6%	*8.10*
relative (% bw)	2.863	2.863	2.760 -3.6%	2.932 +2.4%	3.141	2.972 -5.4%	3.173 +1.0%	3.290 +4.7%
Spleen weight								
absolute (g)[1]	*0.68*	*0.65* -4.4%	*0.71* +4.4%	*0.72* +5.9%	*0.46*	*0.50* +8.7%	*0.49* +6.5%	*0.53* +15.2%
relative (% bw)	0.158	0.152 -3.8%	0.156 -1.3%	0.151 -4.4%	0.179	0.198 +10.6%	0.202 +12.8%	**0.216*** **+20.7%**
Adrenals weight								
absolute (g)[1]	*0.0469*	*0.0483* +3.0%	*0.0530* +13.0%	*0.0549* +17.1%	*0.0724*	*0.0726*	*0.0802* +10.8%	*0.0732* +1.1%
relative (% bw)	0.0108	0.0113 +4.6%	0.0117 +8.3%	0.0116 +7.4%	0.0282	0.0287 +1.8%	**0.0330*** +17.0%	0.0299 +6.0%

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Thymus weight								
absolute (g)[1]	*0.334*	*0.498* +49.1%	*0.442* +32.3%	*0.529* +58.4%	*0.273*	*0.337* +23.4%	*0.337* +23.4%	*0.361* +32.2%
relative (% bw)	0.077	0.115 +49.4%	0.097 +26.0%	0.110 +42.9%	0.106	0.132 +24.5%	0.137 +29.2%	**0.146*** **+37.7%**
Pituitary weight								
absolute (g)[1]	*0.0103*	*0.0082* -20.4%	*0.0104* +1.0%	*0.0122* +18.4%	*0.0153*	*0.0148* -3.3%	*0.0140* -8.5%	*0.0134* -12.4%
relative (% bw)	0.0024	**0.0019*** **-20.8%**	0.0023 -4.2%	0.0026 +8.3%	0.0060	0.0059 -1.7%	0.0058 -3.3%	0.0054 -10.0%

* (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 6.5.2-6 Histopathology findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 6 month interim sacrifice

	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 (B.6.5.2.1), Ref.: *Donaubauer et al., 1985a,* Doc. No. A31880, Hoechst Report No. 85.0688

B.6.5.2.1.2. 12 months interim kill

Reference:	Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Chronic feeding study in rats (interim killing after 12 months)
Author(s). year:	[redacted] 1983b
Report/Doc. number:	Hoechst Report No. 83.0613 / A29693
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	Please refer to [redacted]. *1985* (at the beginning of this section, B.6.5.2.1).
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
Please refer to [redacted] *1985* (at the beginning of this section, B.6.5.2.1)

Findings (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 6.5.2-7 Body weight data, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Initial body weight (g)	134	132 -1.5%	131 -2.2	139 +3.7%	120	116 -3.3%	115 -4.2%	109 -9.2%
Terminal body weight (g)	496	522 +5.2%	511 +3.0%	530 +6.9%	282	297 +5.3%	296 +5.0%	280 -0.7%
Bodyweight gain (g)	362	390 +7.7%	380 +5.0%	391 +8.0%	162	181 +11.7%	181 +11.7%	171 +5.6%

* (p<0.05); significantly different from controls

Food consumption: Food consumption was similar in controls and treatment groups.

Haematology: Statistical significance was only reached in females of the 30 ppm group which showed increases in haemoglobin and haematocrit 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 6.5.2-8 Relevant clinical chemistry findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Cholesterol (mmol/L)	3.00	2.81 -6.3%	2.67 -11.0%	**2.36*** **-21.3%**	2.86	2.58 -9.8%	**2.10*** **-26.6%**	**1.87*** **-34.6%**
Total lipids (g/L)	4.71	**4.02*** **-14.6%**	4.28 -9.1%	3.60* -23.6%	4.05	3.53 -12.8%	3.94 -2.7%	3.19* -21.2%

* (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 6.5.2-9 Absolute[1] and relative organ weights, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 12 month interim sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Adrenals weight								
absolute (g)[1]	*0.0443*	*0.0473* +6.8%	*0.0538* +21.4%	*0.0574* +29.6%	*0.0722*	*0.0706* -2.2%	*0.0662* -8.3%	*0.0711* -1.5%
relative (% bw)	0.0090	0.0091 +1.1%	**0.0106*** **+17.8%**	**0.0108*** **+20.0%**	0.0258	0.0238 -7.8%	0.0227 -12.0%	0.0254 -1.6%
Liver weight								
absolute (g)[1]	*14.16*	*14.21*	*13.35* -5.7%	*14.53* +2.6%	*8.78*	*8.49* -3.3%	*8.22* -6.4%	*8.00* -8.9%
relative (% bw)	2.864	2.722 -5.0%	**2.599*** **-9.3%**	2.742 -4.3%	3.120	2.868 -8.1%	2.791 -10.5%	2.862 -8.3%
Heart weight								
absolute (g)[1]	*1.36*	*1.20* -11.8%	*1.41* +3.7%	*1.49* +9.6%	*0.97*	*0.97*	*0.90* -7.2%	*0.91* -6.2%
relative (% bw)	0.275	0.232 -15.6%	0.281 +2.2%	0.283 +2.9%	0.345	0.328 -4.9%	**0.308*** **-10.7%**	0.326 -5.5%
Thyroid weight								
absolute (g)[1]	*0.0240*	*0.0266* +10.8%	*0.0248* +3.3%	*0.0294* +22.5%	*0.0296*	*0.0197* -33.4%	*0.0197* -33.4%	*0.0195* -34.1%
relative (% bw)	0.0048	0.0051 +6.3%	0.0049 +2.1%	0.0056 +16.7%	0.0105	**0.0067*** **-36.2%**	**0.0067*** **-36.2%**	0.0070 -33.3%
Pituitary weight								
absolute (g)[1]	*0.0113*	*0.0130* +15.0%	*0.0110* -2.7%	*0.0117* +3.5%	*0.0171*	*0.0166* -2.9%	*0.0140* -18.1%	*0.0136* -20.5%
relative (% bw)	0.0023	0.0025 +8.7%	0.0022 -4.3%	0.0022 -4.3%	0.0061	0.0056 -8.2%	**0.0048*** **-21.3%**	0.0049 -19.7%

* (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 6.5.2-10 Pathology findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 12 months interim sacrifice

	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 -moderate -severe	3/10	4/10	3/10 2/10	2/10 3/10	5/10 3/10	3/10 2/10	4/10	2/10 2/10 6/10

* (p< 0.05); significantly different from controls

Conclusion:
Please see overall conclusion at the beginning of this section (B.6.5.2.1), Ref.: [redacted]., *1985a*, Doc. No. A31880, Hoechst Report No. 85.0688.

B.6.5.2.1.3. Determination of hepatic enzyme levels

Reference:	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
Author(s). year:	[redacted]., 1984
Report/Doc. number:	Hoechst Report No. 84.0639 / A29694
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	Please refer to [redacted]. *1985* (at the beginning of this section, B.6.5.2.1).
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Please refer to [redacted]., *1985a* (at the beginning of this section, B.6.5.2.1)

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.

Materials and Methods:
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 peroxisome proliferation, there were no signs of increased catalase activity. However, carnitine acetyltransferase activity was increased in both sexes at 180 ppm. Carnitine acetyltransferase 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 peroxisome 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 6.5.2-11 Special biochemical investigations of hepatic enzyme levels, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 12 months interim sacrifice

	Dose group level (ppm)							
	Males				**Females**			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Aminopyrine N-demethylase (U/g liver)	0.503	0.539 +7.2%	0.533 +6.0%	**0.597*** **+18.7%**	0.0395	0.0642 +62.5%	0,0586 +48.4%	**0,0883*** **+123.5%**
Anisic acid ester O-demethylase (U/g liver)	0.156	**0.175*** **+12.2%**	**0.184*** **+17.9%**	**0.195*** **+25.0%**	0.0609	0.0341 -44.0%	0.0423 -30.5%	0.0658 +8.0%
Ethoxycoumarin O-deethylase (U/g liver)	0.0306	0.0297 -2.9%	**0.0235*** **-23.2%**	**0.0260*** **-15.0%**	0.0448	**0.0533*** **+19.0%**	**0.0587*** **+31.0%**	0.0524 +17.0%
Cytochrome c-reductase (U/g liver)	9.98	**8.06*** **-19.2%**	**6.50*** **-34.9%**	**6.06*** **-39.3%**	6.95	**5.23*** **-24.7%**	**4.46*** **-35.8%**	6.02 -13.4%
Lipoperoxidation (E/g liver)	0.917	0.976 +6.4%	0.895 -34.9%	0.911 -39.3%	0.0349	**0.0236*** **-24.7%**	**0.0198*** **-35.8%**	**0.0232*** **-13.4%**
Glucuronyltransferase I (U/g liver)	nd	nd	nd	nd	0.0956	0.0608 -36.4%	0.0737 -22.9%	0.0691 -27.7%
Glucuronyltransferase II (U/g liver)	nd	nd	nd	nd	0.614	0.673 +9.6%	0.663 +8.0%	**0.881*** **+43.5%**
ALP (U/g liver)	0.471	0.447 -5.1%	0.398 -15.5%	0.394 -16.3%	0.459	0.418 -8.9%	0.393 -14.4%	0.360 -21.6%
Catalase (R/g liver)	12510	13260 +6.0%	9878 -21.0%	5459 -56.4%	3735	2562 -31.4%	1992 -46.7%	1911 -48.8%

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Carnitine acetyl transferase (E/g liver)	0.00351	0.00465 +32.5%	0.00606 +72.6%	**0.01888*** **+437.9%**	0.00821	0.00848 +3.3%	0.01146 -46.7%	**0.03309*** **-48.8%**
LDH (U/g liver)	277	313 +13.0%	333 +20.2%	**400*** **+44.4%**	147	160 +8.8%	157 +6.8%	**205*** **+39.5%**
Glycerophosphate dehydrogenase (U/g liver)	21.8	**15.3*** **-29.8%**	**15.2*** **-30.3%**	**13.4*** **-38.5%**	6.75	8.79 +30.2%	7.13 +5.6%	**10.15*** **+50.4%**
Malate enzyme (U/g liver)	1.008	**0.755*** **-25.1%**	**0.388*** **-61.5%**	**0.404*** **-59.9%**	0.585	**0.461*** **-21.2%**	**0.444*** **-24.1%**	**0.320*** **-45.3%**

* (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 peroxisome proliferation. However, it was not investigated if the increased activity of carnitine acteyltransferase at 180 ppm derived from peroxisomes or from mitochondria.

B.6.5.2.1.4. Chronic 24-months study

Reference:	Hoe 33171 – active ingredient technical (Code Hoe: 33171 0 H AS201). Chronic feeding study (24 months) in rats
Author(s). year:	[redacted]., 1984a
Report/Doc. number:	Hoechst Report No. 84.0632 / A30807
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	Please refer to [redacted]. *1985* (at the beginning of this section, B.6.5.2.1).
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Please refer to [redacted]., *1985a* (at the beginning of this section, B.6.5.2.1)

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: Haematology 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 6.5.2-12 Mortality rates, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 24 months sacrifice

	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

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
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

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 6.5.2-13 Body weight data, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 24 months sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Initial body weight (g)	130	128 -1.5%	128 -1.5%	122 -6.2%	118	114 -3.4%	113 -4.2%	112 -5.1%
Terminal body weight (g)	529	542 +2.5%	513 -3.0%	526 -0.6%	344	352 +2.3%	319 -7.3%	324 -5.8%
Bodyweight gain (g)	399	414 +3.8%	385 -3.5%	404 +1.3%	226	238 +5.3%	206 -8.8%	212 -6.2%

* (p< 0.05); significantly different from controls

Food and water consumption: No significant differences were noted among the control and treatment groups.

Haematology: 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 6.5.2-14 Relevant clinical chemistry findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 24 month sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
Cholesterol (mmol/L)								
Initial	2.15	2.36 +9.8%	**3.09*** +43.7%	**2.65*** **+23.3%**	2.25	2.57 +14.2%	2.49 +10.7%	2.59 +15.1%
Week 26	2.41	2.71 +12.4%	2.52 +4.6%	**1.96*** **-18.7%**	2.67	2.65 -0.7%	2.64 -1.1%	2.38 -10.9%
Week 54	3.43	3.74 +9.0%	3.58 +4.4%	**2.69*** **-21.6%**	3.53	3.03 -14.2%	2.90 -17.8%	2.89 -18.1%
Week 79	3.46	4.38 +26.6%	4.03 +16.5%	3.14 -9.2%	2.88	2.54 -11.8%	2.97 +3.1%	2.76 -4.2%
Terminal (Week 106)	4.92	4.84 -1.6%	4.36 -11.4%	**3.85*** **-21.7%**	3.58	3.08 -14.0%	3.35 -6.4%	3.33 -7.0%
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 -9.5%	6.67 +0.2%	**4.98*** **-25.2%**	5.25	5.55 +5.7%	4.75 -9.5%	4.76 -9.3%

* (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 evidence 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 6.5.2-15 Relevant absolute and relative organ weights, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 24 month sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Liver weight								
absolute (g)	16.78	16.51 -1.6%	15.47 -7.8%	**14.89*** **-11.3%**	11.25	11.83 +5.2%	10.01 -11.0%	10.32 -8.3%
relative (% bw)	3.168	3.039 -4.1%	3.023 -4.6%	**2.844*** **-10.2%**	3.251	3.320 +2.1%	3.129 -3.8%	3.196 -1.7%

* ($p < 0.05$); 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 (B.6.5.2.1), Ref.: [redacted]., *1985a*, Doc. No. A31880, Hoechst Report No. 85.0688

B.6.5.2.1.5. Residue determinations in organs and tissues

Reference:	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
Author(s). year:	[redacted]., 1985
Report/Doc. number:	A30804 / Hoechst Report No. 85.0205
Guideline(s):	-
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Please refer to [redacted]., *1985a*, at the beginning of this section

Special investigation on residues of the test substance: Groups of 10 male and 10 female rats each were fed with 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 6.5.2-16 Residue levels in various organs and tissues after 6, 12, 18 and 24 months, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats

	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
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.

B.6.5.2.1.6. Carcinogenicity analysis

Reference:	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)
Author(s). year:	[redacted] 1985b Amendment to Report No. 85.0682, Krieg, 1987, Doc. No. A36064 / Hoechst Report No.871219
Report/Doc. number:	A31878 / Hoechst Report No. 85.0682
Guideline(s):	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.
Deviations to OECD GD 453 (2009):	Please refer to [redacted]. *1985* (at the beginning of this section, B.6.5.2.1).
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Please refer to [redacted] 1985a, in this section (B.6.5.2.1).

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 6.5.2-17 Mortality rates, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations

	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

Body weight: The body weight gain 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 6.5.2-18 Absolute and relative organ weights, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Liver weight								
absolute (g)	16.40	15.84 -3.4%	**15.13*** **-7.7%**	15.38 -6.2%	11.40	10.93 -4.1%	10.86 -4.7%	10.66 -6.5%
relative (% bw)	3.306	3.194 -3.4%	**2.903*** **-12.2%**	**2.960*** -10.5%	3.411	3.362 -1.4%	3.395	3.231 -5.3%
Brain weight								
absolute (g)	2.26	2.24	2.27	2.26	2.08	2.03 -2.4%	**2.00*** **-3.8%**	2.06
relative (% bw)	0.459	0.457	0.438 -4.6%	0.439 -4.4%	0.629	0.636 +1.1%	0.634 +0.8%	0.639 +1.6%

* ($p < 0.05$); 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 6.5.2-19 Pathology findings, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations

	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
malignant tumours	13	14	6	9	16[1]	12[2]	18[2]	8
single tumour	23	26	25	28	23	24	28	29
2 tumours	11	12	10	9	20	18	16	11
≥ 3 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

Table 6.5.2-20 Histopathology: benign neoplastic findings in rats at study termination, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Benign neoplasms								
Skin								
- Fibroma	-	2 (60)	-	-	-	-	-	1 (59)
- Fibrolipoma	-	1 (60)	-	-	-	-	-*	-
- Fibromyxoma	2 (60)	-	-	-	-	-	1 (60)	
Pituitary gland								
- adenoma	12 (60)	10 (60)	15 (60)	7 (60)	31 (59)	23 (60)	33 (60)	33 (59)
- Invasive tumour of anterior lobe	-	4 (60)	-	-	1 (59)	2 (60)	-	-
Thyroid gland								
- Follicular cell adenoma	2 (60)	3 (60)	3 (60)	2 (60)	1 (59)	-	1 (60)	2 (59)
- Parafollicular cell adenoma	4 (60)	2 (60)	2 (60)	4 (60)	1 (59)	1 (60)	1 (60)	2 (59)
Parathyroid								
- Adenoma	2 (60)	-	-	-	-	-	-	-
Adrenals								

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Benign neoplasms								
- Adenoma	3 (60)	4 (60)	2 (60)	4 (60)	5 (59)	2 (60)	1 (60)	2 (59)
- Phaeochromocytoma	3 (60)	1 (60)	2 (60)	6 (60)	-	1 (60)	1 (60)	1 (59)
- Immature ganglioneuroma	1 (60)	-	-	1 (60)	-	-	-	-
Pancreas								
- Islet-cell adenoma	5 (60)	6 (60)	8 (60)	3 (60)	5 (59)	4 (60)	4 (60)	1 (59)
- Adenoma (exocrine)	1 (60)	1 (60)	-	1 (60)	-	-	-	-
Testes								
- Leydig cell tumor	-	2 (60)	2 (60)	5 (60)				
Ovaries								
- Papillary Cystadenoma					1 (59)	-	-	-
- Theca granulosa cell tumour					-	3 (60)	1 (60)	4 (59)
- Tubular adenoma					-	-	-	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	-	-	-	-	1 (59)	-	-	1 (59)
- Papillomatosis	-	1 (60)	-	1 (60)	-	-	-	-
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)	-	-	-
- Ependymoma	-	1 (60)-	-	-	-	-	-	-

Table 6.5.2-21 Histopathology: benign neoplastic findings in rats at study termination, Combined chronic toxicity and carcinogenicity study of fenoxaprop-ethyl in Wistar rats, 28 month sacrifice, final investigations

Diet concentration (ppm)	males				females			
	0	5	30	180	0	5	30	180
Malign neoplasms								
Skin								
- Sarcoma	2 (60)	2 (60)	3 (60)	1 (60)	1 (59)	-	-	-
- Carcinoma	-	1 (60)	-	1 (60)	1 (60)	-	-	1 (60)
Thyroid gland								
- Follicular cell carcinoma	1 (60)	-	1 (60)	-	-	-	1 (60)	-
- Parafollicular cell carcinoma	-	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					1 (59)	1 (60)	1 (60)	2 (59)
- Carcinoma					4 (59)	1 (60)	3 (60)	-
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	-	1 (60)	-	-	-	1 (60)-	-	-
- Carcinoma	-	-	1 (60)	-	-	-	-	-
Abdominal cavity								
- Mesothelioma	-	-	-	-	-	-	1 (60)	-
- Reticularsarcoma	-	-	-	1(60)	-	-	-	-
- Fibrosarcoma	-	-	-	-	-	-	-	1 (59)
Lymph nodes								
- Lymphoma	2 (60)	-	1 (60)	1 (60)	1 (59)	2 (60)	-	-
Brain								
- Meningeal sarcoma	1 (60	-	-	-	-	-	-	-
- Astroblastoma	1 (60)	1 (60)	-	-	-	-	-	-
- Oligodendroglioma	-	-	-	-	-	-	1 (60)	-
Spinal cord								
- Immature ganglioneuroma	-	-	-	-	-	1 (60)	-	-
Bone								
- Haemangioma	-	1 (60)	-	-	-	-	-	-
- Osteosarcoma	1 (60)	-	-	2 (60)	-	-	-	-

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.

B.6.5.3. Oral studies in mice with fenoxaprop-ethyl

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.

B.6.5.3.1. 24-month study

Reference:	Hoe 33171 – active ingredient technical (Code Hoe: 33171 0H AS201). Carcinogenicity study in mice (24-month feeding study)
Author(s). year:	[redacted] 1985c
Report/Doc. number:	A30816 / Hoechst Report No. 85.0046
Guideline(s):	OECD guideline 451 (adopted 1981); EPA guideline 83-2 (1982)
Deviations to OECD GD 451 (2009):	Pathology for some organs (e.g. aorta, gall bladder, thyroids…) not assessed.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
60 male and 60 female mice per dose group were treated orally with 0, 2.5, 10 or 40 ppm of Fenoxaprop-ethyl. Of these mice, 10 per 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.

Test material	Hoe 33171 0H AT201
Purity:	94.0% (according to certificate of analysis No. 01888)
Test animal:	NMRI mice, NMRKf(SPF71), source [redacted] 3-4 weeks old, mean bw of 22 g (♂) and 19.5 g (♀)
Number of animals:	60 per sex per dose group (incl. 10 for interim sacrifice)

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.

Table 6.5.3-1 Test substance intake mg/kg bw/d, Carcinogenicity study in NMRI mice

Dietary level	Test substance intake in mg/kg bw/d			
	Males		Females	
	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

Behaviour and general health conditions (neurological disturbances, eyes, dental growth and oral mucosa) were observed twice daily.
Body weights and food consumption were determined once weekly.
Haematology (weeks 52 and 105) was performed on non-starved animals and included haemoglobin, erythrocytes, haematocrit, 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 oesophagus, 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 macroscopically) and any other organs with macroscopic findings.

Statistical evaluation was performed for the following parameters: body weight, haemoglobin, erythrocytes, haematocrit, leucocytes, thrombocytes, ALAT, ASAT, ALP, gamma-glutamyl transferase, hepatic enzymes and all relative organ weights.

Findings:
Following results refer to the 24 month sacrifice. Results of the interim sacrifice at 12 months are reported 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 6.5.3-2 Mortality rates, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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
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 6.5.3-3 Bodyweight data, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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
Bodyweight gain (g)	15	14	15	15	15	15	15	15

* $p<0.05$; significantly different from controls

Food consumption: Food consumption, both absolute and relative, at all concentration levels corresponded to that of the controls.

Haematology: 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 6.5.3-4 Relevant haematology and clinical chemistry findings, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Haematology								
Haemoglobin (g/L)	143	147 +2.8%	144	145	132	138 +4.5%	142 +7.6%	**146*** **+10.6%**

	Dose group level (ppm)							
	Males				Females			
	0	2.5	10	40	0	2.5	10	40
Leucocytes (10^9/L)	19.9	10.0 -49.7%	17.1 -14.1%	5.9 -70.4%	10.8	**4.4*** **-59.3%**	25.1 +132.4%	39.8 +268.5%
Clinical chemistry								
γ-glutamyl transferase	4.4	3.4 -22.7%	2.3 -47.7%	3.8 -13.6%	7.4	2.5 -66.2%	**3.9*** **-47.3%**	**1.3*** **-82.4%**

* 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 peroxisome 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 6.5.3-5 Absolute[1] and relative organ weights, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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* +5.8%	*2.01*	*1.76* -12.4%	*1.69* -15.9%	*1.71* -14.9%
relative (% bw)	4.773	4.729	4.651 -2.6%	4.933 +3.4%	5.841	5.186 -11.2%	**4.959*** -15.1%	**5.017*** -14.1%
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 +2.8%	1.418	1.358 -4.2%	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 substance. No treatment-related effect was detected in the incidence or distribution of tumour types. 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 6.5.3-6 Histopathology in females, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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
% historical control range [1]	0-12%			

[1] Historical control value presented in an additional report (*Langer K.H. et al.*, 1987, A37096) along with a photographic documentation (*Krieg K.*, 1988, A37251)

Table 6.5.3-7 Histopathology: neoplastic findings in mice at study termination, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

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
- 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

Diet concentration (ppm)	males				females			
	0	2.5	10	40	0	2.5	10	40
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 peroxisome 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.

B.6.5.3.1.1. 12 months interim kill

Reference:	Hoe 33171 – active ingredient technical (Code Hoe: 33171 0H AS201). Chronic feeding study in mice (Interim killing after 12 months)
Author(s). year:	[redacted] 1983c
Report/Doc. number:	A29695 / Hoechst Report No. 83.0654
Guideline(s):	OECD guideline 451 (adopted 1981); EPA guideline 83-2 (1982)
Deviations:	Histopathology was not performed on sternum and femur.
Deviations to OECD GD 451 (2009):	Please refer to [redacted]., *1985c*, in this section (B.6.5.3.1).
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Please refer to [redacted]., *1985c*, in this section (B.6.5.3.1).

Findings:
The following results refer to the 12 month interim sacrifice and 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 6.5.3-8 Bodyweight data, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 12 month interim sacrifice

	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
Bodyweight gain (g)	13	12	15	13	9	10	11	10

Food consumption: Food consumption, both absolute and relative, at all concentration levels corresponded to that of the controls.

Haematology: 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 peroxisome 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 6.5.3-9 Absolute[1] and relative organ weights, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 12 month interim sacrifice

	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* -7.5%	*1.72* +8.2%	*1.70* +6.9%	*1.44*	*1.45*	*1.50* +4.2%	*1.44*
relative (% bw)	4.657	4.333 -7.0%	4.688 +0.7%	4.827 +3.7%	4.820	4.859	4.862	4.852
Kidneys weight								
absolute (g)[1]	*0.55*	*0.56*	*0.62* +12.7%	*0.63* +14.5%	*0.42*	0.*42*	*0.44*	*0.45*
relative (% bw)	1.620	1.663 +2.7%	1.704 +5.2%	1.774 +9.5%	1.398	1.423 +1.8%	1.440 +3.0%	**1.515*** **+8.4%**

* ($p < 0.05$); 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 (B.6.5.3.1), Ref.: *Donaubauer et al., 1985(c),* Doc. No. A30816, Hoechst Report No. 85.0046.

B.6.5.3.1.2. Determination of hepatic enzyme levels

Reference:	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
Author(s). year:	[redacted] 1984b
Report/Doc. number:	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(s):	Not applicable.
GLP:	Not applicable.

Material and Methods:
Please refer to [redacted] *1985c*, in this section (B.6.5.3.1).

Findings:

The following results relate 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 6.5.3-10 Special biochemical investigations of hepatic enzyme levels, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 12 month interim sacrifice

	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 +3.7%	0.304 -6.7%	0.375 +15.0%	0.225	0.183 -18.7%	0.195 -13.3%	0.192 -14.7%
Anisic acid ester O-demethylase (U/g liver)	0.0706	0.0571 -19.1%	**0.0402*** **-43.1%**	0.0555 -21.4%	0.0336	0.0204 -39.3%	0.0272 -19.0%	0.0292 -13.1%
Ethoxycoumarin O-deethylase (U/g liver)	0.0603	0.0661 +9.6%	0.0606	0.0673 +11.6%	0.0654	0.0653	0.0734 +12.2%	0.0661
Cytochrome c-reductase (U/g liver)	0.84	3.28 +290.5%	**3.99*** **+375.0%**	**4.29*** **+410.7%**	4.65	4.28 -8.0%	4.83 +3.9%	**6.24*** **+34.2%**
Lipoperoxidation (E/g liver)	3.79	3.89 +2.6%	4.20 +10.8%	4.23 +11.6%	3.24	4.31 +33.0%	3.73 +15.1%	3.26
Glucuronyltransferase I (U/g liver)	0.182	**0.253*** **+39.0%**	0.230 +26.4%	**0.221*** **+21.4%**	0.281	0.296 +5.3%	0.289	0.294
Glucuronyltransferase II (U/g liver)	0.406	0.430 +5.9%	0.470 +15.8%	0.473 +16.5%	0.429	**0.636*** **+48.3%**	**0.603*** **+40.6%**	**0.613*** **+42.9%**
Catalase (R/g liver)	4137	3323 -19.7%	2694 -34.9%	2070 -50.0%	2478	1954 -21.1%	**713*** **-71.2%**	1902 -23.2%
ALP (U/g liver)	1.19	1.16	1.15	1.24 +4.2%	1.50	1.53	1.60 +6.7%	1.44 -4.0%
Glycerophosphate dehydrogenase (U/g liver)	15.1	13.5 -10.6%	11.1 -26.5%	11.4 -24.5%	11.6	14.6 +25.9%	12.8 +10.3%	9.9 -14.7%
LDH (U/g liver)	202	**127*** **-37.1%**	**112*** **-44.6%**	**131*** **-35.1%**	142	**186*** **+31.0%**	151 +6.3%	139 -2.1%
Malate enzyme (U/g liver)	0.717	0.607 -15.3%	0.951 +32.6%	0.968 +35.0%	0.719	0.555 -22.8%	0.746	0.878 +22.1%

* ($p<0.05$); 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 peroxisome proliferation was excluded.

B.6.5.3.2. Carcinogenicity study

Reference:	Fenoxaprop-ethyl – substance technical (Code Hoe 033171 00 ZD96 0005). Carcinogenicity study in mice
Author(s). year:	[redacted] 1996
Report/Doc. number:	A57500 / Hoechst Report No. 96.0880 Supplement to Report No. 96.0880, Durchfeld-Meyer B., 1996; Doc No. A58176
Guideline(s):	OECD guideline 451 (1981); EPA guideline 83-2 (revised 1984); Jap. MAFF 59 NohSan No. 4200 (1985)
Deviations to OECD GD 453 (2009):	Pathology and histopathology for some organs (cervix, coagulating gland, Harderian gland, lacrimal gland) not assessed.
GLP:	Yes.
Acceptability:	Yes.

Materials 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.

Test material: Hoe 033171 00 ZD96 0005
Purity: 96.8% (according to certificate of analysis No. 4663 (1991))

Test animal: NMRI mice, NMRKf(SPF71), source [redacted]
5-6 weeks old, mean bw of 22.1 g (♂) and 20.8 g (♀)
Number of animals: 50 per sex per dose group

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.

Table 6.5.3-11 Test substance intake in mg/kg bw/d, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

Dietary level	Test substance intake in mg/kg bw/d	
	Males	Females
40 ppm	5.67	6.83
115 ppm	16.59	19.44
320 ppm	44.63	53.68

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.

Haematology 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, haematological examinations comprised erythrocyte count, haemoglobin, haematocrit, total leucocyte count, platelet count, differential blood count, reticulocyte count, Heinz bodies, and 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, haematocrit, 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 6.5.3-12 Clinical signs, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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 6.5.3-13 Mortality rates, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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

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 6.5.3-14 Bodyweight data, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Initial body weight (g)	22.4	22.1	21.7 -3.1%	22.0	20.9	20.7	20.9	20.8
Terminal body weight (g)	37.8	38.4 +1.6%	37.5	38.9 +2.9%	32.8	33.2	34.9 +6.4%	35.9 +9.5%
Bodyweight gain (g)	15.4	16.3 +5.8%	15.8	16.9 +9.7%	11.9	12.5 +5.0%	14 +17.6%	15.1 +26.9%

* (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.

Haematology: 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 6.5.3-15 Absolute and relative organ weights, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	40	115	320	0	40	115	320
Liver weight								
absolute (g)	1.87	1.94 +3.7%	2.06 +10.2%	**2.34*** **+25.1%**	1.78	1.76 -1.1%	1.90 +6.7%	2.13 +19.7%
relative (% bw)	4.92	5.03 +2.2%	5.47* +11.2%	6.01* +22.2%	5.36	5.28 -1.5%	5.45 +1.7%	5.99 +11.8%
Kidneys weight								
absolute (g)	0.58	0.61 +5.2%	0.58	**0.64*** **+10.3%**	0.43	0.44	0.46 +7.0%	**0.50*** **+16.3%**
relative (% bw)	1.54	1.58	1.56	**1.66*** **+7.8%**	1.31	1.33	1.33	1.42 +8.4%

* (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 6.5.3-16 Macroscopic findings, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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	-

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 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.

Table 6.5.3-17 Non-neoplastic findings, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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 (predominantly 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 pre-neoplastic lesions.

Table 6.5.3-18 Neoplastic findings of the liver, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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

In the adrenal glands, an increased number of adenomas of the subcapsular cells of type B was found in males of the highest dose group, which was considered a random event as there was no statistical significant difference between the number of lesions in the historical control group and the 320 ppm group of this study.

Table 6.5.3-19 Neoplastic findings of the adrenals, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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	32.0[1]				-			

* (p< 0.05); significantly different from controls
[1] Historical control value which was presented in the study report. In an addendum which was issued in 1997 (*Durchfeld-Meyer et al.*, Doc. No. A58838) further historical control data on the incidence of adrenal adenoma was presented. Data from 4 studies was re-evaluated using the new WHO nomenclature. Subcapsular cell type B adenomas were found in 27.8 %, 29.6 %, 52.3 % and 19.6 % of the control animals, resp.

Table 6.5.3-20 Histopathology: benign neoplastic findings in mice at the study termination, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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.	6 (50)	7 (50)	9 (50)	4 (50)	3 (49)	3 (50)	2 (50)	4 (50)
- Haemangioma	-	-	-	-	-	1 (50)	-	-
Forestomach								
- Pappiloma squamous	-	-	-	-	-	-	1 (24)	-
Duodenum								
-Adenoma	-	1 (9)	1 (7)	1 (38)	-	1 (11)	-	-
Liver								
-Haemangioma	0	1 (49)	1 (50)	-	1 (49)	-	-	1 (50)
- Adenoma hepatocell.	1 (50)	1 (49)	2 (50)	12 (50)	-	-	-	-
Pancreas								
- Islet-cell adenoma	1(50)	-	-	-	-	-	-	-
- Adenoma acinar cell	-	-	-	-	-	-	-	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					4 (49)	3 (37)	2 (37)	5 (48)
- Tum.sex cord stromal					7 (49)	2 (37)	2 (37)	2 (48)
- Tum. granulosa c. ben.					6 (49)	5 (37)	3 (37)	7 (48)
- Thecoma					1 (49)	2 (37)	-	-
- Adenoma tubulostrom.					2 (49)	2 (37)	1 (37)	2 (48)
- Cystadenoma					6 (49)	5 (37)	5 (37)	8 (48)
- Haemangioma					1 (49)	-	1 (37)	1 (48)
Uterus								
- Polyp stromal					3 (49)	2 (34)	3 (38)	5 (50)
- Polyp glandular					1 (49)	3 (34)	-	2 (50)
- Haemangiom					3 (49)	-	2 (38)	2 (50)
- Fibroma					-	-	-	1 (50)
- Leiomyoma					2 (49)	-	-	1 (50)
- Granular cell tumour					4 (49)	1 (34)	1 (38)	4 (50)
Pituitary gland								
- Adenoma pars distal.	-	-	-	-	3 (37)	-	-	1 (39)
- Adenoma pars interm.	-	-	-	-	1 (37)	-	-	-
Thyroid gland								
- Adenoma c-cell	1 (47)	-	-	-	-	-	-	-
- Adenoma follicular cells	-	-	-	2 (47)	-	-	-	-
Parathyroid glands								
- Adenoma	1 (39)	-	-	1 (39)	-	-	1 (15)	1 (43)
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)

	Males				Females			
Diet concentration (ppm)	**0**	**40**	**115**	**320**	**0**	**40**	**115**	**320**
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 - Tumour hair foll. ben	- -	- -	- -	1 (50) -	- -	- 1 (21)	- -	- -
Bone - Ossifying fibroma	-	-	1 (1)	1 (1)	-	-	-	-

Table 6.5.3-21 Histopathology: malign neoplastic findings in mice at the study termination, Carcinogenicity study of fenoxaprop-ethyl in NMRI mice, 24 month sacrifice

	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)	-	-

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 (predominantly 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 predominantly 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.
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.
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).

B.6.5.4. Oral study in dogs with fenoxaprop-ethyl

Reference:	Toxicological testing of Hoe 33171 – active ingredient technical (Code: Hoe 033171 0H ZC94 0001) by repeated oral administration to beagle dogs for 2 years
Author(s). year:	[redacted], 1985
Report/Doc. number:	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(s):	No guideline is mentioned in the study report. However, the study design is similar to OECD guideline 452 (adopted 1981).
Deviations to OECD GD 452 (2009):	- Detailed clinical observations were not performed at end of first week and monthly, but every 3 months and before study termination. - Haematology: MCV, MCHC and activated partial thromboplastin time not assessed - Urinalysis: volume not assessed. - Organ weight of epididymides not assessed. - Histopathology for some organs not assessed (cervix, coagulating gland, Harderian gland, lacrimal gland, peripheral nerve, seminal vesicle, spinal cord and vagina). - Inadequate exsanguinations of animals
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
6 male and 6 female Beagle dogs per dose group received diets containing 0, 3, 15 or 75 ppm Fenoxaprop-ethyl for two years (see Table 6.5.4-1 for substance intake).

Test material	Hoe 033171 0H ZC94 0001
Purity:	94 % (according to certificate of analysis dated 27 April 1982)
Test animal:	Beagle dogs (strain: BEAK, source: [redacted]) 11 months old, mean bw of 13.3 kg (♂) and 11.9 kg (♀)
Number of animals:	6 per sex per dose group

The test substance had a purity of 94 % 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.

Table 6.5.4-1 Test substance intake in mg/kg bw/d, Chronic toxicity study of fenoxaprop-ethyl in Beagle dogs

Dietary level	Test substance intake in mg/kg bw/d	
	Males	Females
3 ppm	0.2	0.18
15 ppm	1.1	0.9
75 ppm	5.2	4.6

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 (flexor, patellar, anal, cutaneous, corneal, pupillary and blink reflexes, visual and tactile placing, righting reactions), 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, haematocrit, 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, colour, 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), oesophagus, 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. Dose-response related decrease in bodyweight gain was observed in males but not in females.

Table 6.5.4-2 Bodyweight data, Chronic toxicity study of fenoxaprop-ethyl in Beagle dogs, 24 month sacrifice

	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 -3.3%	12.0
Terminal body weight (g)	17.1±1.0	16.5±1.7 -3.5%	**15.2*±0.8** **-11.1%**	15.5±0.6 -9.4%	15.9±0.9	15.0±0.6 -5.7%	15.1±1.0 -5%	**14.0*±1.0** **-12.6%**
Bodyweight gain (g)	3.5	2.9 -17.1%	2.7 -22.9%	2.0 -42.9%	3.8	3 -21.1%	3.4 -10.5%	2.0 -47.4%

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

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

Neurological status: No changes in reflex excitability and postural reactions as compared with the initial status.

Haematology, clinical chemistry and urinalysis: At the beginning and throughout the study various statistical significances 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 significances are presented in the following table. A dose-related and statistically significant increase of ASAT was noted starting from the mid-dose in both sexes. Triglycerides were also increased, however only in females starting from the mid dose and statistically significant at the high dose.

Table 6.5.4-3 Haematology and clinical chemistry findings, Chronic toxicity study of fenoxaprop-ethyl in Beagle dogs, 24 months sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Haematology								
Erythrocytes (10^{12}/L)	7.74	7.49 -3.2%	7.50 -3.1%	**6.80*** **-12.1%**	7.29	7.21	7.36	6.74 -7.5%
Haemoglobin (g/L)	183	175 -4.4%	174 -4.9%	**157*** **-14.2%**	172	167	173	158 -8.1%
Haematocrit (unity)	0.55	0.52	0.52	**0.48*** **-12.7%**	0.52	0.50	0.52	0.47 -9.6%
Reticulocytes (unity)	0.012	0.008 -33.3%	0.008 -33.3%	**0.006*** **-50.0%**	0.010	0.006 -40.0%	0.008 -20.0%	**0.005*** **-50.0%**
Thrombocytes (10^9/L)	326	337 +3.4%	382 +17.2%	369 +13.2%	356	407 +14.3%	362 +1.7%	**443*** **+24.4%**
Clinical chemistry								
Cholesterol (mmol/L)	3.89	3.63 -6.7%	3.53 -9.3%	3.73 -4.1%	4.81	**6.51*** **+35.3%**	4.62 -4.0%	5.48 +13.9%
Triglycerides (mmol/L)	0.38	0.22 -42.1%	0.47 +23.7%	0.42 +10.5%	0.46	0.62 +34.8%	0.57 +23.9%	**0.76*** **+65.2%**
Total lipids (g/L)	5.30	6.36 +20.0%	5.62 +6.0%	**6.54*** **+23.4%**	6.73	6.83	6.42 -4.6%	6.42 -4.6%
ASAT (U/L)	13	13	**18*** **+38.5%**	**19*** **+46.2%**	11	13	**15*** **+36.4%**	**16*** **+45.5%**
ALAT (U/L)	32	**17*** **-46.9%**	27 -15.6%	21 -34.4%	16	17	20 +25.0%	16
LDH (U/L)	94	90	**56*** **-40.4%**	100	81	108 +33.3%	71 -12.3%	**154*** **+90.1%**

* ($p<0.05$); 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 significance was 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. Biologically relevant and dose-related changes were found in the relative brain weight and relative thyroid weight of males, and, in relative liver weight as well as absolute and relative ovary weights of females. The changes of the absolute and relative uterus weights were quite strong but not dose-related.

Table 6.5.4-4 Absolute and relative organ weights, Chronic toxicity study of fenoxaprop-ethyl in Beagle dogs, 24 month sacrifice

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Liver weight								
absolute (g)	495	545 +10.1%	528 +6.7%	504 +1.8%	453	525 +15.9%	531 +17.2%	530 +17.0%
relative (% bw)	2.903	3.307 +13.9%	**3.488*** **+20.2%**	3.256 +12.2%	2.858	3.503 +22.6%	3.536 +23.7%	**3.821*** **+33.7%**

	Dose group level (ppm)							
	Males				Females			
	0	3	15	75	0	3	15	75
Lungs weight								
absolute (g)	137.5	133.2 -3.1%	129.0 -6.2%	149.7 +8.9%	127.2	130.5 +2.6%	124.8 -1.9%	128.3
relative (% bw)	0.807	0.807	0.850 +5.3%	**0.968*** **+20.0%**	0.803	0.872 +8.6%	0.832 +3.6%	**0.930*** **+15.8%**
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 +2.3%	0.564 +9.5%	0.569 +10.5%	0.507	0.559 +10.3%	0.535 +5.5%	**0.591*** **+16.6%**
Thyroid weight								
absolute (g)	723	780±133 +7.9%	753±146 +4.1%	885±247 +22.4%	756	815±176 +7.8%	715±77 -5.4%	826±180 +9.3%
relative (% bw)	0.0042	0.0047 +11.9%	0.0050 +19.0%	**0.0057*** **+35.7%**	0.0048	0.0054 +12.5%	0.0047	0.0059 +22.9%
Ovaries weight								
absolute (g)					1279	1825 +42.7%	2099 +64.1%	**2268*** **+77.3%**
relative (% bw)					0.0080	0.0123 +53.8%	0.0139 +73.8%	**0.0165*** **106.3%**
Uterus weight								
absolute (g)					10.8	19.3 +78.7%	**29.2*** **+170.4%**	**25.2*** **+133.3%**
relative (% bw)					0.067	0.130 +94.0%	**0.192*** **+186.6%**	**0.182*** **+171.6%**

* ($p<0.05$); 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 exsanguinations by the study author.
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).

The applicant submitted a position paper in response to RMS' comment on the abovementioned effects, which is summarized in the following section.

Reference:	**Fenoxaprop-P-ethyl, AE F046360 – Response to a request of the RMS Austria within the EU-re-approval process**
Author(s). year:	Bomann W., 2017
Report/Doc. number:	
Acceptability:	Yes

RMS had the following comment: '*Due to effects observed in the thyroid weight in males, and, the weights of ovaries and uterus in females in the 2-year and 1-year dog studies, the setting of NOAEL values should be re-considered. Attached please find the relevant tables from studies A31854* and A29692.

We would appreciate historical control data and further information about the stated shortcomings – could you please elaborate more on inadequate exsanguinations, and how the oestrus phase might have an effect on the weights of ovaries and uterus?

In addition to the highly altered lipid metabolism seen in most of the studies, these are also effects that concern ED-related organs.

Therefore argumentation on ED properties of this substance would be helpful later for the peer-review.'

A question was also raised on available ToxCast and Tox21 Activity Data.

These questions and comments are addressed in this paper. For clarity, only the section regarding the 2-year dog study is summarized here.

Organ weight effects in the 2-year dog study

In a 2-year toxicity study with the racemic mixture AE F033171 in dogs (Brunk, R.; Kramer, M.; 1987; M-109895-02-1, A31854), experimental phase: April 1982-May 1984) some organ weight changes were seen, which were explained by the study director with inadequate exsanguination (liver, lung, brain, thyroid) and/or different phases of the estrous cycle in female dogs (ovaries, uterus).
An overview of the relevant endocrine organ weights is given in the Table 6.5.4-5.

Table 6.5.4-5 Weights of relevant endocrine organs, 2-year dog study (Brunk, R.; Kramer, M.; 1987; A31854)

Organ weights[a] (% changes vs. control in brackets)	**Dose level in ppm (mg/kg bw/d)**							
	Males				**Females**			
	0	**3(0.2)**	**15(1.1)**	**75(5.2)**	**0**	**3(0.18)**	**15(0.9)**	**75(4.6)**
Body weight (kg)	17.1±1.0	16.5±1.7 (-3.5%)	**15.2±0.8* (-11.1%)**	**15.5±0.6* (-9.4%)**	15.9±0.9	15.0±0.6 (-5.7%)	15.1±1.0 (-5%)	**13.9±1.0* (-12.6%)**
Body weight gains (kg)[b]	3.52	2.92 (-17.1%)	2.65 (-24.7%)	1.92 (-45.5%)	3.8	3.03 (-21.3%)	3.38(-11.1%)	1.83 (-51.8%)
Thyroid weight absolute (mg)	723±85	780±133 (+7.9%)	753±146 (+4.1%)	885±247 (+22.4%)	756±96	815±176 (+7.8%)	715±77 (-5.4%)	826±180 (+9.3%)
Thyroid weight relative (% of BW)	0.0042±0.0005	0.0047±0.005 (+11.9%)	0.0050±0.0008 (+19.0%)	**0.0057±0.0014* (+35.7%)**	0.0048±0.0005	0.0054±0.0012 (+12.5%)	0.0047±0.0004 (-2.1%)	0.0059±0.0009 (+22.9%)
Ovary weight absolute (mg)					1279±412	1825±406 (+42.7%)	2099±856 (+64.1%)	**2268±2268* (+77.3%)**
Ovary weight relative (% of BW)					0.008±0.0080	0.0123±0.0031 (+53.8%)	0.0139±0.0139 (+73.8%)	0.0165±0.0034 (+106.3%)
Uterus weight absolute (g)					10.8±6.9	19.3±7.3 (+78.7%)	**29.2±15.3* (+170.4%)**	**25.2±2.3* (+133.3%)**
Uterus weight relative (% BW)					0.067±0.039	0.130±0.050 (+94.0%)	**0.192±0.097* (+186.6%)**	**0.182±0.018* (+171.6%)**

[a] Mean ± SD
[b] No SD for body weight gain given in the report
* ($p<0.05$); significantly different from controls
BW = body weight

It can be seen that the organ weight data show a high variability (high standard deviations) which according to the study director was due to differences in exsanguination, but also due to general high variability which especially because of the lower animal number in dog studies can lead to changes between groups giving an impression of a dose relationship which however, is spurious and artificial. This is especially true for the mentioned organ weight changes of liver, lung and brain (not shown in the table) and also for the uterus weights which did not show a clear dose-response relationship.
Another likely contributing reason is the marked reduction of the body weight in males and especially in females at the highest dose with -9.6 % in males and -12.6 % in females. Body weight gains were even more severely reduced in the highest dose by - 45.5 % and - 51.8 % in males and females, respectively. Such marked effects on body weights with even more marked effects on body weight gains alone can explain the observed organ weight effects and put them in perspective. In addition, the differences of ovary and uterus weights were explained by the fact that the females were in different phases of their estrous cycle. It is known that ovary weights show changes within the different phases of the estrous cycle, with highest weight during estrus, followed by the weight during diestrus and lower weights during anestrus and proestrus (Chandra et al, 2008). Therefore, it is concluded that together with severe body weight effects, technical aspects of study conduct and females being in different phases of the estrous cycle, led to a spurious bias in this study. The noted changes of the thyroid weights did not show a clear dose–response relationship in females or males, although there seems to be a trend of an increase of the absolute and relative weight at the highest dose in males. However, based on the remarks of the study director, this is most likely due to the differences in the exsanguination between the animals and groups. Most importantly, if real treatment-related effects on these organs are occurring, then correlated histopathological changes in the affected organs would have to be expected. However, no histopathological findings were observed in any of the specified organs, therefore, it is concluded that the aforementioned effects are spuri-

ous and not treatment-related. Thus, there is no reason to change the NOAEL of 15 ppm in this study, which was established based on the body weight effects at 75 ppm.

Comparison of organ weight data with historical control data (HCD)

The organ weights were furthermore within published historical background ranges from Beagle dogs. Historical organ weight data from the publication of Jackson, B. et al, 1964, where observed organ weight data from 1-year Beagle dog studies from 1958 to 1961, were used. In this publication, no body weight data were provided, the age of the dogs given was from 8 to 38 months.
Although the HCD are from a different time period, big differences are not expected, since no breeding changes in Beagle dogs occurred over the extended time period of when the fenoxaprop dog studies were conducted and since the organ weights in adult dogs should be comparable in untreated Beagles. Therefore, they are appropriate for this comparison. The relevant endocrine organ weights of the one- and two-year dog study are presented (only means without SD) in comparison with the HCD ranges of this publication in the following tables.

Table 6.5.4-6 Comparison of selected endocrine organ weights of the 2-year dog study

Study/Organ weights of males	Dose level in ppm				HCD Beagle dogs (Jackson *et al*, 1964)
	0	3	15	75	
males					
Body weight (kg)	17.1	16.5	15.2	15.5	na
Thyroid weight absolute (mg)	723	780	753	885	500-1600
Thyroid weight relative (% of BW)	0.0042	0.0047	0.0050	0.0057*	0.005-0.014
females					
Body weight (kg)	15.9	15.0	15.1	13.9	Na
Thyroid weight absolute (mg)	756	815	715	826	400-1300
Thyroid weight relative (% of BW)	0.0048	0.0054	0.0047	0.0059	0.004-0.013
Ovary weight absolute (mg)	1279	1825	2099	2268	600-2300
Ovary weight relative (% of BW)	0.008	0.0123	0.0139	0.0165	0.005-0.019
Uterus weight absolute (g)	10.8	19.3	29.2*	25.2*	3.1-25
Uterus weight relative (% BW)	0.067	0.130	0.192	0.182	0.033-0.276

na = no data available
* = outside HCD

RMS' conclusion

RMS does not agree to some of the arguments of the applicant:

- Changes in bodyweight were not dose-related and only biologically relevant (≥10%) in the mid dose group of males and high dose group of females. A dose-related decrease of bodyweight gain was observed in males, while in females this was not the case. Therefore the effect of bodyweight changes is considered not sufficient to explain the alteration of organ weights (i.e. thyroid, ovaries and uterus).
- The applicant provided publicly available historical control data, which were obtained from control groups of toxicological studies conducted with dogs from at least 23 years before this study was performed. The data do not fulfil the criteria as pointed out in Commission Regulation (EU) No 283/2013, in which it is stated that historical control data should be provided from studies conducted in the same laboratory not later than 5 years. Therefore they cannot be considered valid and acceptable.

- The applicant mentioned the publication by Chandra *et al.* (2008) for reasoning the differences in ovary and uterus weights to be affected by the oestrous phase. Aside from the fact that this publication was not provided, information about the state of the oestrous phase of the individual animals would be necessary in order to take these effects into account. However, such information was not available in the study report.

However, RMS agrees to the conclusions that no histopathological changes were observed in any of the organs affected - no microscopic changes were described and seem to have occurred in the thyroid, ovaries and uterus. Statistically significant changes were only observed at the high dose in organ weights of thyroid (relative to bodyweight) and of ovary, while for uterus also the mid dose was affected. However, changes in uterus weight did not follow a dose relation, and thyroid weights were only altered in males and not in females. Furthermore no changes in thyroid weights was observed in rat and mice studies, which could be expected as rodents are more susceptible to thyroid effects than dogs. Therefore the effects observed in dogs are considered to be incidential and driven by high variability and one dog in the control with comparable low relative thyroid weight.
Therefore RMS proposed the NOAEL as mentioned above.

B.6.5.5. Bridging of long-term toxicity/carcinogenicity studies

No long-term toxicity studies have been performed with Fenoxaprop-P-ethyl (Hoe 046360). For bridging of the data derived from studies conducted with Fenoxaprop-ethyl (Hoe 033171), results from acute and short term toxicity studies are considered. These data show that the toxicological profiles of Hoe 046360 and 033171 are comparable. Not only the pattern of effects but also the dose levels when effects occur are very similar (for discussion see chapter 6.3 short term toxicity studies). A detailed comparison of the toxicological profile was presented by [redacted] 1989, Hoechst Report No. 89.0416, Doc. A40415. It is concluded that it appears justified to base the evaluation of chronic toxicity and carcinogenicity and the ADI level for Hoe 046360 on the long-term studies with Hoe 033171.

B.6.6. REPRODUCTIVE TOXICITY

For fenoxaprop-P-ethyl developmental toxicity studies conducted in rats and rabbits were reported. For fenoxaprop-ethyl a multi-generation study in rats, developmental toxicity studies in rats, mice and monkeys were available. As the short-term and developmental toxicological profiles of fenoxaprop-ethyl were similar to that of fenoxaprop-P-ethyl, the multigeneration study of fenoxaprop-ethyl was used for the evaluation of the reproductive toxicity of fenoxaprop-P-ethyl.
These studies were evaluated during the first Annex I review of fenoxaprop-P-ethyl. They were presented in the monograph (Vol.3, Annex B, Section B6. Point B.6.6, August 2007). The overall data package for assessment of reproductive toxicity was considered in general compliance with test guidelines and appropriate to address data requirements under Regulation (EC) No. 1107/2009.
The summary of all essential data, relevant to support the renewal application of fenoxaprop-P-ethyl, is presented in the following sections.

Summary of reproductive toxicity with fenoxaprop-P-ethyl
No multigeneration study has been performed with Fenoxaprop-P-ethyl.
Teratogenicity studies with Fenoxaprop-P-ethyl have been carried out in rats and rabbits. 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 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 were reduced. These findings were confirmed in the embryo- and postnatal toxicity study in Wister 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 a fetotoxic effect. However, no effect on offspring was observed in the embryo- and postnatal toxicity study. In conclusion, the NOAEL was 32 mg/kg bw/d for maternal toxicity and 10 mg/kg bw/d for fetal toxicity. No teratogenicity was observed in these studies.

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. No teratogenicity was observed in this study.

According to Annex VI of the EC Council Directive 67/548/EEC, no classification or labelling of Fenoxaprop-P-ethyl regarding developmental toxicity is required.

Summary table of developmental toxicity studies with fenoxaprop-P-ethyl

Study, reference	Dose levels	NOAEL	Main effects/target organs
Developmental toxicity study in rats (Wistar) [redacted]., *1985a*, A33810 CA 5.6.2/01 Supplements [redacted]., *1988°* A37496, CA 5.6.2/02 [redacted]., *1990°* A42779, CA 5.6.2/03	0, 10, 32 and 100 mg/kg bw/d oral gavage on gestation days 7 - 16	Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 10 mg/kg bw/d	Maternal toxicity: - decreased food consumption - decreased body weight - reduced placentae weight - reduced heart weight Fetal toxicity: - embryonic death - reduced pup weight - reduced pup length - skeletal findings (delayed or non-ossification)

Study, reference	Dose levels	NOAEL	Main effects/target organs
Embryotoxicity and postnatal development study in rats (Wistar) [redacted] *1987a,* Doc. No. A35687 CA 5.6.2/07 Supplement [redacted] *1990°* A42781, CA 5.6.2/08	0, 10, 32 and 100 mg/kg bw/d oral gavage on gestation days 7 - 16	Maternal NOAEL: 32 mg/kg bw/d Offspring NOAEL: 100 mg/kg bw/d	Maternal toxicity: - decreased food consumption - decreased body weight Offspring toxicity: -
Developmental toxicity study in rabbits (Himalayan) [redacted]., *1986a;* A33302 CA 5.6.2/10 Supplement [redacted]., *1990* A42780, CA 5.6.2/11	0, 10, 32 and 100 mg/kg bw/d oral gavage on gestation days 7 - 19	Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 32 mg/kg bw/d	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

Summary of reproductive toxicity with fenoxaprop-ethyl

A multigeneration study according to GLP and EPA guideline has been conducted 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.

Teratogenicity 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 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, 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 13th 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 %). 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 %). According to the RAC opinion and the CLH report, maternal mortality at 200 mg/kg is considered excessive as it was greater than 10% (13.3%). According to the Guidance on the Application of the CLP Criteria, the data for that dose level 'shall not be considered for further evaluation'. 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 fetotoxicity or teratogenicity were 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.

Summary table of reproduction and developmental toxicity studies with fenoxaprop-ethyl

Study, reference	**Dose levels**	**NOAEL**	**Main effects/target organs**
Multi-generation study in rats (Wistar) [redacted] *1986a,* A32781, CA 5.6.1/01 [redacted] *1986b* A33840, CA 5.6.1/02	0, 5, 30 and 180 ppm during prepairing, pairing, postmating, gestation and lactation (0-0.24-1.42-8.77 mg/kg bw/d for males)	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)	- organ weight changes (liver, kidney) - clinical chemistry parameters
		Systemic offspring NOAEL: 30 ppm (1.42 - 6.06 mg/kg bw/d)	- reduced bw gain during lactation - organ weight changes (liver, kidney) - clinical chemistry parameters
Developmental study in rats (Wistar) [redacted] *1982a,* A26170 CA 5.6.2/04 Supplements [redacted] *1986* A32696, CA 5.6.2/05 [redacted]., *1989* A41709, CA 5.6.2/06	0, 10, 32 and 100 mg/kg bw/d oral gavage on gestation days 7 - 16	Maternal NOAEL: 32 mg/kg bw/d Fetal NOAEL: 32 mg/kg bw/d	Maternal toxicity: - clinical signs (piloerection) - decreased food consumption - decreased body weight Fetal toxicity: - embryonic death - reduced pup weight - reduced pup length - slightly delayed ossification
Embryotoxicity and postnatal development study in rats (Wistar) [redacted] *1986b,* A35783 CA 5.6.2/09	0, 10, 32 and 100 mg/kg bw/d oral gavage on gestation days 7 - 16	Maternal NOAEL: 32 mg/kg bw/d Offspring NOAEL: 32 mg/kg bw/d	Maternal toxicity: - decreased food consumption - decreased body weight Offspring toxicity: - embryonic death
Developmental toxicity study in mice (CD-1) [redacted] *1983;* Doc. No. A30282 CA 5.6.2/17	0, 2, 10 and 50 mg/kg bw/d oral gavage on gestation days 6 - 15	Maternal NOAEL: 10 mg/kg bw/d Fetal NOAEL: 50 mg/kg bw/d	Maternal toxicity: - increased liver weight Fetal toxicity: -

Study, reference	Dose levels	NOAEL	Main effects/target organs
Developmental toxicity study in rabbits (Himalayan) [redacted] *1982b;* A24756 CA 5.6.2/12 Supplements [redacted]*.,* *1986* A32692, CA 5.6.2/13 [redacted] *1989* A41707, CA 5.6.2/14	0, 12.5, 50 and 200 mg/kg bw/d oral gavage on gestation days 7 - 19	Maternal NOAEL: 12.5 mg/kg bw/d Fetal NOAEL: 50 mg/kg bw/d Teratogenicity NOAEL: 50 mg/kg bw/d	Maternal toxicity: - decreased food consumption - stagnant body weight gain during treatment period - 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: - diaphragm hernias
Developmental toxicity study in rabbits (Himalayan) [redacted] *1983;* A29690 CA 5.6.2/15 Supplement [redacted] *1986* A32695, CA 5.6.2/16	0, 2, 10 and 50 mg/kg bw/d oral gavage on gestation days 7 - 19	Maternal NOAEL: 10 mg/kg bw/d Fetal NOAEL: 10 mg/kg bw/d	Maternal toxicity: - decreased food consumption - decreased defecation - slightly increased number of resorptions sites Fetal toxicity: - reduced number of live fetuses/dam
Developmental toxicity study in Cynomolgus monkeys (Macaca fascicularis) [redacted] *1984* A29702 CA 5.6.2/18 Supplement [redacted] *1984* A38394, CA 5.6.2/19	10 and 50 mg/kg bw/d, historical control data oral gavage on gestation days 20 - 50	No NOAELs could be established due to limited study design. The study is of supplementary information only.	

B.6.6.1. Generational studies

B.6.6.1.1. Rat reproduction toxicity with fenoxaprop-P-ethyl

No single or multi-generation study has been performed with Fenoxaprop-P-ethyl.

B.6.6.1.2. Rat reproduction toxicity with fenoxaprop-ethyl

Reference:	Multiple generation study on Hoe 033171 substance technical grade (Code: Hoe 033171 0H ZC97 0001) in rats, Report Part I
Author(s). year:	[redacted] 1986a
Report/Doc. number:	A32781 / RCC Project No. 034896; [redacted] 1987, A36185, Amendment to RCC Project No. 034896 [redacted] 1986b, A33840 / RCC Project No. 034896, Part III (Pathology Report F1 parents)
Guideline(s):	EPA Guideline 83-3 (1982), Japanese Pesticide Information No. (1973)
Deviations to OECD 416:	Anogenital distance, estrus cyclicity, sperm parameter and preputial separation were not assessed.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:

Groups of 30 rats per sex of the F0 parent animals received Fenoxaprop-ethyl orally via diet at concentrations of 0, 5, 30 or 180 ppm. F0 parent animals received the diet before and during pairing (on a basis of 1 male to 1 female), during gestation and lactation periods for breeding the F1a and F1b pups.

Test material	Hoe 033171 0H ZD97 0001
Purity:	97.2 %
Test animal:	Wistar rats (strain: Wistar/Han, source: [redacted]) 7 weeks old, bw of 154-197g (♂) and 124-166g kg (♀)
Number of animals:	30 per sex per dose group

On day 21 post-partum, one F1a male and one F1a female pup per litter were sacrificed and examined macroscopically. Specified organs were weighed and tissues preserved against contingency of histopathological examination. All other F1a pups were sacrificed on or shortly after day 21 post-partum and examined macroscopically and discarded. Approximately 10 days after weaning of the F1a pups, F0 males and females were paired again employing alternative pairings for a period of 12 days.
On day 21 post-partum, one F1b male pup and one F1b female pup per litter were sacrificed and examined macroscopically. Specified organs were weighed and tissues preserved against contingency of histopathological examination. At this date, 30 male and 30 female pups per group were selected to form the F1 parent animals. All other pups were sacrificed on or shortly after day 21, examined macroscopically and discarded. Shortly after the F1b pups had been weaned, all F0 adults were sacrificed and examined macroscopically.
From all adults, specified organs were weighed and tissues were preserved. The uteri of apparently non-pregnant females were checked for possible implantation sites. The testes, prostate and seminal vesicles of males failing to induce pregnancy at the second mating were weighed and examined histopathologically. The selected F1 parent animals were reared on their respective diets for 101 days prior to pairing. The same procedure was then followed as with F0 parental animals, leading to F2a and F2b pups. All pups were sacrificed on or shortly after day 21 post-partum, as well as all F1 adults.
The animals were examined for viability, mortality and clinical signs at least twice daily. Food consumption and body weights were recorded weekly with the exception of the pairing period.
Pregnancy rate, mating and duration of gestation were determined as well as lactation and litter data. Dams and pups were weighed individually on day 1, 4, 7, 14 and 21 of lactation. The day was recorded upon the following developmental parameters were observed: pinna unfolding, incisor eruption, coat development, eye opening, and testes descensus or vaginal opening (only F1b pups).
Clinical chemistry: Blood samples were collected from the retro-orbital plexus under light ether anaesthesia. The parent animals of the F0 and F1 generations and the pups of the F1a, F1b, F2a and F2b generations were fasted overnight prior to blood sampling. Randomly selected blood samples were collected from at least one male and at least one female pup of each generations litter, but no sample was taken from any animal previously selected for breeding. The dates of investigations were: F0 parents on day 36 of treatment (pre-pairing period), F1a, F1b, F2a and F2b pups during week 4 post-partum, F1b parent males and females on day 35 and day 36 of treatment (pre-pairing period), respectively. Clinical parameters assessed were: glucose, urea, total cholesterol, triglycerides, total lipids, total proteins and ALP.
Organ weights: The following organ weights were recorded from animals selected for detailed pathology: brain (including entire brain stem), testes or uterus, heart, kidneys, liver, thyroid, adrenals, spleen, ovaries, pituitary, thymus in pups or where present, epididymides, lung, prostate and seminal vesicles.

Histopathological examination: The following organs were examined in F1 and F2b animals of the control and high dose group selected for detailed pathology: adrenals, bone marrow, brain (cerebrum, cerebellum, brain-stem), eyes, small intestine (duodenum, jejunum), kidneys, liver (at least two lobes), lung (with mainstream bronchi), lymph nodes (cervical, mesenteric), mammary gland, ovaries, pancreas, pituitary, prostate, seminal vesicles, skin, spleen, stomach, testes, thymus, thyroids, urinary bladder and uterus.
Analyses of the test substance and its content, homogeneity and stability in the diet were performed before the beginning of the study. Content and homogeneity were additionally checked at the start of mating and the end of gestation / start of lactation periods.

Findings:
Mortality / Clinical Signs: No treatment-related mortalities occurred in either the F0 and F1 parental animals throughout the study period. No clinical signs of toxicity were evident in any animal of any group in any generation.

Food consumption: No treatment-related differences in the mean food consumption of the F0 and F1 parent males and females of all dose groups and during all recording periods were noted when compared to the controls.

Test substance intake: The intake of test substance was similar for F0 and F1 parental animals during the entire study. During the lactation phase, the female food consumption was about twice higher as compared with the prepairing period. Detailed information on the test substance intake is presented in the following table:

Table 6.6.1-1 Average daily substance intake (mg/kg bw/day) in males, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)					
	F0 generation (males)			F1 generation (males)		
	5	30	180	5	30	180
Prepairing*	0.31-0.56	1.86-3.43	11.16-19.78	0.29-0.87	1.78-5.24	10.29-30.69
Postmating for breeding F1a / F2a*	0.25-0.28	1.54-1.69	9.19-10.65	0.24-0.27	1.42-1.66	8.77-9.99
Postmating for breeding F1b / F2b*	0.25-0.27	1.47-1.55	9.07-9.46	0.25	1.46-1.51	8.92-8.94

* ranges for different weeks of the study

Table 6.6.1-2 Average daily substance intake (mg/kg bw/day) in females, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)					
	F0 generation (females)			F1 generation (females)		
	5	30	180	5	30	180
Prepairing*	0.38-0.54	2.25-3.44	13.75-20.13	0.35-0.86	2.16-5.10	11.94-30.99
Gestation for breeding F1a / F2a*	0.35-0.41	2.09-2.46	13.07-15.21	0.34-0.39	2.14-2.39	12.81-14.21
Lactation for breeding F1a / F2a*	0.59-1.00	3.40-5.73	22.10-35.01	0.56-1.01	3.59-6.06	23.17-35.98
Gestation for breeding F1b / F2b*	0.33-0.38	1.97-2.26	12.13-13.50	0.31-0.35	1.93-2.08	11.38-12.52
Lactation for breeding F1b / F2b*	0.58-1.01	3.20-5.92	20.22-34.84	0.56-0.99	3.19-5.68	20.54-33.36

* ranges for different weeks of the study

Food conversion ratio: The food conversion ratios corresponded to the food consumption and body weights in both sexes without treatment-related effects. The food conversion of both generations was similar during all periods.
Body weights, parental animals: For the F0 and F1 parental animals, no treatment-related effects on body weight gain were observed in males. Females had increased bodyweight gain during lactation period, which was dose-related in the F0 generation during lactation for breeding F1b.

Table 6.6.1-3 Body weight gain in males (g), Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)

	0	5	30	180
F0 generation (males)				
Prepairing (days 1 – 80)	214	218	219	206
Postmating for breeding F1a (days 1 – 55)	48	50	50	45
Postmating for breeding F1b	24	22	24	23
F1 generation (males)				
Prepairing (days 1 – 101)	347	343	345	345
Postmating for breeding F2a (days 1 – 52)	37	34	38	40
Postmating for breeding F2b (days 1 – 14)	14	14	14	14

Table 6.6.1-4 Body weight gain in females (g), Reproductive toxicity study in rats with fenoxaprop-P-ethyl

	Dose group level (ppm)			
	0	**5**	**30**	**180**
F0 generation (females)				
Prepairing (days 1 – 80)	91	95	98	89
Gestation for breeding F1a (days 0 – 21)	107	111	108	108
Lactation for breeding F1a (days 1 – 21)	29	26	28	27
Gestation for breeding F1b (days 0 – 21)	108	106	108	101
Lactation for breeding F1b (days 1 – 21)	32	35 +9.4%	40 +25%	44 +37.5%
F1 generation (females)				
Prepairing (days 1 – 101)	179	174	182	181
Gestation for breeding F2a (days 0 – 21)	105	104	106	104
Lactation for breeding F2a (days 1 – 21)	19	23	23	30 +57.9%
Gestation for breeding F2b (days 0 – 21)	103	112	104	106
Lactation for breeding F2b (days 1 – 21)	23	27 +17.4%	22	33 +43.5

Reproduction parameters: No significant differences in any parameter recorded were noted between all groups of both generations during breeding F1a, F1b, F2a or F2b litters. The following parameters were evaluated: number of females paired, mated, pregnant, bearing and breeding, precoital time, percentage of mating, fertility index, conception rate, gestation index, duration of gestation, parturition and nursing, number of pups (dead, living) and breeding loss.

Pup development: A test substance related decrease of the mean body weights of the pups of the 180 ppm dose group was noted in any pup generation (F1a, F1b, F2a, F2b) on postnatal day 21. The weight gain differences for the combined sexes compared to the respective control groups were of statistical significance: -4.9 % (F1a), -4.4 % (F1b), -7.1 % (F2a) and -7.5 % (F2b).

Table 6.6.1-5 Pup body weight on PND1 and 21 in F1a, F1b, F2a and F2b litters in g, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	**5**	**30**	**180**	**0**	**5**	**30**	**180**
F1a[1)] PND 1	6.2	6.2	6.1	6.1	5.9	5.9	5.8	5.8
PND 21	34.7	35.7	34.6	33.5	34.1	34.7	34.0	32.1
F1b[1)] PND 1	6.2	6.3	6.0	6.3	5.8	6.0	5.8	6.0
PND 21	41.5	43.0	41.5	39.7	39.9	42.3	40.5	38.0
F2a[1)] PND 1	5.9	6.1	6.0	6.1	5.5	5.7	5.8	5.7
PND 21	39.9	40.3	40.2	37.4	38.5	39.4	39.2	35.4
F2b[1)] PND 1	6.3	6.1	6.2	6.2	5.8	5.7	5.9	5.9
PND 21	39.7	38.4	37.9	36.2	37.6	36.9	37.0	35.1

[1)] Statistical significancies were only calculated for the body weight gain differences (see text above)

Except the finding of slightly spread toes and wavy-deformed tail in three F2b pups (2 males, 1 female) of one litter in the 180 ppm group, no malformed or anomalied pup was found in any group. Similar sex ratios were noted in all groups. The number of pups which died during the lactation and rearing periods was similar between all groups. There was no difference in physical development, health conditions, viability and appearance of the pups of all groups. The stages of development and the time of their respective appearance were similar in all

groups. In the necropsy of pups not selected for histopathological examinations or recording of organ weights, no test substance related findings were noted in any pup generation.

Clinical chemistry, parental animals and pups: The following slight but statistically significant effects on clinical chemistry parameters were reported: F0 parents (day 36 of treatment): decreased cholesterol for males at 180 ppm, decreased total protein for females at 5 and 30 ppm and both sexes at 180 ppm. F1 parents (day 35 / 36 of treatment): decreased total lipid levels for both sexes of all groups, decreased total cholesterol levels for males of all groups and a decreasing trend for females at 30 and 180 ppm, and a decreased total protein level for males at 180 ppm. F1a pups (week 4 post partum): increased ALP activity for males at 30 and both sexes at 180 ppm. F1b pups (week 4 post partum): increased urea level for both sexes at 180 ppm and increased ALP activity for both sexes at 30 and 180 ppm. F2a pups (week 4 post partum): increased ALP for both sexes at 30 and 180 ppm. F2b pups (week 4 post partum): increased total lipid level for females at 30 and 180 ppm, increased total cholesterol for both sexes at 180 ppm, and increased ALP for both sexes at 180 ppm.

Table 6.6.1-6 Clinical chemistry data for parental animals and pups, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Cholesterol, total (mmol/L)								
F0 parents	1.86	1.76 -5.4%	1.68 -9.7%	**1.35*** **-27.4%**	1.88	**1.69*** **-10.1%**	1.73 -8.0%	1.73 -8.0%
F1 parents	1.96	**1.73*** **-11.7%**	**1.65*** **-15.8%**	**1.26*** **-35.7%**	2.12	2.14	1.95 -8.0%	1.99 -6.1%
F1a pups	2.94	2.86	2.91	3.09	3.11	2.98	2.95	3.08
F1b pups	2.69	2.58	2.59	2.58	2.75	2.71	2.70	2.56
F2a pups	2.49	2.57	2.36	2.45	2.47	2.50	2.38	2.58
F2b pups	2.17	2.26	2.18	**2.37*** **+9.2%**	2.18	2.23	2.21	**2.47*** **+13.3%**
Lipids, total (g/L)								
F0 parents	2.8	2.7	2.9	2.5	3.1	2.9	2.9	2.8
F1 parents	3.6	**2.7*** **-25.0%**	**2.4*** **-33.3%**	**1.6*** **-55.6%**	3.3	**2.8*** **-15.2%**	**2.4*** **-27.3%**	**2.3*** **-30.3%**
F1a pups	6.0	5.7	5.7	5.4	5.5	5.9	5.8	5.5
F1b pups	6.0	5.9	5.7	5.6	5.9	5.8	6.1	5.9
F2a pups	6.7	7.4	6.3	6.6	6.8	6.8	6.7	7.0
F2b pups	4.6	5.1 +10.9%	5.4 +17.4%	5.5 +19.6%	5.0	5.6 +12.0%	**6.0*** **+20.0%**	**6.3*** **+26.0%**
Proteins, total (g/L)								
F0 parents	67.3	66.5	65.8	**63.6*** **+5.5%**	66.4	**63.9*** **-3.8%**	**63.9*** **-3.8%**	**63.9*** **-3.8%**
F1 parents	64.2	63.6	64.2	**62.1*** **-3.3%**	66.6	67.8	66.2	65.9
F1a pups	45.6	47.4	45.8	46.8	46.9	46.9	46.3	46.4
F1b pups	48.1	48.7	49.8	48.8	49.4	49.0	49.9	49.0
F2a pups	49.2	48.9	**47.3*** **-3.9%**	**47.4*** **-3.7%**	48.6	48.2	48.0	47.9
F2b pups	47.9	48.2	48.6	48.2	49.3	48.2	49.2	49.2
ALP (µkat/L)								
F0 parents	4.42	4.23	4.39	4.30	2.19	2.36	2.16	2.37
F1 parents	6.82	6.50	6.93	7.01	3.76	3.81	3.99	4.20
F1a pups	8.96	9.53 +6.4%	**11.33*** **+26.5%**	**10.73*** **+19.8%**	9.86	10.15	10.77 +9.2%	**11.79*** **+19.4%**
F1b pups	12.26	13.09 +6.8%	**14.66*** **+19.6%**	**14.86*** **+21.2%**	11.70	12.79 +9.3%	**13.55*** **+15.8%**	**13.82*** **+18.1%**
F2a pups	12.14	13.49 +11.1%	**15.35*** +26.4%	**15.63*** **+28.7%**	11.46	12.53 +9.3%	**14.07*** **+22.8%**	**14.38*** **+25.5%**
F2b pups	12.08	12.34	13.48 +11.6%	**14.19*** **+17.5%**	12.02	12.16	13.47 +12.1%	**13.64*** **+13.5%**
Urea (mmol/L)								
F0 parents	7.81	8.21	8.25	7.95	8.65	7.97	8.35	8.49
F1 parents	6.97	7.10	7.10	**7.76*** **+11.3%**	6.68	6.27	6.39	7.02
F1a pups	6.73	6.73	6.40	7.44	6.51	6.94	6.78	7.13

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
F1b pups	7.18	6.85	6.89	**8.08*** **-12.5%**	7.56	7.17	7.14	**8.72*** **+15.3%**
F2a pups	5.65	5.60	5.48	6.14	6.21	6.39	5.78	6.80
F2b pups	6.82	7.49	6.82	7.29	7.32	7.34	6.97	7.58

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

Organ weight analysis, parental animals: Changes of organ weights were only observed at the highest dose level of 180 ppm. In F0 parental males, relative liver and kidney weights were increased. In F1 parental animals, liver weight (absolute, relative, and relative to brain weight) was increased in males. The weight of kidneys (absolute, relative) was elevated in males and females. Furthermore, epididymides weight was decreased in males and pituitary weight was decreased in females (both: absolute, relative, and relative to brain weight). By the study authors, the organ weight changes in epididymides and pituitary were discussed to be not related to treatment.

Table 6.6.1-7 Statistically significant organ weight findings in F0 and F1 parents, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Liver weight F0								
absolute (g)	14.63	14.11	14.20	15.27	13.57	13.63	13.39	13.88
relative (% bw)	3.113	**2.968***	**2.997***	**3.277****	4.549	4.515	**4.247****	4.438
relative to brain weight	700.6	674.1	674.4	735.7	711.2	717.2	695.8	718.3
F1								
absolute (g)	15.39	15.11	15.69	**16.65***	13.48	12.42	13.01	13.25
relative (% bw)	3.16	3.06	3.16	**3.38****	4.58	4.31	4.41	4.40
relative to brain weight	719.0	708.0	739.0	**787.4****	705.4	646.8	664.3	676.4
Kidney weight F0								
absolute (g)	2.38	2.38	2.40	2.48	1.86	1.95	1.92	1.95
relative (% bw)	0.506	0.502	0.508	**0.534***	0.623	0.646	0.614	0.626
relative to brain weight	113.8	113.8	114.0	**119.5***	97.36	102.88	99.88	100.84
F1								
absolute (g)	2.50	2.57	2.49	**2.80***	1.87	1.87	1.89	**2.03****
relative (% bw)	0.51	0.52	0.50	**0.57****	0.64	0.65	0.64	**0.68***
relative to brain weight	116.7	120.6	117.4	**132.4****	97.95	97.24	96.37	103.69
Epididymides weight F0								
absolute (g)	1.435	1.472	1.493	1.385	-	-	-	-
relative (% bw)	0.307	0.311	0.316	0.299				
relative to brain weight	68.73	70.43	70.91	66.70				
F1								
absolute (g)	1.410	1.416	1.368	1.269	-	-	-	-
relative (% bw)	0.290	0.286	0.278	**0.258****				
relative to brain weight	65.94	66.06	64.36	**60.10****				
Pituitary weight F0								
absolute (g)	0.010	0.011	0.010	0.010	0.014	0.015	0.015	0.014
relative (% bw)	0.002	0.002	0.002	0.002	0.005	0.005	0.005	0.004
relative to brain weight	0.491	0.525	0.491	0.466	0.747	0.776	0.756	0.711
F1								
absolute (g)	0.010	**0.011***	0.011	0.009	0.014	0.014	0.013	**0.012***
relative (% bw)	0.002	0.002	0.002	0.002	0.005	0.005	0.005	**0.004***
relative to brain weight	0.459	**0.515***	0.503	0.445	0.713	0.726	0.651	**0.620****

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

Organ weight analysis, pups: Several organ weight changes were observed in the pup generations. The study authors considered only the organ weight changes in livers and kidneys to be related to treatment. Weights (absolute and/or relative) of livers were increased at the highest dose level of 180 ppm while kidney weights were occasionally increased at 30 ppm and predominantly at 180 ppm (see table). Further organ weight changes were observed in the several organs which were considered to be incidental by the study authors:
Lungs: reduced absolute and organ to brain weight at 30 and 180 ppm in F1a females; reduced absolute and organ to brain weight at 180 ppm in F1b males; reduced absolute and organ to brain weight at 180 ppm and rela-

tive to body weight at 30 ppm in F1b females; reduced absolute weight and organ to brain weight at 180 ppm in F2a females; reduced absolute and organ to brain weight at 30 and 180 ppm in F2b males; reduced absolute and organ to brain weight at 30 and 180 ppm
Pituitary: reduced absolute and relative weights at 30 and 180 ppm in F1a females
Spleen: reduced relative weights at 180 ppm in F1a females; reduced absolute and organ to brain weights at 180 ppm in F1b females; reduced weight and ratios at 180 ppm in F2a females; reduced weight and ratios in F2b males; reduced weight and ratios at 180 ppm and reduced ratios also at 30 ppm in F2b females
Thymus: reduced weight and ratios at 180 ppm in F2a females; reduced weight and ratios at 180 ppm in F2b males; reduced absolute and organ to brain weight at 180 ppm in F2b females
Uterus: reduced absolute and organ to brain weight at 180 ppm in F1b females; reduced absolute and organ to brain weight at 180 ppm in F2a females
Epididymides: reduced absolute and organ to brain weight at 180 ppm in F2a males
Testes: reduced absolute and organ to brain weight in at 180 ppm in F2b males

Table 6.6.1-8 Organ weight findings in F1a, F1b, F2a and F2b pups, Reproductive toxicity study in rats with fenoxaprop-ethyl

	Dose group level (ppm)							
	Males				Females			
	0	5	30	180	0	5	30	180
Liver weight F1a								
absolute (g)	1.46	1.44	1.43	**1.80****	1.35	1.33	1.39	**1.66****
relative (% bw)	4.110	3.992	4.051	**5.291****	3.913	3.757	4.029	**5.107****
relative to brain weight	103.9	103.8	101.2	**128.9****	100.48	98.37	102.28	**125.7****
F1b								
absolute (g)	1.71	1.75	1.78	**2.07****	1.56	1.60	1.63	**1.85****
relative (% bw)	4.002	3.972	4.106	**5.063****	3.831	3.745	3.914	**4.819****
relative to brain weight	120.1	121.2	123.3	**140.6****	114.5	114.8	116.9	**135.1****
F2a								
absolute (g)	1.61	1.59	1.67	**1.84****	1.49	1.47	1.52	**1.66***
relative (% bw)	3.92	3.86	4.03	**4.90****	3.75	3.60	3.80	4.61
relative to brain weight	112.4	111.0	115.6	**129.6****	107.4	106.5	109.2	**121.6****
F2b								
absolute (g)	1.56	1.45	1.53	**1.82****	1.48	1.36	1.44	**1.71****
relative (% bw)	3.90	3.74	3.90	**4.87****	3.81	3.64	3.84	**4.76****
relative to brain weight	107.9	100.0	106.0	**125.9****	106.86	98.72	103.5	**122.9****
Kidney weight F1a								
absolute (g)	0.38	0.38	0.39	**0.42***	0.37	0.38	0.38	0.40
relative (% bw)	1.061	1.054	**1.111***	**1.237****	1.072	1.075	1.111	**1.235****
relative to brain weight	26.82	27.33	27.71	**30.26****	27.52	28.13	28.18	**30.52****
F1b								
absolute (g)	0.44	**0.49***	0.46	**0.51****	0.43	0.46	0.46	**0.47***
relative (% bw)	1.027	**1.111***	1.073	**1.246****	1.050	1.073	1.113	**1.221****
relative to brain weight	30.74	34.00	32.18	**34.67***	31.41	32.90	33.19	**34.14***
F2a								
absolute (g)	0.41	0.43	0.45	0.45	0.42	0.43	0.44	0.44
relative (% bw)	1.01	1.04	**1.09****	**1.21****	1.05	1.05	1.10	**1.23****
relative to brain weight	28.80	30.03	31.04	**31.91***	29.94	31.07	31.59	32.43
F2b								
absolute (g)	0.42	0.41	0.42	0.44	0.42	0.40	0.42	0.44
relative (% bw)	1.05	1.05	1.07	**1.19****	1.07	1.07	**1.11****	**1.22****
relative to brain weight	28.98	28.18	28.97	30.78	29.97	29.08	29.96	31.62

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

Macroscopic and histopathological examination: No treatment-related effects were observed in F1 parents and F2b pups.

Analytical method: According to the analytical method described in attachment 1 of the report of [redacted], 1987 (Doc No. A32781) the LOQ was determined as 10 ppm (for details refer to Volume 3 CA B-5).

Conclusion:

No effects on reproduction were observed in this study. The NOAEL for reproductive toxicity therefore is 180 ppm (equivalent to a dose range of 8.77-30.69 mg/kg bw/d in males and equivalent to a dose range of 11.38 - 35.98 mg/kg bw/d in females).
Regarding systemic toxicity, effects were noted in both parents and offspring. In parental animals, significant absolute and/or relative liver and kidney weight changes were observed in both F0 and F1. Additionally, slight significant changes in some clinical chemistry parameters appeared starting at the lowest dose of 5 ppm. Taken together, organ weight changes and effects on clinical chemistry parameters appeared coincidentally at 180 ppm leading to a systemic parental toxicity NOAEL of 30 ppm (equivalent to a dose range of 1.42 – 5.24 mg/kg bw/d in males and equivalent to a dose range of 1.93 - 6.06 mg/kg bw/d in females).
The offspring showed a reduced body weight gain during lactation at the highest dose of 180 ppm. An increased absolute and relative organ weight of the target organs (liver, kidney) was observed in all offspring generations receiving 180 ppm. Sporadically, absolute and/or relative kidney weights were increased also at 30 ppm but this was without consistency regarding dose relation or between sexes. Clinical chemistry parameters were predominantely changed at 180 ppm. In conclusion, a systemic offspring toxicity NOAEL of 30 ppm is considered (equivalent to a dose range of 1.42 – 5.24 mg/kg bw/d in males and equivalent to a dose range of 1.93 - 6.06 mg/kg bw/d in females).

B.6.6.2. Developmental toxicity studies

B.6.6.2.1. Rodent teratogenicity (oral) studies with fenoxaprop-P-ethyl

B.6.6.2.1.1. Rat teratogenicity (study 1)

Reference:	Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Wistar rats following oral administration
Author(s). year:	[redacted], 1985a
Report/Doc. number:	A33810 / Hoechst Report No. 85.1239 Supplement to Report No. 85.1239, [redacted] 1988a, A37496 / Hoechst Report No. 88.0094; Supplement to Report No. 85. 1239, [redacted]., 1990a; Doc. No. A42779 / Hoechst Report No. 90.0250
Guideline(s):	No guideline is mentioned in the study report.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Groups of female rats 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). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Test material	Fenoxaprop-P-ethyl, Hoe 046360 0H ZB99 0002
Purity:	99 % according to certificate of analysis No. 02327 (1983)
Test animal:	Female Wistar rats Hoe WISKf(SPF71), source: Hoechst 65-70 days old, mean bw of 192 ± 14 g
Number of animals:	20-23 per dose group

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.

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. A decrease in food consumption was noted in the highest dose group of 100 mg/kg bw/d during treatment period. After termination of treatment, the nutritive deficiency was compensated by a slight increase in food consumption during days 17-21. Dams of the highest dose group of 100 mg/kg bw/d showed a retardation of body weight when compared to the concurrent controls.

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 6.6.2-1 Maternal effects, Developmental toxicity study of fenoxaprop-P-ethyl in Wistar rats

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw) GD 1 – 7	9.79	9.40	9.74	9.28
GD 7 – 14	7.96	7.44	7.53^{+}	**5.17*** **-35.1%**
GD 14 – 17	7.58	7.45	7.28	**7.28*$^{1)}$** **-4.0%**
GD 17 – 21	8.34	8.54	8.45	**9.46*** **+13.4%**
Body weight (g) GD 21	336	**315*** **-6.3%**	323 -3.9%	**292*** **-13.1%**
Body weight gain (g) GD 0-21$^{2)}$	142 $^{2)}$	**127** $^{2)x}$ **-10.5%**	129 $^{2)}$ -9.2%	**99** $^{2)xxx}$ **-31.3%**
Body weight gain (%) GD 0-21	+73.2%	**+67.6%**	+66.5%	**+51.3%**
Heart weight of dams (g)	0.86	**0.78 *** **-9.3%**	0.84 $^{+}$ +2.3%	**0.71**$^{-\ xxx}$ **-17.4%**
Heart weight relative to bw (%)	0.26	0.25 $^{n.s.}$	0.24	0.24 $^{n.s.}$

GD: gestation day; * ($p<0.05$); significantly different from controls; $^{+}$ n=19; $^{-}$ n=18; $^{n.s.}$ statistically not significant
$^{1)}$ 2 extreme values (19.97g and 11.52g f. c. per 100g bw) excluded: 6.34g/100g bw ±1.5 (-16.4% of control group)
$^{2)}$ statist. analysis performed by RMS: student's t-test, ^{x} $p<0.05$, ^{xxx} $p<0.001$; significantly different from controls

Table 6.6.2-2 Mean food consumption of dams (g/100g bw), Developmental toxicity study of fenoxaprop-P-ethyl in Wistar rats

Dose mg/kg bw/d	**Day of pregnancy**			
	1-7	**7-14**	**14-17**	**17-21**
Control	9.79 ^{N} (±0.85)	7.96 (±0.74)	7.58 ^{N} (±0.85)	8.35 ^{N} (±0.65)
10	9.40 ^{N} (±0.95)	7.44 (±0.88)	7.45 ^{N} (±1.18)	8.54 ^{N} (±0.70)
32	9.76 ^{N} (±0.78)	7.58 (±0.71)	7.35 ^{N} (±0.75)	8.58 ^{N} (±0.54)
100	9.28 ^{N} (±0.71)	**5.42** (±1.21)	**7.53** ^{*A} (±3.51)	**9.46** ^{*A} (±1.40)

^{N} within normal range
^{*A} outside normal range, significantly different from controls ($p<0.05$)
For days 7-17, the area under the curve was used for statistical evaluations.

Table 6.6.2-3 Mean Bodyweight (g) of dams, Developmental toxicity study of fenoxaprop-P-ethyl in Wistar rats

Dose	**Day of pregnancy**

mg/kg bw/d	**0**	**7**	**14**	**17**	**21**
Control	193 ^{N} (±13)	230 (±15)	260 (±18)	282 ^{N} (±20)	335 ^{A} (±25)
10	187 ^{N} (±11)	218 (±12)	244 (±15)	263 ^{*N} (±17)	315 $^{(*A)}$ (±23)
32	194 ^{N} (±13)	229 (±15)	257 (±16)	275 ^{N} (±20)	327 $^{(A)}$ (±24)
100	194 ^{N} (±13)	227 (±12)	**233** (±18)	**245** ^{*A} (±14)	**300** $^{(*N)}$ (±22)

^{N} within normal range, ^{A} outside normal range
$^{(..)}$ the control group lies outside the normal range
* significantly different from controls (p< 0.05)
For days 7-17, the area under the curve was used for statistical evaluations.

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 6.6.2-4 Maternal and developmental effects, Developmental toxicity study of fenoxaprop-P-ethyl in Wistar rats

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Dams with live fetuses	20	20	19	18

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
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)	31 ± 9.6 % (13.1 min. - max. 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)	38.3 ± 13.7 % (min. 13.5 - max. 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, where skeletal effects occurred in the historical control range. No teratogenicity was observed.

B.6.6.2.1.2. Rat teratogenicity (study 2)

Reference:	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
Author(s). year:	[redacted] 1987a
Report/Doc. number:	A35687 / Hoechst Report No. 87.0309 [redacted] 1990a, Supplement to Report No. 87.0309, A42781 / Hoechst Report No. 90.0251
Guideline(s):	Postnatal toxicity study, no guideline available. In the study report it is stated that the study was conducted according to OECD guideline 414
Deviations to OECD GD 414 (2001)	No examination of uterine contents was performed. Sex of fetuses not determined.
GLP:	Yes.
Acceptability:	Yes.

The aim of the study was to determine whether Fenoxaprop-P-ethyl impaired the postnatal development of offspring following repeated dosing during gravidity.

Material and Methods:
Groups of female rats were treated orally by gavage on gestation days 7 – 16 with 0, 10, 32 or 100 mg/kg fenoxaprop-P-ethyl (vehicle: sesame oil). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Test material	Fenoxaprop-P-ethyl, Hoe 046360 0H ZC96 0002
Purity:	95.6 % (according to certificate of analysis No. 02912 (1985))
Test animal:	Female Wistar rats Hoe WISKf(SPF71), source: [redacted] 65-70 days old, mean bw of 190 ± 6.7 g
Number of animals:	20-21 per dose group

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 postnatal 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 6.6.2-5 Maternal effects, Developmental and postnatal toxicity study of fenoxaprop-P-ethyl in Wistar rats

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw) GD 0-7	9.9	9.8	9.6	9.6
GD 7-17	8.2	8.2	7.8	**6.8*** **-17.1%**
GD 17-21	8. 6	8.3	8.6	**9.4*** **+9.3%**
Body weight (g) GD 21	329	325	319	**305**** **-7.3%**
Body weight gain (g) GD 0-21[1)]	138[1)]	136[1)]	129[1)] -6.6%	**116 [1)]**** **-15.9%**
Body weight gain (%) GD 0-21	+72.3%	+72.0%	+67.9%	**61.4%**

GD: gestation day; * ($p < 0.05$) significantly different from controls;
** statistical analysis performed by RMS using student's t-test: ($p<0.01$) signif. different from controls
[1)] statistical analyses were performed on medians and showed significant differences between control and 100 mg/kg group; statistical analysis with means performed by RMS using student's t-test

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 6.6.2-6 Maternal and developmental effects, Developmental and postnatal toxicity study of fenoxaprop-P-ethyl in Wistar rats

	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	12.7	12.4	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)] 34.1[1)]	**5.5[1) xxx]** 34.3[1)]	**5.6[1) xxx]** **35.5[1) xx]**	**5.5[1) xxx]** **32.8[1) xx]**
Survival rate (%) day 21	95.3	98.8	98.8	97.6
Morphological anomalies in offspring				
External anomalies: Toe anomalies	0	2 (1)[2)]	1 (1)[2)]	1
Historical control data (Doc. No. A42781)	0.0-2.1 % 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; **statist. analysis performed by RMS: student's t-test, [x] p<0.05, [xx] p<0.01, [xxx] p<0.001; significantly different from controls**
[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. No significant effects on the fetuses were observed. Therefore the NOAEL for offspring toxicity was considered as 32 mg/kg bw/d.

B.6.6.2.2. Non-rodent teratogenicity (oral) study with fenoxaprop-P-ethyl

Reference:	Hoe 046360 – active ingredient (Code: Hoe 046360 0H ZB99 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration
Author(s). year:	[redacted], 1986a
Report/Doc. number:	A33302 / Hoechst Report No. 86.0488 [redacted], 1990, Supplement to Report No. 86.0488, A42780 / Report No. 90.0249
Guideline(s):	No information on study guidelines is presented in the study report.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
15 gravid female rabbits 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). The stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Test material	Fenoxaprop-P-ethyl, batch Hoe 046360 0H ZB99 0002
Purity:	99 % (according to certificate of analysis No. 02327 (1983))
Test animal:	Himalayan rabbits (Hoe HIMK(SPFWiga), source: Hoechst) 7 months old, mean bw of 2525 ± 173 g
Number of animals:	15 per dose group

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. A decrease in food consumption was noted in the highest dose group of 100 mg/kg bw/d during treatment period. This also accounts for the reduced faecal excretions in some of the animals of this group. The food consumption could not be determined regularly for all of the dams since a number of animals scattered their feed out of the racks.

The body weight gains among the dams of the highest dose group of 100 mg/kg bw/d stagnated during the treatment period, but continued to increase normally after the end of treatment.

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 6.6.2-7 Maternal effects, Developmental toxicity study of fenoxaprop-P-ethyl in Himalayan rabbits

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Body weight gain (g) GD 7 – 20[1)]	101	107	82	**-3****
- median	110	110	90	30
Body weight gain (g) GD 20 – 29[1)]	177	153[n.s.]	175	197
- median	180	130	180	160
Kidney weight of dams (g)	15.54	15.52	15.80	**16.85* +8.4%**
Liver weight of dams (g)	55.12	55.17	57.11	59.71
Spleen weight of dams (g)	0.55	0.62	0.56	**0.68* +23.6%**

GD: gestation day
* ($p < 0.05$); significantly different from controls
[1)] no statistical analysis was performed; statistical analysis using student's t-test performed by RMS, **p<0.01, statistically different from control

Table 6.6.2-8 Mean food consumption of dams (g/100g bw), Developmental toxicity study of fenoxaprop-P-ethyl in Himalayan rabbits

Dose mg/kg bw/d	Day of pregnancy			
	1-7	**7-14**	**14-17**	**20-29**
Control	4.68 [A] (±0.66)	4.32 (±0.59)	4.15 [A] (±0.77)	4.04 [N] (±0.42)
10	4.49 [(A)] (±0.50)	4.26 (±0.56)	4.24 [(N)] (±0.57)	4.04 [N] (±0.33)
32	4.52 [(A)] (±0.52)	4.32 (±0.55)	3.84 [(N)] (±1.07)	4.24 [N] (±0.46)
100	4.51 [(N)] (±0.67)	3.39 (±1.30)	2.39 [(*N)] (±1.70)	4.19 [A] (±0.55)

[N] within normal range, [A] outside normal range
[(..)] the control group lies outside the normal range
* significantly different from controls ($p < 0.05$)
For days 7-17, the area under the curve was used for statistical evaluations.

Table 6.6.2-9 Mean Bodyweight (g) of dams, Developmental toxicity study of fenoxaprop-P-ethyl in Himalayan rabbits

Dose mg/kg bw/d	Day of pregnancy				
	0	**7**	**14**	**17**	**21**
Control	2495 (±180)	2523 (±168)	2560 (±169)	2624 (±168)	2801 (±176)
10	2529 (±192)	2551 (±162)	2605 (±165)	2658 (±154)	2826 (±206)

32	2511 (±168)	2547 (±154)	2596 (±149)	2643 (±147)	2834 (±149)
100	2571 (±201)	2610 (±147)	2607 (±180)	2595 (±147)	2834 (±134)

All values were within normal range, no significant differences from controls ($p < 0.05$)

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 ([redacted] 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 6.6.2-10 Maternal and developmental effects, Developmental toxicity study of fenoxaprop-P-ethyl in Himalayan rabbits

	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%)

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 ([redacted]., 1982b; Doc. No. A24756), leading to a NOAEL for fetal toxicity of 32 mg/kg. No teratogenicity was observed in this study.

B.6.6.2.3. Rodent teratogenicity (oral) studies with fenoxaprop-ethyl

B.6.6.2.3.1. Rat teratogenicity (study 1)

Reference:	An oral embryotoxicity study of Hoe 33171 0H AT204 in Wistar rats
Author(s). year:	[redacted], 1982a
Report/Doc. number:	A26170 / Hoechst Report No. 613/82 Baeder *et al.* 1986, Supplement to Rep. No. 613/82, A32696 / Rep. No. 86.0047 Baeder *et al.* 1989, Supplement 2 to Rep. No. 613/82, A41709 / Rep. No. 89.1153
Guideline(s):	No information on study guidelines is presented in the study report.
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-ethyl was administered to the animals by oral gavage on gestation days 7 to 16. 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 stability of the test substance preparations was guaranteed by analytical analysis.

Test material	Fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity:	93.0 % according to certificate of analysis No. 01711, 1982
Test animal:	Female Wistar rats (Hoe WISKf(SPF71), source: Hoechst) 70 days old, mean bw of 185 ± 13 g
Number of animals:	20 per dose group (in total 80 + 20)

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 orientation 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 6.6.2-11 Maternal effects, Developmental toxicity study of fenoxaprop-ethyl in Wistar rats

	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*** **-15.8%**	**5.54*** **-27.8%**
GD 14 – 17	7.65	7.48	7.64	**6.92*** **-9.6%**	**5.90*** **-12.9%**
GD 17 – 21	8.16	8.18	8.30	8.47	**8.77*** **+7.5%**
Body weight (g) GD 21	317	313	308	**299*** **+5.7%**	**285*** **+10.1%**

	Dose group level (mg/kg bw/day)				
	0	**10**	**32**	**100**	**100 (repetition)**
Body weight gain (g) GD 0-21[1)]	127[1)]	125[1)]	126[1)]	115[1)]	105[1)]
Body weight gain (%)	+66.8%	+66.5%	+69.2%	+62.5%	+58.3%

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 (up to 0.9%, 1976-1988). In these studies, the highest frequency of occurrence found was 2 from 216 fetuses, corresponding to a rate of 0.9 %.

Table 6.6.2-12 , Developmental toxicity study of fenoxaprop-ethyl in Wistar rats

	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*** **-11.1%**	**2.85*** **-14.7%**
Crown rump length (cm)	3.61	3.60	3.59	3.53	**3.47*** **-3.9%**
Mean placental weight (g)	0.49	0.50	0.50	0.46	**0.44*** **-10.2%**
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.

B.6.6.2.3.2. Rat teratogenicity (study 2)

Reference:	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
Author(s). year:	[redacted] 1986b
Report/Doc. number:	A35783 / Hoechst Report No. 86.0133
Guideline(s):	Postnatal toxicity study, no guideline available; in the study report it is stated that the study was conducted according to OECD guideline 414
Deviations:	Not applicable, due to postnatal conducted study.
GLP:	Yes.
Acceptability:	Yes.

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. The animals were treated by oral gavage on gestation days 7 – 16 with 0, 10, 32 or 100 mg/kg Fenoxaprop-ethyl (vehicle: sesame oil). 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.

Test material	Fenoxaprop-ethyl, batch Hoe 033171 0H ZD98 0001
Purity:	97.9 % (Code: Hoe 033171 0H ZD98 0001), according to certificate of analysis No. 03098 (1985)
Test animal:	female Wistar rats (Hoe WISKf(SPF71), source: [redacted]) 65 – 70 days old, mean bw of 194 ± 12.8 g
Number of animals:	20 per dose group

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 6.6.2-13 Maternal effects, Developmental and postnatal toxicity study of fenoxaprop-ethyl in Wistar rats

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**

	Dose group level (mg/kg bw/day)			
	0	**10**	**32**	**100**
Food consumption (g/100g bw)				
GD 0-7	8.5	8.1	8.2	8.5
GD 7-17	6.9	6.7	**6.3* (-8.7%)**	**5.9* (-14.5%)**
GD 17-21	7.5	7.5	7.7	**8.6* (+14.7%)**
Body weight (g) GD 7-17 (mean)	245	249	241	**233* (-4.9%)**
GD 0-21 (mean)	276	289	275	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 6.6.2-14 Maternal and developmental effects, Developmental and postnatal toxicity study of fenoxaprop-ethyl in Wistar rats

	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
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.

B.6.6.2.3.3. Mouse teratogenicity

Reference:	A study of the effect of the active ingredient Hoe 33171 technical on the pregnancy of the mouse (Code: Hoe 33171 0H ZC96 0002)
Author(s). year:	[redacted]., 1983
Report/Doc. number:	A30282 / Report No. HST 221/222-R/83666
Guideline(s):	EPA, section F. Hazard evaluation, humans and domestic animals section 83-3 (Teratology study)
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
The effects of Fenoxaprop-ethyl on pregnancy and fetal development were tested. Groups of animals 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. The solutions were made daily and dosed on the day of preparation.

Test material: Fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity: 96.2 % according to certificate of No. 02183 (1983)

Test animal: CD-1 mice (source: [redacted]), age not stated (but sexually mature animals) and bw of 27.7-28.6g
Number of animals: 30 per dose group

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 6.6.2-15 Maternal effects, Developmental toxicity study of fenoxaprop-ethyl in CD-1 mice

	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)	2.407	2.469	2.482	3.022
relative to body weight	2.430	2.482	2.500	**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 6.6.2-16 Maternal and developmental effects, Developmental toxicity study of fenoxaprop-ethyl in CD-1 mice

	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.

B.6.6.2.4. Non-rodent teratogenicity (oral) studies with fenoxaprop-ethyl

B.6.6.2.4.1. Rabbit teratogenicity (study 1)

Reference:	An oral embryotoxicity study of Hoe 33171 active ingredient (technical grade, Code: Hoe 33171 0H AT204) in Himalayan rabbits
Author(s). year:	[redacted], 1982b
Report/Doc. number:	A24756 / Hoechst Report No. 667/82 [redacted] 1986, Supplement to Report No. 667/82, A32692 / Report No. 86.0022 [redacted] 1989, Supplement to Report No. 667/82, A41707 / Report No. 89.1154
Guideline(s):	No information on study guidelines is presented in the study report
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Fenoxaprop-ethyl was administered to gravid animals 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 stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Test material	Fenoxaprop-ethyl, batch Hoe 33171 0H AT204
Purity:	93 % according to certificate of analysis No. 01711 (1981)
Test animal:	female Himalayan rabbits (Hoe HIMK(SPFWiga), source: [redacted]) 9 - 11 months old, mean bw of 2688 ± 207 g
Number of animals:	15 per dose group

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, while body weight was stagnant at 50 mg/kg and even declined during treatment period at 200 mg/kg.
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 6.6.2-17 Maternal effects, Developmental toxicity study of fenoxaprop-ethyl in Himalayan rabbits

	Dose group level (mg/kg bw/day)			
	0	**12.5**	**50**	**200**
Pre-terminal deaths	-	1	-	2
Reduced defecation	4	3	8	15
Body weight (g) GD 7	2647	2664	2707	2648
Body weight (g) GD 20	2673	2723	2695	2351 (-12.0%)
Body weight (g) GD 29	2833	2862	2820	2710 (-4.3%)
Bodyweight gain (g) GD 0-29	222	203	128 (-42.3%)	63 (-71.6%)
Liver weight of dams (g)	53.51	55.69	56.66	**63.54* (+18.7%)**
Spleen weight of dams (g)	0.61	0.72	0.72	**1.09* (+78.7%)**

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 (during 1974-1988), only one such hernia had been encountered, which represents a spontaneous rate of 0-1.4% (litters: 0-8.3). 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 increase 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.

All other anomalies and variations observed in the treatment groups were considered to be spontaneously.

Table 6.6.2-18 , Developmental toxicity study of fenoxaprop-ethyl in Himalayan rabbits

	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* (-18.9%)**
Crown rump length (cm)	9.8	9.7	9.8	**9.2* (-6.1%)**
Mean placental weight (g)	5.68	5.80	5.79	**5.08* (-10.6%)**
Survival rate after 24 hours (%)	92.5	95.3	92.2	**61.2* (-33.9%)**
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, 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.

B.6.6.2.4.2. Rabbit teratogenicity (study 2)

Reference:	Hoe 33171 – active ingredient technical (Code: Hoe 033171 0H ZC96 0002) Testing for embryotoxicity in Himalayan rabbits following oral administration
Author(s). year:	[redacted]., 1983
Report/Doc. number:	A29690 / Hoechst Report No. 83.0516 Baeder C. and Langer, 1986, Supplement to Report No. 83.0516, A32695 / Report No. 86.0019
Guideline(s):	No information on study guidelines is presented in the study report
GLP:	Yes.
Acceptability:	Yes.

Material and Methods:
Groups of animals 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 stability and homogeneity of the test substance preparations were guaranteed by chemical analysis.

Test material: Fenoxaprop-ethyl, batch Hoe 033171 0H ZC96 0002
Purity: 96.2 % according to certificate of analysis No. 02183 (1983)

Test animal: female Himalayan rabbits (Hoe HIMK(SPFWiga), source: [redacted])
9 - 10 months old, mean bw of 2646 ± 184 g
Number of animals: 15 per dose group

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. The food intake subsequently returned to normal. Food intake could not be determined in all animals because a number of them scattered their feed from the racks. Body weight gains remained unaffected by treatment.
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 6.6.2-19 Maternal effects, Developmental toxicity study of fenoxaprop-ethyl in Himalayan rabbits

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
Pre-terminal deaths	-	-	-	1[1)]
Reduced defecation	2	2	4	8

* ($p < 0.05$); 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 6.6.2-20 , Developmental toxicity study of fenoxaprop-ethyl in Himalayan rabbits

	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
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)]

	Dose group level (mg/kg bw/day)			
	0	**2**	**10**	**50**
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 reduced food intake and defecation, and an increased number of resorptions sites compared to historical controls, though the latter finding was statistically not significant when compared to concurrent controls. 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.

B.6.6.2.4.3. Monkey teratogenicity

Reference:	Hoe 033171, technical grade (Code: Hoe033171 0H ZC96 0002), oral embryotoxicity study in the Cynomolgus monkey
Author(s). year:	[redacted] 1984
Report/Doc. number:	A 29702 / Report No. 245-169/6 Osterburg I., 1984, Supplement to Doc. No. A29702, A38394 / Report No. 245-169/6
Guideline(s):	EPA Guideline 83-3 (1982), Japanese Pesticide Information No. (1973)
GLP:	Yes.
Acceptability:	Supplementary, due to missing controls. Furthermore, only three fetuses were available for morphological examination of the high dose group.

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.

Material and Methods:
The monkeys were obtained sexually mature. 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.

Test material	Fenoxaprop-ethyl, batch Hoe 033171 0H ZC96 0002
Purity:	96.2 % according to certificate of analysis No. 02183 (1983)
Test animal:	Cynomolgus monkey, breeding station at [redacted] Age not given (but sexually mature), bw between 2.4 and 4.7 kg
Number of animals:	21 at low dose

11 at high dose

All animals were examined at least once daily for clinical signs, behavioural change, food intake, faeces 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. Four females died during the dosing period (GD27-48) and 1 female four days after the treatment period (GD 54). The necropsy showed the following findings: nephritis (female no. 4204), tubular nephrosis (female no. 4171), enteritis and haemorrhagic ulcer in the stomach (female no. 4266), chronic nephropathy and haemorrhagic ulcer 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 6.6.2-21 Maternal effects, Developmental toxicity study of fenoxaprop-ethyl in Cynomolgus monkeys

	Dose group level (mg/kg bw/day)	
	10	**50**
Mortality	-	5 / 11
Reduced food intake and / or diarrhea	21 / 21	11 / 11
Body weight (kg)		
Day 20 (beginning of treatment)	3.3	3.7
Day 48 (close to end of treatment)	3.2	3.5
Day 100 (terminal body weight)	3.9	4.3
Body weight gain (Days 20 – 100, kg)	0.6	0.6
Cholesterol (mg/dl)		
Day 20 (beginning of treatment)	161.33	126.39
Day 48 (close to end of treatment)	116.43	82.62
Day 83 (no treatment)	74.50	60.97
Triglycerides (mg/dl)		
Day 20 (beginning of treatment)	65.80	55.93
Day 48 (close to end of treatment)	41.69	38.88
Day 83 (no treatment)	33.91	29.68
Total lipids (g/L)		
Day 20 (beginning of treatment)	7.16	4.67
Day 48 (close to end of treatment)	5.85	3.17
Day 83 (no treatment)	4.43	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 (no information about time period of studies was given). 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, which 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 6.6.2-22 Maternal and developmental effects, Developmental toxicity study of fenoxaprop-ethyl in Cynomolgus monkeys

	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 lack of a 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.

B.6.6.3. Bridging of the reproduction toxicity study (multigeneration study)

No multigeneration study has been performed with Fenoxaprop-P-ethyl (Hoe 046360). For bridging of the data derived from studies conducted with Fenoxaprop-ethyl (Hoe 033171), results from short term toxicity studies and developmental toxicity studies are considered. These data show that the toxicological profiles of Hoe 046360 and 033171 are comparable. Not only the pattern of effects but also the dose levels when effects occur are very similar (for discussion see chapter 6.3 short term toxicity studies and the comparison of developmental toxicity in this chapter).

A detailed comparison of the toxicological profile was presented by [redacted] 1989, Hoechst Report No. 89.0416, Doc. A40415. It is concluded that it appears justified to base the evaluation of chronic toxicity and carcinogenicity and the ADI level for Hoe 046360 on the long-term studies with Hoe 033171.

Comparison of developmental toxicity studies with Hoe 046360 and Hoe 033171

Teratogenicity studies with Fenoxaprop-P-ethyl and Fenoxaprop-ethyl have been carried out in rats and rabbits. Furthermore, studies on embryotoxicity and postnatal development were conducted in rats.

In the developmental toxicity studies in Wistar rats, maternal toxicity was observed at the highest dose of 100 mg/kg Hoe 046360 or Hoe 033171, which induced decreased food consumption and decreased body weight gain. This was confirmed in the embryo- and postnatal toxicity study in Wister rats, where a decrease in food consumption, a decrease in body weight and a slightly increased duration of gravidity was noted at 100 mg/kg of Hoe 046360 or Hoe 033171. Fetal toxicity was demonstrated by embryonic death / empty implantation sites, reduced pup weight and pup length at a dose level of 100 mg/kg of Hoe 046360 or Hoe 033171. Furthermore, in the study conducted with Hoe 046360, first indication of 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 a fetotoxic effect. In the study conducted with Hoe 033171, delayed ossification was observed at a dose level of 100 mg/kg. Taken together, similar effects occurred in the studies conducted with Hoe 046360 and Hoe 033171 at the same dose levels, with the exception of an increased rate of weak or non-ossification of at least 1 cranial bone which was observed already at 32 mg/kg in the study with Hoe 046360. No teratogenicity could be observed. The NOAELs for Hoe 046360 were 32 mg/kg (maternal toxicity) and 10 mg/kg (fetal toxicity), and for Hoe 033171 both NOAELs (maternal, fetal) were 32 mg/kg.

Embryotoxicity studies in Himalayan rabbits were conducted at different dose levels for Hoe 046360 (10, 32 and 100 mg/kg bw) and Hoe 033171 (first study: 12.5, 50 and 200 mg/kg; second study: 2, 10 and 50 mg/kg). In the study conducted with Hoe 046360, maternal toxicity (decreased food consumption, decreased body weight gain during treatment period, and slightly increased kidney weights) was observed at the highest dose level of 100 mg/kg. In the studies performed with Hoe 033171, 200 mg/kg led to 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 of Hoe 033171. With respect to fetotoxicity, the only effect observed in the study with Hoe 046360 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. In the studies conducted with Hoe 033171, this finding was confirmed at the dose level of 200 mg/kg. Furthermore, embryonic death, reduced pup weight and reduced pup length were noted at this dose level. At 200 mg/kg of Hoe 033171 an increased incidence of diaphragmatic hernia was noted. However, according to the RAC opinion and the CLH report, 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'. In the second rabbit study with Hoe 033171, a single case of diaphragmatic hernia was observed at 50 mg/kg, where it remains questionable if this finding was related to treatment. In conclusion, maternal toxicity was similar between the studies conducted with Hoe 046360 and Hoe 033171. The NOAELs for Hoe 046360 were considered to be 32 mg/kg for both maternal and fetal toxicity. The NOAELs for Hoe 033171 are in the same order of magnitude (10 mg/kg), also for both maternal and fetal toxicity.

B.6.7. NEUROTOXICITY

Reference:	Statement on neurotoxic potential of Hoe 046360, substance technical
Author(s). year:	Leist K.-H., Ehling G., 1993
Report/Doc. number:	A50069 / Hoechst, Pharma Development Central Toxicology
Guideline(s):	Not applicable.
GLP:	Not applicable.

The following statement on neurotoxicity potential was presented in relation to 5.7 "Neurotoxicity Studies" registration document according to Council Directive 91/414/EEC:

"Hoe 046360 (Fenoxaprop-P-ethyl) is the optically active enantiomer of the racemate Hoe 033171 (Fenoxaprop-ethyl), a herbicide for selective control of weed grasses, which is based biologically on an inhibition of lipid biosynthesis.
Hoe 046360 / Hoe 033171 belong to a chemical class of compounds which are known to interfere with the lipid metabolism in rats and mice, leading to an enhanced lipid turnover and peroxisomal proliferation in the liver cells. Peroxisome proliferators are not known to cause neurological disturbances.
A series of acute toxicity studies on rats, mice and dogs were carried out with either Hoe 033171 or Hoe 046360 – active ingredient. In these studies, only non-specific clinical signs of intoxication were observed. No signs of interference with the central nervous system could be detected at lethal and / or sublethal doses and no other specific symptoms (changes in neurobehaviour) were observed in the animals, which could be related to an acute neurotoxic potential of the test compound. Lethally intoxicated animals generally died several days after treatment indicating interaction with general physiology. Necropsies revealed effects mainly on the liver.
In numerous subchronic and chronic toxicity studies in rats, mice and dogs, neither neurobehavioural changes nor any morphological changes in the CNS or in the peripheral nerves following intensive histopathological examination has been detected. Even in reproduction toxicity study, no indication of neurotoxicity in dams and pups has been evaluated. The liver and kidneys only proved to be the target organs in these studies. Thus, there was no indication of central nervous effects after repeated exposure.

Conclusion
Since there was no reason to assume that Hoe 046360 / Hoe 033171 possess any neurotoxic potential, no specific studies on acute neurotoxicity (5.7.1) and / or delayed neurotoxicity testing (5.7.2) were conducted with the test compound."
RMS agrees with the statement.

B.6.7.1. Neurotoxicity studies in rodents
Studies not considered necessary - no data submitted (statement in B.6.7.1).

B.6.7.2. Delayed polyneuropathy studies
Studies not considered necessary - no data submitted (statement in B.6.7.1).

B.6.8. OTHER TOXICOLOGICAL STUDIES

B.6.8.1. Toxicity studies on metabolites and relevant impurities
The following statement has been provided in Tier 2 Summary of Toxicological and Metabolism Studies for Fenoxaprop-P-ethyl (MCA, Section 5, Toxicity studies of metabolites):
No toxicity studies are required based on the results from the toxicity and/or metabolism studies with the parent compound. The degradation of fenoxaprop-P-ethyl in plants follows the same metabolic pathway as in the rat. The toxicological examination with fenoxaprop-P-ethyl adequately covers all relevant metabolites found in plants.

However, one study on the chlorobenzoxazolone metabolite (AE F054014), (which is covered by toxicological testing on the parent compound), was performed by Rhone Poulenc before the merger into Aventis CropScience and this study report is now available in the common data base of Bayer CropScience. This study has been summarized below.

Reference:	6-Chlorobenzoxazolone: 13 week oral (dietary administration) toxicity study in the rat with a 28 day treatment-free period
Author(s). year:	[redacted] 1985
Report/Doc. number:	R012455 / M-186025-01-1
Guideline(s):	--
Deviations to OECD Guideline 408 (1998):	Sensory reactivity of animals was not assessed. Haematology: blood clotting time/potential was not assessed. Clinical biochemistry: total cholesterol levels were not assessed. Organ weight analysis for epididymides, uterus, thymus, spleen, brain and heart not assessed. Histopathological examination not conducted for some organs (spinal cord, thymus, oesophagus, trachea, accessory sex organs and skin)
GLP:	No
Acceptability:	Yes.

Materials and methods:
This study was performed to assess the toxicity of 6-chlorobenzoxazolone (AE F054014) when administered orally in the diet to the rat for 13 weeks at doses of 0, 5, 15 and 45 mg/kg bw/day, and to investigate the effects of a subsequent 28 day treatment-free period for selected high dose animals.

Test material	6-chlorobenzoxazolone 11 881 R.P. (AE F054014), batch no ICA 83 34900
Purity:	99.9 %
Test animal:	Rat, Sprague-Dawley (Crl: CD(SD)BR), [redacted] 3-4 weeks old, bw ♂ 142.9-215.8g and ♀ 128.5-161.7g
Number of animals:	15 per sex per group, for treatment-free period additional 10 per sex were used for control and high dose groups

The animals were checked for viability twice daily and observed daily for clinical signs. A full external examination was made at weekly intervals and recorded individually.
Ophthalmoscopic examinations were performed using a Keeler direct ophthalmoscope after the previous instillation of a mydriatic agent, before the start of dosing and the control and high dose only during week 13 and towards the end of the 28-day treatment-free period.
Body weights were recorded individually before treatment on the first day of the study, at weekly intervals throughout the study and on the day of necropsy. Food consumption by each cage of animals was recorded weekly throughout the study.
For haematology analysis, blood samples were collected from all animals during week 13. The samples were obtained by orbital sinus puncture under light ether anaesthesia (Diethyl ether, Analar grade, BDH Chemicals Ltd., Speke) following an overnight fasting of about 16 hours. The following parameters were determined: Hb concentration, MCV, RBC count and indices, MCH, PCV, MCHC, total and differential WBC, and platelet count. All measurements were made on blood collected into EDTA anticoagulant.
The following clinical chemistry parameters were estimated: GOT, GPT, ALP, BUN, glucose, sodium ions, calcium ions, potassium ions, inorganic phosphorus, chloride ions, creatinine, bilirubin, total proteins, albumin and Albumin/Globulin ratio. Plasma and red cell cholinesterase levels were determined on 10 males and 10 females from the control and high dose groups pre-dose and again after 1 week of treatment.
Necropsy was performed after killing of the animals by an intraperitoneal injection of pentobarbitone sodium (Euthatal, 200mg/ml, May&Baker, Dagenham). A full external and internal examination was made and all lesions recorded. Necropsies were spread over 5 days for the main study kill and over 2 days for the treatment-free kill. Some animals from all groups were necropsied each day.
The following organs were weighed before fixation: adrenals, gonads, kidneys and liver. Paired organs were weighed separately. Samples of the following tissues from all animals (with the exception of the eyes which were fixed in Davidson's fluid and the bone marrow smears which were fixed in methanol) were preserved in 10% neutral buffered formalin: adrenals, aorta, brain (3 sections), caecum, colon, duodenum, heart, ileum, jejunum, kidneys, liver, lungs with mainstem bronchi, mammary glands, oesophagus, pancreas, prostate/uterus, sciatic nerve, sternum (with bone marrow), thymus, urinary bladder, mesenteric lymph node, ovaries/testes, pituitary, rectum, spleen, stomach, thyroids with parathyroids (if identified) and gross lesions.

Findings:

Mortality / Clinical Signs: There were no deaths during the study and no unequivocal treatment-related clinical signs. No substance induced damages to the eyes were found in the ophthalmologic examinations.

Bodyweight and Food Consumption: For male animals a treatment-related suppression of weight gain was noted in comparison with controls over the 13 week treatment period. The greatest suppression (11%) was in the high dose group (significant at p<0.01) although it was not strictly dose-related. For female animals over the same period, only the high dose group showed any suppression (6%) in comparison with the controls. This suppression was not statistically significant. A compensatory increase in weight gain was noted for the high dose animals maintained on the treatment-free period compared with the controls (60% for males, 3% for females), which was statistically significant for males (p<0.05).

Table 6.8.1-1 Group food consumption and mean bodyweight after treatment (13 w) and recovery (17 w), 13 week feeding study in rats with 6-Chlorobenzoxazolone

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
Food consumption (g/d)								
13 weeks	160.8	156.9	161.2	159.0	108.8	111.4	107.4	118.3
17 weeks	184.6	-	-	192.6	138.3	-	-	142.6
Body weight on day 1 (g)	180.1	193.0	188.1	183.0	144.3	144.2	143.9	144.8
Terminal body weight (g)								
13 weeks	513.7	487.6	493.6	480.5	258.1	257.7	258.4	252.0
17 weeks	544.1	-	-	529.0	276.7	-	-	271.2
Bodyweight gain (g)								
13 weeks	333.6	294.6 -11.7%	305.5 -8.4%	297.5 -10.8%	113.8	113.5	114.5	107.2 -5.8%
17 weeks	364.0	-	-	346.0 -4.9%	132.4	-	-	126.4 -4.5%

Haematology and clinical chemistry: There were no unequivocal treatment-related changes in the haematological parameters. The only values to achieve levels of significance greater than 5% were the white blood cell counts for male intermediate and high dose animals which showed a significant reduction (p<0.01) in week 13. As this change was not supported by the female groups and all values were within normal ranges, this finding is thought to be of doubtful significance.
There were no unequivocal treatment-related changes in the blood chemistry parameters examined. The only consistent statistically significant change noted was an increase in chloride levels for high dose males and females compared with controls at week 13. However, as all values were within normal limits this finding is regarded as questionable.
The plasma and red cell cholinesterase levels determined after 1 week of treatment were similar for treated and control animals.

Table 6.8.1-2 Haematology findings 13 weeks after treatment with chlorobenzoxazolone, 13 week feeding study in rats with 6-Chlorobenzoxazolone

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
Hb (g/dL)	16.8 ± 0.4	16.6 ± 0.4	16.4 ± 0.8	16.7 ± 0.5	15.9 ± 0.5	15.7 ± 0.5	15.4 ± 1.6	15.8 ± 0.6
RBC (mL/cm)	8.27 ± 0.24	8.30 ± 0.26	8.01 ± 0.49	8.28 ± 31	7.69 ± .28	7.52 ± 0.28	7.43 ± 0.71	7.72 ± 0.31
Haematocrit (%)	46 ± 1	46 ± 1	45 ± 2	46 ± 2	44 ± 1	43 ± 2	42 ± 4	44 ± 2
MCH (pg)	20.3 ± 0.7	20.0 ± 0.5	20.5 ± 0.8	20.2 ± 0.5	20.7 ± 0.7	20.9 ± 0.6	20.8 ± 0.6	20.5 ± 0.4
MCHC (g/dL)	36 ± 1	37 ± 1	37 ± 1	36 ± 1	36 ± 1	37 ± 1	36 ± 1	36 ± 1
MCV (cum)	56 ± 2	55 ± 1	56 ± 2	56 ± 2	57 ± 2	58 ± 2	57 ± 2	57 ± 2
Platelets (1000/cm)	880 ± 176	956 ± 264	980 ± 350	921 ± 178	1004 ± 288	921 ± 304	935 ± 233	815 ± 153

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
WBC Total (1000/cm)	17.38 ± 2.98	16.57 ± 2.84	13.87 ± 3.03	14.75 ± 2.81	11.24 ± 2.85	9.17 ± 2.27	12.11 ± 4.53	10.31 ± 2.06

Table 6.8.1-3 Clinical chemistry findings, 13 week feeding study in rats with 6-Chlorobenzoxazolone

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
GOT (Iu/L)	91 ± 34	66 ± 8	88 ± 28 [E]	78 ± 16	77 ± 36	69 ± 18	72 ± 14	73 ± 10
GPT (Iu/L)	34 ± 6	27 ± 4	32 ± 6 [E]	31 ± 7	31 ± 10	25 ± 5	26 ± 4	26 ± 5
Alk. P (Iu/L)	196 ± 51	179 ± 21	166 ± 47	178 ± 41	106 ± 21	97 ± 21	119 ± 43	115 ± 31
Na^{2+} (mEq/L)	141 ± 2	140 ± 3	140 ± 3	140 ± 3	140 ± 3	139 ± 3	136 ± 10	139 ± 3
K^{+} (mEq/L)	4.2 ± 0.5	4.0 ± 0.5	4.1 ± 0.4	4.2 ± 0.5	3.2 ± 0.3	3.4 ± 0.3	3.5 ± 0.4	3.3 ± 0.3
Cl^{-} (mEq/L)	97 ± 3	98 ± 3	97 ± 4	99 ± 3	96 ± 3	97 ± 4	98 ± 4	101 ± 4
Ca^{2+} (mEq/L)	9.7 ± 0.3	9.5 ± 0.3	9.6 ± 0.2	9.4 ± 0.4	9.9 ± 0.4	9.8 ± 0.4	9.8 ± 0.6	9.6 ± 0.4
Glucose (mg/dL)	128 ± 17	140 ± 17	101 ± 16	124 ± 16	103 ± 16	104 ± 12	99 ± 8	100 ± 12
BUN (mg/dL)	15 ± 1	16 ± 2	16 ± 2	15 ± 1	17 ± 3	16 ± 3	16 ± 2	17 ± 3
Creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.2 ± 0.2
Total Bilirubin (mg/dL)	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.0
Total Protein (g/dL)	6.3 ± 0.2	6.2 ± 0.2	6.3 ± 0.3	6.4 ± 0.2	6.6 ± 0.3	6.8 ± 0.4	6.7 ± 0.3	6.7 ± 0.4
Albumin (g/dL)	3.5 ± 0.1	3.5 ± 0.2	3.5 ± 0.2	3.5 ± 0.2	4.0 ± 0.3	4.1 ± 0.4	3.8 ± 0.6	4.1 ± 0.3
A/G ratio	1.2 ± 0.1	1.3 ± 0.2	1.3 ± 0.1	1.2 ± 0.2	1.5 ± 0.1	1.5 ± 0.2	1.4 ± 0.4	1.6 ± 0.4
Inactive P (mg/dL)	6.4 ± 0.3	6.0 ± 0.5	6.1 ± 0.4	4.2 ± 0.5	4.7 ± 0.6	4.4 ± 0.4	4.8 ± 0.9	4.9 ± 0.6

[E] extreme outlier value of one animal was excluded (417 for GOT and 210 for GPT); total mean ± SD would be 110 ± 89 (GOT) and 44 ± 46 (GPT)

Organ weight analysis: The organ weights and organ body weight ratios were similar for treated and control animals. There were no macroscopic or microscopic abnormalities that could be directly attributed to treatment.

Table 6.8.1-4 Bodyweight and Organ weight data, 13 week feeding study in rats with 6-Chlorobenzoxazolone

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
Bodyweight	501	469	469	462	242	261	239	235
Liver	10.77	12.04	11.13	10.78	6.46	6.21	6.06	5.99
% bw	2.15%	2.57%	2.37%	2.33%	2.67%	2.38%	2.54%	2.55%
Gonads total	3.555	3.376	3.544	3.559	0.073	0.073	0.076	0.07
% bw	0.71%	0.72%	0.76%	0.77%	0.03%	0.03%	0.03%	0.30%
Adrenals	0.053	0.048 -9.4%	0.051	0.054	0.049	0.053 +8.2%	0.056 +14.3%	0.05

	Dose group level (mg/kg bw/d)							
	Males				Females			
	0	5	15	45	0	5	15	45
% bw	0.01%	0.01%	0.01%	0.01%	0.02%	0.02%	0.02%	0.02%
Kidneys	2.4	2.34	2.41	2.39	1.44	1.45	1.42	1.37
% bw	0.48%	0.50%	0.51%	0.52%	0.60%	0.56%	0.59%	0.58%

Macroscopic and microscopic findings: A few animals had focal or diffuse discoloration of the lung and occasionally changes were found in other areas such as the liver, appendages and oral cavity.
Histopathological findings were generally infrequent and usually of a minor nature. The more frequent findings included inflammatory cell infiltrates in the lung and liver, and mineralisation in the kidney of females. The incidence of these changes was similar in all groups and they were considered to be part of the background pathology of these animals. There were no changes of any unusual nature or incidence to suggest any toxic effect.
The pathology findings in animals necropsied after the treatment-free period were generally similar to those at the terminal kill. There was no evidence of any delayed toxic effects following cessation of treatment.

Conclusion:
In this study in rats which were given 6-chlorobenzoxazolone orally in the diet at dose levels of 0, 5, 15 and 45 mg/kg bw/day for 13 weeks, the only effect of treatment was a suppression of weight gain for all treated males (without a clear dose response relationship) and high dose females. A compensatory increase in weight gain was observed when the high dose animals of both sexes were given a 28 day treatment-free period. An oral dose of 45 mg/kg/day, daily for 13 weeks, is therefore, close to the no effect level in rats.

B.6.8.2. Supplementary studies on the active substance

Supplementary studies on the active studies were submitted for the renewal of this dossier, containing the previously evaluated three intraperitoneal studies in rat and the repeated dose toxicity study with combined administration of fenoxaprop-P-ethyl and the safener Hoe 107892, as well as an immunotoxicity study that was newly submitted for the renewal of the active substance. The study results are shortly summarized in the following tables (newly submitted studies in **bold)**.

Summary table of supplementary studies on fenoxaprop-P-ethyl

Study, reference	Dose levels	Endpoint	Main effects/target organs
Acute intraperitoneal toxicity study in male and female rats [redacted] *1985c*, A37244, CA 5.8.2/08	♂: 1000, 1600 and 2000 ♀: 1000, 2000 mg/kg bw i.p. injection	♂ LD_{50} = 1,490 ♀ LD_{50} > 2,000 mg/kg bw (supplementary information)	After treatment: Reduced spontaneous activity, contracted flanks, ataxic gait and mucous faeces in both sexes. Observation period: Clinical signs like squatting position, prone or lateral position, high-legged and uncoordinated gait, crawling locomotion
Combined repeated dose toxicity study with fenoxaprop-P-ethyl and the safener Hoe 107892 [redacted] *1996;* A57200, CA 5.8.2/07	Hoe046340 + Hoe107892: 0 + 0, 10 + 5, 80 + 40, 640 + 320 ppm in diet	NOAEL: 10 + 5 ppm (♂: 0.74 + 0.37 ♀: 0.81 + 0.41 mg/kg bw/d)	640 + 320 ppm: reduction of food consumption and bw, findings in haematology 80 + 40 ppm: effects on the liver (lipid parameter, liver enzyme activity, ketonuria, increased organ weight, discoloration and cellular hypertrophy)
28-day immunotoxicity study in the female rat [redacted] *2011* SA 10132, CA 5.8.2/11	**0, 70, 210 und 630 ppm (equiv. 5.5, 16, 47 mg/kg bw/day)**	**Not immunotoxic up to 630 ppm (47 mg/kg bw/day)**	**No SRBC-specific IgM change, no effects on spleen or thymus weight.**

Summary table of supplementary studies on fenoxaprop-ethyl

Study, reference	Dose levels	Endpoint	Main effects/target organs

Study, reference	Dose levels	Endpoint	Main effects/target organs
Acute intraperitoneal toxicity study in male rats [redacted]., *1979c* A24681, CA 5.8.2/09	500, 800, 1250, 2000, 3150, 5000 mg/kg bw i.p. injection	LD_{50} = 739 mg/kg bw (supplementary information)	Clinical signs like squatting, horripilation, abdominal position and passiveness. ⇩ bodyweight 7 days after treatment Light-brown discolouring of parts of liver and suprarenal glands.
Acute intraperitoneal toxicity study in female rats [redacted] *1979d,* A24690, CA 5.8.2/10	315, 500, 800, 1250, 2000, 3150 mg/kg bw i.p. injection	LD_{50} = 864 mg/kg bw (Supplementary information)	Clinical signs like squatting, horripilation, abdominal position and passiveness. ⇩ bodyweight 7 days after treatment Partly light-brown discolouring of liver.

B.6.8.2.1. Acute intraperitoneal study with fenoxaprop-P-ethyl

Reference:	Testing for acute intraperitoneal toxicity in the male and female Wistar rat
Author(s), year:	[redacted]; 1985c
Report/Doc. number:	A37244 / Hoechst Report No. 85.1197
Guideline(s):	-
GLP:	Yes
Acceptability:	Supplementary, as route of exposure does not represent physiological conditions.

Material and Methods:
Groups of 5 Wistar rats/sex/dose received intraperitoneal injections of Fenoxaprop-P-ethyl suspended in sesame oil. Dose groups were 1000, 1600 or 2000 mg/kg bw for males, while females received either 1000 or 2000 mg/kg bw. During the 14-day observation period the animals were observed daily and weighed weekly. Animals found dead during the study and animals sacrificed at study termination were examined for macroscopic changes.

Test material: fenoxaprop-P-ethyl, Hoe 046360 0H ZC96 0002
Purity: 95.6 %

Test animals: Wistar rat, Strain WISKf(SPF71), [redacted]
8-9 weeks old, bw of 172 to 227 g
Number of animals: 5 rats per sex per dose

Findings:
Clinical signs and mortality: No mortality occurred in the lowest dose group of 1000 mg/kg in both sexes. At 1600 mg/kg bw 4/5 males died 2 and 3 days after treatment. At 2000 mg/kg bw, 4/5 males and 2/5 females died 2 days after treatment. On the day of treatment reduced spontaneous activity, contracted flanks, ataxic gait and mucous faeces were observed in males and females. During observation period additional clinical signs were observed up to study day 13 in both males and females: squatting position, prone or lateral position, piloerection, high-legged and uncoordinated gait, crawling locomotion, straddling of the legs, severe emaciation, narrowed palpebral fissure, increased lacrimation, blood-crusted eye margins and snout, jerky breathing, increased startle reflex, drowsiness, reduced placing reflex and narcosis.
During the first week of the study, body weight was decreased in some of the males and females but was recovered by the end of the observation period.
Pathology: Macroscopic examination of the males and females found dead during the study revealed the following changes: abdominal cavity filled with oily fluid, all abdominal organs coated with a white-grey film, stomach taut with food, intestine filled with clear yellowish fluid, rectum filled with bloody-mucous mass, adrenals and spleen either dark or very light in colour, pancreas reddened and blood in urine. The males killed at the end of the observation period were free of macroscopically visible changes. One female in the 2000 mg/kg bw dose group exhibited a grey-white film over parts of the liver and deposits of test substance in the mesentery. All of the other females were free of macroscopically visible abnormalities.

Conclusion:
The acute intraperitoneal LD_{50} for Fenoxaprop-P-ethyl (suspended in sesame oil) in Wistar rats was calculated to be 1490 mg/kg bw for males and > 2000 mg/kg bw for females.

B.6.8.2.2. Acute intraperitoneal studies with fenoxaprop-ethyl

Reference:	Hoe 33171 0H AT203. Acute intraperitoneal toxicity to the male rat
Author(s), year:	[redacted]; 1979c
Report/Doc. number:	A24681 / Hoechst Report No. 421/79
Guideline(s):	-
GLP:	Yes
Acceptability:	Supplementary, as route of exposure does not represent physiological conditions.

Material and Methods:
Groups of 10 rats/dose weighing received single doses of 500, 800, 1250, 2000, 3150 or 5000 mg/kg bw of a 12.5 % suspension of Fenoxaprop-ethyl in sesame oil by intraperitoneal injection. Clinical symptoms, body weight gain and mortality were registered during the 14-day follow-up period. Animals found dead during the study and animals sacrificed at study termination were examined for macroscopic changes.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT 203
Purity: 97 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: Male Wistar rat, strain WISKf(SPF71), [redacted]
Age not stated, bw of 193 to 226 g
Number of animals: 10 rats per dose

Findings:
Clinical signs and mortality: The following mortality rates were recorded in the various dose groups: 2/10 at 500 mg/kg bw, 8/10 at 800 mg/kg bw, 7/10 at 1250 and 2000 mg/kg bw, 8/10 at 3150 mg/kg bw, and 10/10 at 5000 mg/kg bw. The LD50 of 739 mg/kg bw was calculated by probit analysis. Lethally intoxicated animals died 1 to 6 days after treatment. The following clinical symptoms were recorded: squatting, horripilation, abdominal position and passiveness. The time frame in which clinical signs showed up is not reported. A decrease in body weight was recorded in some of the animals 7 days after treatment. From day 7 to 14 an increase in body weight was noted in all surviving animals.

Pathology: 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.

Conclusion:
The acute intraperitoneal LD_{50} for Fenoxaprop-ethyl (suspended in sesame oil) in male Wistar rats was calculated to be 739 mg/kg bw.

Reference:	Hoe 33171 0H AT203. Acute intraperitoneal toxicity to the female rat
Author(s), year:	[redacted]; 1979d
Report/Doc. number:	A24690 / Hoechst Report No. 422/79
Guideline(s):	-
GLP:	Yes
Acceptability:	Supplementary, as route of exposure does not represent physiological conditions.

Material and Methods:
Groups of 10 rats/dose received single doses of 315, 500, 800, 1250, 2000 or 3150 mg/kg bw of a 12.5 % suspension of Fenoxaprop-ethyl in sesame oil by intraperitoneal injection. Clinical symptoms, body weight gain and mortality were registered during the 14-day follow-up period. Animals found dead during the study and animals sacrificed at study termination were examined for macroscopic changes.

Test material: fenoxaprop-ethyl, batch Hoe 33171 0H AT 203
Purity: 97 %; not included in the study report, but presented by the notifier in a separate report (A18371)

Test animals: female Wistar rat, strain WISKf(SPF71), [redacted]
Age not stated, bw of 180 to 231 g
Number of animals: 10 rats per dose

Findings:
Clinical signs and mortality: No mortality was observed at 315 and 500 mg/kg bw. At higher doses, mortality rates were 6/10 at 800 mg/kg bw, 9/10 at 1250 mg/kg bw, 10/10 at 2000 mg/kg bw and 9/10 at 3150 mg/kg bw. The LD_{50} of 864 mg/kg bw was calculated by probit analysis. Lethally intoxicated animals died 1 to 3 days after treatment. The following clinical symptoms were recorded: squatting, horripilation, abdominal position and passiveness. The time frame in which clinical signs showed up is not reported. A decrease in body weight was recorded in some of the surviving animals 7 days after treatment. From day 7 to 14 the body weight increased in almost all animals.

Pathology: 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.

Conclusion:
The acute intraperitoneal LD_{50} for Fenoxaprop-ethyl (suspended in sesame oil) in female Wistar rats was calculated to be 864 mg/kg bw.

B.6.8.2.3. Combined repeated dose toxicity study on fenoxaprop-P-ethyl and the safener Hoe107892

Reference:	13-week oral toxicity (feeding study) with Hoe 046360 + Hoe 107892 (2:1) in the rat. Influence of the coadministration of Hoe 107892 on toxicological profile of Hoe 046360.
Author(s). year:	[redacted] 1996
Report/Doc. number:	A57200 / RCC Project No. 610121
Guideline(s):	OECD guideline 408 (1981), EPA guideline 82-1 (1984), EEC Directive 87/302/EEC B.p.8 (1998), MAFF guideline 59 NohSan No. 4200 (1985)
Deviations:	None.
GLP:	Yes.
Acceptability:	Yes.

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 ([redacted]; 1987; Doc. No. A36566) to permit the detection of even minor changes in the toxicological profile of Hoe 046360.

The purity of Fenoxaprop-P-ethyl was 96.1 % (according to certificate of analysis No. AZ 05581) and the purity of the safener Hoe 107892 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.

Test materials: fenoxaprop-P-ethyl, batch Hoe 046360 00 ZC97 0002, purity 96.1%
safener Hoe 107892, batch Hoe 107892 00 ZC97 0001, purity 94.5%

Test animal: Wistar rat, [redacted]
4 weeks old, bw of 61-91 g (♂) and 57-81 g (♀)
Number of animals 10 per sex per dose

Groups of 10 male and 10 female rats 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. The intake of test substance is listed in the following table:

Table 6.8.2-1 Intake of test substance (mg/kg bw/d), combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	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

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 pre-test 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.
Haematology consisted of erythrocyte count, haemoglobin, haematocrit, 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), creatinine 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, colour, 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, oesophagus, 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 6.8.2-2 Group food consumption and mean bw after 13 weeks, combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	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 +5.0%	21.2 -3.6%	18.4 -16.4%	15.4	15.4	15.1 -1.9%	13.4 -13.0%

	Dose group level (ppm)							
	Males				Females			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Body weight on day 1 (g)	125	129 +3.2%	126 +0.8%	125	105	109 +3.8%	106 +1.0%	108 +2.9%
Body weight on day 85 (g)	375	409 +9.1%	377 +0.5%	**302**** **-19.5%**	225	227 +0.9%	225	**197**** **-12.4%**
Body weight gain (g)	250	280 12.0%	251	**177** **-29.2%**	120	118 -1.7%	119 -0.8%	**89** **-25.8%**

* (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.

Haematology: A marginal decrease in the haemoglobin concentration, haematocrit 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 6.8.2-3 Relevant haematology findings after 13 weeks, combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	Dose group level (ppm)							
	Males				Females			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Haemoglobin (mmol/L)	10.3	10.1 -1.9%	10.0 -2.9%	**9.8*** **-4.9%**	10.1	10.2 +1.0%	10.1	9.9 -2.0%
Haematocrit (L/L)	0.48	0.48	0.47 -2.1%	**0.47*** **-2.1%**	0.47	0.47	0.47	0.46
Platelets (g/L)	925	881 -4.8%	860 -7.0%	**799*** **-13.6%**	857	834 -2.7%	879 +2.6%	806 -6.0%
High reticulocyte fluorescence ratio (%)	6.4	6.5 +1.6%	10.0 +56.3%	**11.6*** **+81.3%**	9.2	7.4 -19.6%	9.7 +5.4%	9.7 +5.4%
TT (sec)	12.4	**12.8**** **+3.2%**	12.5 +0.8%	**13.1**** **+5.6%**	13.3	13.4 +0.8%	**12.7**** **-4.5%**	**12.6**** **-5.3%**

* (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 6.8.2-4 Relevant clinical chemistry findings after 13 weeks, combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	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 +6.1%	5.13 -5.4%	**4.76**** **-12.2%**	5.16	5.57 +7.9%	5.15	4.71 -8.7%

	Dose group level (ppm)							
	Males				Females			
	0	**10+5**	**80+40**	**640+320**	**0**	**10+5**	**80+40**	**640+320**
Creatinine (µmol/L)	37.6	34.7 -7.7%	34.0 -9.6%	**32.9*** **-12.5%**	43.8	42.9 -2.1%	42.3 -3.4%	40.4 -7.8%
Uric acid (µmol/L)	10.7	10.7	12.2 +14.0%	**13.8**** **+29.0%**	25.3	24.3 -4.0%	26.1 +3.2%	26.3 +4.0%
Total bilirubin (µmol/L)	2.8	2.9 +3.6%	**2.4**** **-14.3%**	**2.4**** **-14.3%**	3.4	**3.0**** **-11.8%**	**2.7**** **-20.6%**	**2.6**** **-23.5%**
Direct bilirubin (µmol/L)	0.7	0.8 +14.3%	0.6 -14.3%	0.7	1.1	**0.8**** **-27.3%**	**0.8**** **-27.3%**	**0.8**** **-27.3%**
Total cholesterol (mmol/L)	1.81	1.57 -13.3%	1.55 -14.4%	**0.80**** **-55.8%**	1.71	1.69 -1.2%	1.74 +1.8%	1.54 -9.9%
HDL cholesterol (mmol/L)	1.37	1.25 -8.8%	**1.08**** **-21.2%**	**0.43**** **-68.6%**	1.36	1.43 +5.1%	1.50 +10.3%	1.25 -8.1%
HDL phospholipid (mmol/L)	1.21	1.14 -5.8%	1.08 -10.7%	**0.71**** **-41.3%**	1.51	1.53 +1.3%	1.55 +2.6%	1.44 -4.6%
ASAT (µkat/L)	1.21	1.24 +2.5%	1.21	**1.43**** **+18.2%**	1.15	1.13 -1.7%	1.21 +5.2%	1.28 +11.3%
LDH (µkat/L)	1.43	1.35 -5.6%	1.25 -12.6%	**2.02**** **+41.3%**	1.41	1.21 -14.2%	1.45 +2.8%	1.63 +15.6%
ALP (ukat/L)	2.66	2.68 +0.8%	2.43 -8.6%	**4.61**** **+73.3%**	1.09	1.05 -3.7%	1.22 +11.9%	**1.89**** **+73.4%**
Phosphorus (mmol/L)	1.91	2.01 +5.2%	1.83 -4.2%	**2.06*** **+7.9%**	1.33	1.49 +12.0%	1.39 +4.5%	**1.62*** **+21.8%**
Sodium (mmol/L)	138.9	138.1 -0.6%	140.0 +0.8%	**140.9**** **+1.4%**	138.3	138.8	139.7 +1.0%	**141.4*** **+2.2%**
Total protein (g/L)	68.7	69.3 +0.9%	67.7 -1.5%	**64.4**** **-6.3%**	71.7	70.3 -2.0%	71.2 -0.7%	70.1 -2.2%
Albumin (g/L)	31.3	31.2 -0.3%	32.1 +2.6%	**36.6**** **+16.9%**	34.0	34.3 +0.9%	**36.3*** **+6.8%**	**37.3**** **+9.7%**
Alpha 1-globulin (g/L)	19.4	18.7 -3.6%	18.9 -2.6%	**15.6**** **-19.6%**	18.8	18.4 -2.1%	17.5 -6.9%	**16.9**** **-10.1%**
Alpha 2-globulin (g/L)	4.6	5.0 +8.7%	**3.4**** **-26.1%**	**1.8**** **-60.9%**	4.5	**4.1*** **-8.9%**	**3.7**** **-17.8%**	**3.0**** **-33.3%**
Sum of beta globulins (g/L)	11.8	12.5 +5.9%	11.8	**9.0**** **-23.7%**	12.2	**11.2*** **-8.2%**	11.4 -6.6%	**10.7**** **-12.3%**
Albumin / globulin ratio	0.84	0.82 -2.4%	**0.90*** **+7.1%**	**1.32*** **+57.1%**	0.91	0.96 +5.5%	**1.04*** **+14.3%**	**1.14*** **+25.3%**

* (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 6.8.2-5 Relevant urinalysis findings after 13 weeks, combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	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 6.8.2-6 Organ weight findings after 13 weeks, combined 13 week feeding study with Hoe 046360

	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 +8.3%	9.33 +5.1%	**10.91**** **+22.9%**	5.91	6.02 +1.9%	6.34 +7.3%	**6.66*** **+12.7%**
relative to body weight (%)	2.52	2.48 -1.6%	2.61 +3.6%	**3.85**** **+52.8%**	2.90	2.92 +0.7%	3.09 +6.6%	**3.69**** **+27.2%**
relative to brain weight (%)	435	461 +6.0%	450 +3.4%	**525**** **+20.7%**	307	311 +0.7%	333 +6.6%	345 +27.2%
Kidney								
absolute (g)	2.17	2.35 +8.3%	2.33 +7.4%	2.30 +6.0%	1.44	1.47 +2.1%	1.45 +0.7%	1.51 +4.9%
relative to body weight (%)	0.62	0.61 -1.6%	0.65 +4.8%	**0.81**** **+30.6%**	0.71	0.71	0.71	**0.84**** **+18.3%**
relative to brain weight (%)	107	113 +5.6%	112 +4.7%	111 +3.7%	75	76 +1.3%	76 +1.3%	78 +4.0%

* (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, cortico-medullary 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 6.8.2-7 Macroscopic and microscopic findings after 13 weeks, combined 13 week feeding study with Hoe 046360 and Hoe 107892 in Wistar rats

	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).

B.6.8.2.4. Newly submitted study: Immunotoxicity study

Reference:	Fenoxaprop-P-ethyl – 28-day immunotoxicity study in the female rat by dietary administration
Author(s). year:	[redacted] 2011
Report/Doc. number:	SA 10132 / M-404362-01-1
Guideline(s):	US EPA OPPTS Series 870, Health Effects Testing Guidelines, No. 870.7800
Deviations:	None.
GLP:	Yes.
Acceptability:	Yes

Materials and methods:
Female rats were administered 0, 70, 210 and 630 ppm fenoxaprop-P-ethyl (incorporated into the diet by dry mixing). One additional group of animals were fed cyclophosphamide (batch 068K1131, Sigma-Aldrich) at a dosage volume of 5ml/kg by oral gavage as a positive control.

Test material	Fenoxaprop-P-ethyl, batch EFLC000572
Purity:	94.5%
Test animal:	Female rat, Wistar Rj:WI (IOPS HAN), [redacted] 7 weeks old, bw 182-211g
Number of animals:	10 animals per group

The animals were checked for moribundity and mortality twice daily (once daily on weekends or public holidays).
All animals were observed for clinical signs at least once each day starting on study day 1 and every day throughout the study. The nature, onset, severity, reversibility and duration of clinical signs were recorded. Detailed physical examinations were performed at least weekly during the treatment period. Cages and cage-trays were inspected daily for evidence of ill-health such as blood or loose feces.
Bodyweights of animals was assessed at least weekly during acclimatization period, on the start of treatment (study day 1), then at weekly intervals throughout the treatment period and before necropsy.
Food consumption and remaining food was recorded weekly for all animals during the treatment period. The weekly mean achieved dosage intake in mg/kg bw/d for each week and for weeks 1-4 was calculated (except for the positive control group).
Sheep red blood cell (SRBC) sensitisation was selected as an appropriate antigen, since it has a large size ensuring proper immunization of animals and since it is recommended by the guideline. On study day 26 after the start of treatment, all animals in all groups were anesthetized with Isoflurane and then immunized by i.v. injection in the tail vein (0.5ml/animal) with SRBC preparation ($5x10^8$ cells/ml). Blood samples were taken from all animals in all groups by puncture of the retro-orbital venous plexus 4 days after SRBC immunization (terminal sacrifice). Animals were not fasted prior to terminal sacrifice. Serum was isolated from blood samples.
SRBC-specific IgM levels in response to antigen administration were assessed with an ELISA (Rat Anti-sheep Red Blood Cell IgM ELISA kit, Life Diagnostics, USA).
Animals were sacrificed on study day 30 by exsanguination while under deep anesthesia and necropsy was performed. This included the examination of all major organs, tissues and body cavities. Macroscopic abnormalities were recorded but not sampled. Organ weights of spleen and thymus were determined.

Findings:
Clinical signs of toxicity and mortality: no mortalities occurred at any dose level during the study.

Bodyweight: at 630 ppm, mean bodyweight was reduced by 4-6% (not statistically significant) during the course of the study, when compared to the controls. Between study day 1-8, mean bodyweight gain was reduced by 54% ($p \leq 0.01$) compared to controls. Between study days 8-15 and 15-22, the effect was less pronounced and not statistically significant. Thereafter, bodyweight evolution was unaffected by treatment. Overall mean absolute bodyweight gain between study days 1-29 was reduced by 29% ($p \leq 0.05\%$). At 210 and 70 ppm, bodyweight parameters were unaffected by treatment. The bodyweight parameters of animals treated with cyclophosphamide at 3.5 mg/kg bw/d were not affected by treatment.

Table 6.8.2-8 Mean bodyweight gain per day ±SD

Dose group (mg/kg/d)	0	70	210	630	Positive control CP

Day 8	2.8 ±1.2	2.6 ±0.9	2.4 ±0.7	**1.3 ±1.0***	2.1 ±0.8
Day 15	1.9 ±1.0	1.9 ±1.3	1.7 ±0.6	1.5 ±0.9	1.9 ±0.8
Day 22	1.5 ±1.1	1.5 ±1.0	1.5 ±1.1	1.1 ±1.0	2.0 ±0.7
Day 29	1.1 ±1.6	1.4 ±1.2	1.2 ±0.9	1.3 ± 0.7	1.4 ±0.5

* significantly different from the control at p<0.01

Table 6.8.2-9 Mean achieved dietary intake of fenoxaprop-P-ethyl (weeks 1-4)

Diet concentration (ppm)	Food intake (mg/kg bw/day)
70	5.5
210	16
630	47

Food consumption: at 630 ppm, mean food consumption was lower than controls by between 10%-13 (statistically significant p≤0.05 to p≤0.01) at each weekly interval throughout the study.
At 210 and 70 ppm, there was no effect on mean food consumption compared to controls.
The food consumption of animals in the positive control group was not affected by treatment.

SRBC-specific IgM response: the high mean anti-SRBC IgM concentration observed in the control group confirmed the sensitization of the animals. A high inter-individual variability was noted in all the groups as is usually observed with SRBC sensitization in the rat. No statistically significant difference was noted in anti-SRBC IgM concentrations up to 630 ppm.
For the positive control cyclophosphamide at 3.5 mg/kg/day, anti-SRBC IgM concentrations were lower when compared to the controls. Mean concentration was markedly lower (-92%, p≤0.01), corresponding to the range usually observed with cyclophosphamide within our laboratory conditions. This confirmed the sensitivity of this test model.

Table 6.8.2-10 SRBC-specific IgM change when compared to controls

SRBC specific IgM (µ/ml) mean ±SD					
Dose level (mg/kg bw/d)	0	70	210	630	Positive control (CP)
Study day 30	9575 ±5270	11205 ±8572	8217 ±3393	9467 ±4454	**764 ±290 ***

* p<0.01, statistically significant to control
SD = standard deviation, CP = cyclophosphamide, 3.5 mg/kg/day

Gross pathological findings and organ weights: Lower mean absolute and relative spleen weights were noted at all dose levels when compared to the controls. Since these differences were not dose-related and not statistically significant, they were considered to be incidental in origin and not treatment-related.

Table 6.8.2-11 Total and relative organ weights (mean ±SD)

Dose group (mg/kg/d)	0	70	210	630	Positive control (CP)
Spleen total % to bodyweight	0.841 ±0.17 0.34 ±0.05	0.755 ±0.15 0.30 ±0.05	0.731 ±0.12 0.30 ±0.04	0.678 ±0.11 0.29 ±0.05	**0.702 ±0.102 *** **0.28 ±0.04 ***
Thymus total % to bodyweight	0.551 ±0.07 0.22 ±0.03	0.550 ±0.09 0.22 ±0.03	0.524 ±0.10 0.21 ±0.03	0.517 ±0.10 0.22 ±0.04	0.52 ±0.10 0.21 ±0.03

* p<0.05, statistically significant to control
SD = standard deviation, CP = cyclophosphamide, 3.5 mg/kg/day

Analytical results: According to the analytical method described in attachment J of the report of Repetto *et al.*, 2011 (Doc No. SA 10132) a spike concentration at 10mg/kg was measured once (for details refer to Volume 3 CA B-5).

Conclusion:
Compared to controls, no impairment of the immunological IgM response following immunization with SRBC antigen was observed in animals treated with fenoxaprop-P-ethyl in the diet at dose levels up to 630 ppm for at least 28 days (corresponding to approximately 47 mg/kg bw/day). Therefore, no evidence of an immunotoxic potential was seen in this study.

B.6.8.3. Studies on endocrine disruption

No targeted *in vitro* or *in vivo* screening studies to assess the endocrine disrupting potential of fenoxaprop-P-ethyl (nor fenoxaprop-ethyl) have been submitted. Information from US EPA Endocrine Disruptor Screening Program (EDSP) that involves results from estrogen receptor bioactivity assays has been added to the relevant tables. Additionally, the applicant has provided a position paper including a first analysis of ToxCast and Tox21 activity data that is included below (Bomann W., 2017).

According to the OECD No. 150 Guidance Document on standardized test guidelines for evaluating chemicals for endocrine disruption (ENV/JM/MONO(2012)22) the following information from *in vivo* studies indicate possible ED effects:

- Repeated dose 28-day oral toxicity study in rodents (OECD 407)
- Repeated dose 90-day oral toxicity studies (OECD 408)
- 2-generation reproduction toxicity study (OECD 416)
- Pre-natal developmental toxicity study (OECD 414)

A short summary of study results, where ED relevant parameters were altered, is given in Table 6.8.3-1 and Table 6.8.3-2. To sum up, there is no consistent evidence that fenoxaprop-P-ethyl has an effect on the endocrine system. Fenoxaprop-P-ethyl also does not fulfil the interim criteria for endocrine disruptors stated in the Regulation (EC) No. 1107.

Table 6.8.3-1 Summary of ED relevant results for fenoxaprop-P-ethyl

Study	Results	Accepted / Deviations
EDSP Estrogen Receptor Bioactivity (US EPA) EPA ACToR Code C71283802	ER Agonist AUC: 0 ER Antagonist AUC: 0.000153 ER Bioactivity: 0.000153	-
Fenoxaprop-P-ethyl: Repeated dose 28-day oral toxicity in rats [redacted] *1987a* See B.6.3.1.1 **OECD 407**	No/not biological relevant effects on adrenals, thyroids and testis. ⇩ bodyweight at high dose ⇩ lipid metabolism (strongly in ♂), ⇧ triglycerides (both sexes) ⇧ liver weight (absolute + relative to bodyweight)	Supplementary. Limited organ weight and histopathology.
Fenoxaprop-P-ethyl: Repeated dose 28-day oral toxicity study in mice [redacted] *1987b* See B.6.3.1.2 **OECD 407**	No/not biological relevant effects on adrenals and thyroids. ⇧ bodyweight gain at h.d. ⇩ lipid metabolism at h.d. (strongly in ♂) ⇩ testis weight at h.d. (absolute + relative) Liver: ⇧ clinical parameters at high dose, ⇧ weight (absolute + relative to bodyweight) and histopathological findings	Supplementary. Limited organ weight and histopathology. No haematology and urinalysis.
Fenoxaprop-P-ethyl: 13-week feeding study in rats [redacted] *1987* See B.6.3.2.1 **OECD 408**	No/not biological relevant effects on ovaries, uterus, thyroids, adrenals and pituitary gland. ⇩ bodyweight gain at h.d. ⇩ lipid metabolism at h.d. (strongly in ♂) ⇧ testis weight (relative) at week 13 at h.d. Liver: ⇧ ALP at high dose, ⇧ weight (absolute + relative) at week 13 at high dose	Yes. Missing BUN measurement. Limited pathology and organ weight analysis.
Fenoxaprop-P-ethyl: 40-days inhalation study in rats (28 appliations) with recovery period [redacted] *1989* See B.6.3.3.1 **OECD 412**	No/not biological relevant effects on ovaries, uterus, epididymides, prostate, seminal vesicles, thyroid, adrenals and pituitary. ⇩ cholesterol (both sexes), ⇧ triglycerides (in ♂) and ⇩ a-2-globulin (in ♂) at high dose ⇩ testis weight (absolute) at 41d at high dose ⇧ liver weight (absolute + relative)	Yes. Animal slightly younger. Limited pathology and organ weight analysis. Dry exposure conditions.

Table 6.8.3-2 Summary of ED relevant results for fenoxaprop-ethyl

Study	Results	Accepted / Deviations

EDSP Estrogen Receptor Bioactivity (US EPA) EPA ACToR Code C66441234	ER Agonist AUC: 0 ER Antagonist AUC: 2.96 $\cdot 10^{-7}$ ER Bioactivity: 2.96 $\cdot 10^{-7}$	-
Fenoxaprop-ethyl: Range-finding test in a 32-day study in rats [redacted] *1980a* See B.6.3.4.1 **No guideline (study design similar to OECD 407)**	No/not biological relevant effects on ovaries, uterus, prostate, epididymis, seminal vesicles, thyroids and pituitary gland. ⇩ bodyweight gain ⇩ lipid metabolism ⇧ ALP at high dose ⇧ testis weight at h.d. (relative to bodyweight) ⇧ liver weight (relative to bodyweight) ⇩ adrenals weight in ♀ at h.d. (abs.+rel. to bw)	Yes.
Fenoxaprop-ethyl: Repeated 32-day oral administration to mice [redacted] *1980b* See B.6.3.4.2 (1st study) **No guideline (study design similar to OECD 407)**	No/not biological relevant effects on ovaries, uterus, prostate, epididymides, testis, seminal vesicles, thyroids, adrenals and pituitary. ⇩ terminal bodyweight at high dose Liver: ⇧ ALAT and ALP, ⇩ weight in ♂ (abs. + rel.); ⇧ weight in ♀ (absolute + relative to bw); histopathological changes at h.d. (incl. enlargement of liver cells)	Yes.
Fenoxaprop-ethyl: 30-day oral administration study in mice [redacted] *1981* See B.6.3.4.2 (2nd study) **No guideline (study design similar to OECD 407)**	No/not biological relevant effects on ovaries, uterus, testis, epididymis, prostate, seminal vesicles, thyroid, adrenals, pituitary. Lipid metabolism: ⇧ cholesterol at h.d. in ♀, slightly ⇧ total lipids in ♂ Liver: ⇩weight in ♂ (abs. + rel.); ⇧ weight in ♀ (abs. + rel.); histopathological changes at high doses	Yes.
Fenoxaprop-ethyl: Repeated-dose 30-days oral toxicity study in dogs. [redacted] *1980* See B.6.3.4.3 **No guideline**	No/not biological relevant effects on ovaries, uterus, testis, prostate and pituitary gland. Liver: Lobular marking and fatty degeneration Thyroid: hyperplasia of lymph follicles Adrenals: ⇧ weight, haemorrhages of the cortex	Supplementary. Only two animals per dose group. No analysis of t.s. for concentration, stability and homogeneity.
Fenoxaprop-ethyl: 13-week feeding study in rats [redacted] *1981* See B.6.3.5.1 **No guideline (study design similar to OECD 408)**	No/not biological relevant effects on ovaries, uterus and pituitary glands. ⇩ lipid metabolism Liver: ⇧ ALP in ♂, ⇧ weight in ♂ at h.d. (absolute + relative); enlarged liver cells at h.d. (at first sacrif.) ⇧ thyroid weight in ♂ (absolute + relative) ⇧ adrenals weight in ♀ (absolute + relative)	Yes.
Fenoxaprop-ethyl: 13-week dietary study in mice [redacted] *1993a* See B.6.3.5.2 **EPA GD 82-1**	No/not biological relevant effects on ovaries, uterus, vagina, testis, prostate, epididymides, seminal vesicles, thyroid, mammary glands and pituitary glands. ⇧ triglycerides, total protein in ♂ ⇧ adrenals in ♂ (absolute + relative) Liver: ⇧ ALAT, ALP in ♂, ⇧ weight (absolute + relative); histopathological findings (hypertrophy, necrosis, ⇧ mitosis)	Yes. Limited histopathology and organ weight.
Fenoxaprop-ethyl: Multiple generation study in rats [redacted] *1986* See B.6.6.1.2 **EPA GD 83-3**	No changes in vaginal opening. No/not biological relevant effects on uterus, ovaries, testes, prostate and seminal vesicles. ⇧ bodyweight at lactation (F2a: high dose)	Yes. Anogenital distance, oestrus cyclicity and preputial separation not assessed.

Reference:	**Fenoxaprop-P-ethyl, AE F046360 – Response to a request of the RMS Austria within the EU-re-approval process**
Author(s). year:	Bomann W., 2017
Report/Doc. number:	
Acceptability:	Yes

RMS Austria had the following comment: '*Due to effects observed in the thyroid weight in males, and, the weights of ovaries and uterus in females in the 2-year and 1-year dog studies, the setting of NOAEL values should be reconsidered. Attached please find the relevant tables from studies A31854* and A29692.

We would appreciate historical control data and further information about the stated shortcomings – could you please elaborate more on inadequate exsanguinations, and how the oestrus phase might have an effect on the weights of ovaries and uterus?

In addition to the highly altered lipid metabolism seen in most of the studies, these are also effects that concern ED-related organs.

Therefore argumentation on ED properties of this substance would be helpful later for the peer-review.'

A question was also raised on available ToxCast and Tox21 Activity Data.

These questions and comments are addressed in this paper. For clarity, only the section regarding the endocrine diruption is summarized here.

In a 2-year toxicity study with the racemic mixture AE F033171 in dogs (Brunk, R.; Kramer, M.; 1987; M-109895-02-1, A31854), experimental phase: April 1982-May 1984) some organ weight changes were seen, which were explained by the study director with inadequate exsanguination (liver, lung, brain, thyroid) and/or different phases of the estrous cycle in female dogs (ovaries, uterus). An overview of the other endocrine organ weights which were measured in this study is given in the following table.

Table 6.8.3-3 Weights of relevant endocrine organs in the 2-year dog study

Organ[a] weights (% changes vs. control in brackets)	**Dose group level in ppm (mg/kg bw/d)**							
	Males				**Females**			
	0	**3 (0.2)**	**15 (1.1)**	**75 (5.2)**	**0**	**3 (0.18)**	**15 (0.9)**	**75 (4.6)**
Body weight (kg)	17.1±1.0	16.5±1.7 (-3.5)	**15.2±0.8* (-11.1)**	**15.5±0.6* (-9.4)**	15.9±0.9	15.0±0.6 (-5.7)	15.1±1.0 (-5)	**13.9±1.0* (-12.6)**
Body weight gains (kg)[b]	3.52	2.92 (-17.1)	2.65 (-24.7)	1.92 (-45.5)	3.8	3.03 (-21.3)	3.38 (-11.1)	1.83 (-51.8)
Pituitary weight absolute (mg)	89±11	88±18	92±14	83±11	99±9	102±13	101±13	91±13
Pituitary weight relative (% BW)	0.0005±0.0001	0.0005±0.0001	0.0006±0.0001	0.0005±0.0005	0.0006±0.0006	0.0007±0.0001	0.0007±0.0001	0.0007±0.0001
Testes weight absolute (g)	21.7±3.7	23.8±5.0	20.5±4.7	22.2±1.5				
Testes weight relative (% BW)	0.127±0.023	0.145±0.030	0.136±0.136	0.143±0.008				
Prostate weight absolute (g)	19.7±4.2	20.3±5.5 (+3.0	21.5±7.2 (+9.1)	20.5±5.0 (+4.1)				
Prostate weight relative (% BW)	0.115±0.022	0.122±0.024 (+6.1)	0.141±0.141 (+22.6)	0.132±0.029 (+14.8)				

[a] Mean ± SD
[b] No SD for body weight gain given in the report
* ($p<0.05$); significantly different from controls
BW = body weight

If any endocrine effect would theoretically have occurred, e.g. by estrogenic effects, then changes in other endocrine organs, for example by changed estrogenic and testosterone level ratios could also be expected.
It can be seen that no treatment-related changes were observed in the pituitary and testes weights (therefore no % of control values were calculated). For the prostate weights, which showed some variable weights there is no dose-response relationship.
RMS Austria commented that also in the 1-year dog study (Brunk, R.; Weigand, W.; Kramer, M.; 1984; M-102290-01-1, A29692,) due to effects observed in the thyroid weights in males and to the weights of ovaries and uterus in females, the setting of NOAEL values should be reconsidered.

Table 6.8.3-4 Comparison of selected endocrine organ weights of the 1- and 2-year dog study of males with HCD

Study/Organ weights of males	Dose level in ppm				HCD male Beagle dogs (Jackson et al, 1964)
	0	3	15	75	
2-year study					
Body weight (kg)	17.1	16.5	15.2	15.5	na
Thyroid weight absolute (mg)	723	780	753	885	500-1600
Thyroid weight relative (% of BW)	0.0042	0.0047	0.0050	0.0057*	0.005-0.014
1-year study					
Body weight (kg)	15.1	14.9	15.8	15.8	na
Thyroid weight absolute (mg)	581	801	788	834	500-1600
Thyroid weight relative (% of BW)	0.0039	0.0054	0.0050	0.0053	0.005-0.014

Table 6.8.3-5 Comparison of selected endocrine organ weights of the 1- and 2-year dog study of females with HCD

Study/Organ weights of females	Dose level in ppm				HCD female Beagle dogs (Jackson et al, 1964)
	0	3	15	75	
2-year study					
Body weight (kg)	15.9	15.0	15.1	13.9	na
Thyroid weight absolute (mg)	756	815	715	826	400-1300
Thyroid weight relative (% of BW)	0.0048	0.0054	0.0047	0.0059	0.004-0.013
Ovary weight absolute (mg)	1279	1825	2099	2268	600-2300
Ovary weight relative (% of BW)	0.008	0.0123	0.0139	0.0165	0.005-0.019
Uterus weight absolute (g)	10.8	19.3	29.2*	25.2*	3.1-25
Uterus weight relative (% BW)	0.067	0.130	0.192	0.182	0.033-0.276
1-year study					
Body weight (kg)	13.8	14.3	15.1	14.6	na
Thyroid weight absolute (mg)	777	650	823	790	400-1300
Thyroid weight relative (% of BW)	0.0057	0.0045	0.0055	0.0054	0.004-0.013
Ovary weight absolute (mg)	1079	1063	1596	1710	600-2300
Ovary weight relative (% of BW)	0.0078	0.0074	0.0109	0.0120	0.005-0.019

Study/Organ weights of females	Dose level in ppm				HCD female Beagle dogs (Jackson et al, 1964)
	0	3	15	75	
Uterus weight absolute (g)	7.5	9.3	17.2	17.8	3.1-25
Uterus weight relative (% BW)	0.055	0.066	0.117	0.126	0.033-0.276

na = no data available
* = outside HCD

This comparative overview confirms that the organ weights of thyroids, ovaries and uterus are within normal background ranges. The historical ranges were very large which confirms a high variability of the normal organ weights. Since in the 2- and 1-year study no clear dose response relationship and thus no treatment relationship was obvious and mainly variability and body weight effects on the organ weights were responsible, an endocrine potential of fenoxaprop cannot be derived from these data.
An endocrine effect is furthermore not plausible since other toxicity studies with fenoxaprop did not reveal evidence of an ED potential.
Thus, subchronic toxicity studies in dogs with higher doses did not cause similar organ weight changes. In a subchronic dog toxicity study with the pure optical isomer AE F046360 at doses of 0, 80, 400 and 2000 ppm via the diet, equivalent to 3.0, 15.6 and 77.7 mg/kg bw/d in males and to 3.2, 16.2 and 83.4 mg/kg bw/d in females (Sachsse *et al.*; 1987; M-118393-01-1) no changes of endocrine organ weights were observed.
The same is valid for another subchronic toxicity study with the racemic mixture AE F033171in dogs (Brunk et al, 1981, M-095576-01-1) with doses of 0, 16, 80 and 400 ppm via the diet, equivalent to approximately 0.4, 2 and 10 mg/kg bw/d in males and females in which also no changes of the thyroid, testes and ovary weights were seen. An overview of both studies is given in the following table.

Table 6.8.3-6 Selected endocrine organ weights of subchronic dog studies

Organ weights (% changes vs. control in brackets)	Dose group level in ppm (mg/kg bw/d)							
	Males				Females			
Sachsse et al, 1987; M-118393-01-1	**0**	**80 (3.0)**	**400 (15.6)**	**2000 (77.7)**	**0**	**80 (3.2)**	**400 (16.2)**	**2000 (83.4)**
Body weight (kg)	8.524±705.8	8.910±1587.1 (+4.5)	8.755±820.8 (+2.7)	8.456±235.0 (-0.8)	8.644±621.8	8.685±485.7 (+0.4)	7.962±1181.3 (-7.9)	7.881±1105.4 (-8.8)
Body weight gains[a] (kg)	2.553	2.103 (-11.6)	2.172 (-14.9)	1.500 (-41.2)	2.367	2.519 (+6.4)	1.839 (-22.3)	2.045 (-13.6)
Thyroid weight absolute (g)	0.70±0.06	0.84±0.20	0.79±0.30	0.80±0.15	0.82±0.08	0.75±0.13	0.80±0.18	0.62±0.10
Thyroid weight relative (% BW)	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00	0.01±0.00
Testes weight absolute (g)	10.86±4.24	11.64±1.32	11.30±2.77	11.21±2.41				
Testes weight relative (% BW)	0.13±0.04	0.14±0.01	0.14±0.03	0.14±0.03				
Ovary weight absolute (g)					0.918±0.647	0.670±0.036	0.668±0.173	0.655±0.110
Ovary weight relative (% BW)					0.012±0.010	0.008±0.001	0.009±0.002	0.009±0.001
Brunk et al, 1981; M-095576-01-1	**0**	**16 (~0.4)**	**80 (~2)**	**400 (~10)**	**0**	**16 (~0.4)**	**80 (~2)**	**400 (~10)**
Body weight (kg)[a]	14.08	13.98	14.42	14.17	11.45	12.35	12.83	12.67
Body weight gains (kg)[a]	1.32	1.50	1.00	1.05	0.97	0.58	0.63	0.40
Thyroid weight absolute (g)	0.652±0.069	0.693±0.140	0.689±0.047	0.778± 0.149	0.781± 0.0199	0.669±0.043	0.754±0.128	0.65±0.164
Thyroid weight relative (% BW)	0.0045± 0.0003	0.0051± 0.0012	0.0047± 0.0003	0.0055± 0.0012	0.0067± 0.0015	0.0053± 0.0007	0.0058± 0.0010	0.0053± 0.0015
Testes weight absolute (g)	21.0±2.4	24.0±2.2	21.2±3.9	21.0±2.9				
Testes weight relative (% BW)	0.145±0.013	0.176±0.028	0.144±0.023	0.148±0.020				
Ovary weight absolute (g)					0.915±0.140	1.419±0.153	1.552±0.349	1.203±0.439

Organ weights (% changes vs. control in brackets)	Dose group level in ppm (mg/kg bw/d)							
	Males				Females			
Sachsse et al, 1987; M-118393-01-1	**0**	**80 (3.0)**	**400 (15.6)**	**2000 (77.7)**	**0**	**80 (3.2)**	**400 (16.2)**	**2000 (83.4)**
Ovary weight relative (% BW)					0.0079± 0.0016	0.0113± 0.0022	0.0119± 0.0023	0.0098± 0.0040

[a] No SD given in report
BW = body weight

This tabular overview of determined organ weight results of subchronic dog studies shows that no treatment-related effects on the weights of thyroids, ovaries (uterus weights were not determined) and testes were seen.

Evidence of endocrine effects in other studies
Furthermore, in the other apical toxicology studies in rodents, such as the subchronic and long-term studies in rats and mice no evidence of endocrine effects can be derived from the available organ weight and histopathological data. In addition, in the rat multi-generation study no evidence of endocrine mediated effects was seen. Therefore, from the apical studies in rodents with fenoxaprop no evidence of an endocrine potential is derived.

Lipid metabolism changes
RMS Austria commented that 'In addition to the highly altered lipid metabolism seen in most of the studies, these are also effects that concern ED-related organs.'
In the four dog studies discussed previously, no significant changes of any lipid parameters occurred so that a contribution of lipid effects to the discussed organ weight changes can be ruled out.
However, lipid effects were observed in the rodent studies with fenoxaprop. They are regarded as the consequence of a peroxisome proliferating mode of action of fenoxaprop which is rodent-specific. Also in special studies with fenoxaprop, hypolipidemic effects and effects on oxidative stress (glutathione and catalase levels) were seen which demonstrated that fenoxaprop-P-ethyl has such a peroxisome proliferating mode of action (Ehling, 1993). This mode of action however, is not endocrine-mediated, but triggered by PPARα activation which leads via oxidative stress in the liver cells to the observed lipid effects. This effect is rodent-specific and does not occur similarly in humans. This rodent specific effect is demonstrable in studies with other chemicals that elicit peroxisome proliferator responses with PPARα activation and which demonstrated non-relevance to dogs and humans (Richert et al, 1996; Roberts, 1999). Therefore, this mode of action does neither occur in humans nor in dogs and is not endocrine-mediated so that the aforementioned organ weight changes in dogs are not related to such a mode of action, but to the reasons discussed before.

Conclusion
The relevance of some organ weight changes in a 2- and 1-year toxicity study in dogs is discussed in this paper. The analysis showed that the organ weight data show a high variability which according to the study director was due to differences in exsanguination, but also due to general high variability, especially because of the lower animal number in dog studies which can give an impression of a spurious and artificial dose relationship. This was shown for the organ weight changes of liver, lung and brain, but also for the uterus weights which overall did not show a dose-relationship. In addition, marked effects on body weights and body weight gains could explain the observed organ weight effects and put them in perspective. The observed differences of ovary and uterus weights were additionally explained by the fact that the females were in different phases of their estrous cycle. It is known that ovary weights show changes within the different phases of the estrous cycle, with highest weight during estrus (Chandra et al, 2008). Therefore, it is concluded that together with severe body weight effects, such technical aspects of study conduct and different stage of estrus of female dogs led to a spurious organ weight bias of certain organs in this study.
The noted changes of the thyroid weights in the 2-year study did not show a clear dose–response relationship in females or males, although there seemed to be a trend of an increase of the absolute and relative weight at the highest dose in males. However, based on the remarks of the study director, this was most likely due to the differences in the exsanguination between the animals. The discussed organ weights were furthermore within published historical background ranges from Beagle dogs (Jackson et a, 1964).
Therefore, no evidence of an endocrine potential can be derived based on the discussed changes of the thyroid, ovary and uterus weights. Most importantly, if real treatment effects on these organs had occurred, then supporting histopathological findings would be expected. However, no histopathological findings were observed in any of these organs, so that it is concluded that the aforementioned organ weight effects are spurious and not treatment-related. Therefore, there is no reason to change the NOAEL of 15 ppm in this study which was based on body weight effects at 75 ppm.

Also from the results of the discussed 1-year study, no evidence of an endocrine potential can be derived since the changes of the thyroid, ovary and uterus weights were not clearly dose-related and also within historical control ranges. In addition, no histopathological findings were observed in any of these organs. Therefore, there is also no reason to change the NOAEL of 15 ppm in this 1-year study.
The lack of an endocrine potential is supported by the results of subchronic dog studies in which no treatment-related effects on the weights of thyroids and ovaries (uterus weights were not determined) were seen.
Furthermore, in the other apical toxicology studies in rodents, such as the subchronic and long-term studies in rats and mice no evidence of endocrine effects can be derived from the available organ weight and histopathological data so that overall no evidence of an endocrine potential of fenoxaprop exists.
The discussed altered lipid metabolism is not endocrine-mediated but triggered by PPARα activation caused by fenoxaprop in rodents leading to the observed lipid effects. This effect is rodent-specific and does not occur similarly in humans or dogs so that the aforementioned organ weight changes in dogs are not related to such a mode of action. This is further supported by the fact that this class of chemicals of aryloxyphenoxy-propionate 'FOPs' and its mode of action via inhibition of acetyl CoA carboxylase is not known to cause endocrine effects.
In conclusion, there is no evidence of an endocrine potential of fenoxaprop, based on all available apical study data, including the 2- and 1-year dog studies in which only spurious effects on certain organ weights due to variability, technical study aspects, like different exsanguination and different estrus cycles between animals and groups, and furthermore body weight influences were observed.

Summary of ToxCast and Tox21 Activity Data
Fenoxaprop-P-ethyl (FPE, CASRN 71283-80-2) and fenoxaprop-ethyl (FE, CASRN 66441-23-4) were included in the Tox21 and ToxCast chemical libraries (http://www2.epa.gov/chemical-research/toxcast-chemicals-data-management-and-quality-considerations-overview).
A first analysis by BCS on possible ED results is available and is summarized as follows:
- Some assays for steroidogenesis (H295R) were positive, but at very high concentrations of AC50 of more than 3000 µg/mL which cannot be reached under normal in vivo conditions
- Prediction that neither chemical acts as an estrogen or anti-estrogen
- Prediction that neither chemical acts as an androgen or anti-androgen
- FPE and FE were both negative in four thyroid receptor alpha-related assays in ToxCast/Tox21 and not tested in the one assay for thyroid receptor beta; there is no suggestion that FPE or FE interacts directly with thyroid hormone receptors. FPE was negative in the one assay available to evaluate thyroperoxidase (TPO) inhibition. FE was positive in this assay for TPO, but 2 accompanying assays to indicate non-specific enzyme inhibition were also positive, suggesting this is not likely a specific effect on TPO

Overall, therefore, no evidence of ED potential based on ToxCast and Tox21 Activity Data.

RMS' comments
RMS concludes that although changes in endocrine active organ weights were observed in the 1-year and 2-year dog studies, it is to be noted that no histopathological changes were observed. No hormonal measurements were conducted in any of the studies. Furthermore the effects on ovaries and uterus were not consistently changed in rat studies, which conclude that these effects were not of biological relevance. The changes were not consistent throughout the studies. Additionally, no effects on the thyroid were observed in any of the rodent studies, where this would have been expected since rodents are considered more sensitive for thyroid effects.

B.6.9. MEDICAL DATA AND INFORMATION

Information on medical data was supplied in three reports as given in the table below and in Tier 2, Annex II, Section 3 Summary. A short summary is given in the following table (newly submitted reports in **bold**).

Summary table on available medical data and information about fenoxaprop-P-ethyl

Study	Results
Fenoxaprop-P-ethyl Code: AE F046360 (identical to old code Hoe 046360) MEDICAL DATA. Medical surveillance of manufacturing plant personnel. Proposed first aid measures. *Kaleja R., 1997* A58432, CA 5.9.1/01	No adverse effects on health of industrial workers were reported in response to occupational fenoxaprop-P-ethyl exposure.
Summary of medical data known for Fenoxaprop-P-ethyl. *Steffens W., 2016* M-552833-01-1, CA 5.9.1/02	Summary of study report by *Caiming* (2016) and the publication of *Zawahir et al.* (2009) as well as general information as in this section.
Summary of medical data known for Fenoxaprop-P-ethyl provided to Bayer CropScience AG. *Caiming, 2016* M-553684-01-1, CA 5.9.1/03	No adverse effects on health of industrial workers in response to occupational fenoxaprop-P-ethyl exposure in two different production sites.
Medical surveillance of manufacturing personnel. Fenoxaprop-P-ethyl technical material. *Dong F., 2016* 579 FPE , CA 5.9.1/01	Yearly medical assessments revealed no adverse effects on health of industrial workers at a production site in [redacted].
Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: A prospective observational study. *Zawahir et al., 2009* M-544633-0-1, CA 5.9.2/01	No mortality, symptoms were mostly epigastric pain and vomiting (78% of the patients after forced emesis or gastric lavage) 9% of the patients with reduced consciousness. All normalized after 22 hours.

B.6.9.1. Medical surveillance on manufacturing plant personnel and monitoring studies

Reference:	Fenoxaprop-P-ethyl Code: AE F046360 (identical to old code Hoe 046360) MEDICAL DATA. Medical surveillance of manufacturing plant personnel. Proposed first aid measures.
Author(s). year:	Kaleja R., 1997
Report/Doc. number:	M-142114-01-1 / A58432
GLP:	Not applicable.
Acceptability:	Yes.

Fenoxaprop-P-ethyl has been produced, formulated and packaged in the production plants at [redacted] since 1989. Production took place in closed systems, where exposure was possible during sampling and filling operations and during filter change in the plant. Precautions included suitable exhaustion equipments.

Fenoxaprop-P-ethyl was measured in the workplace atmosphere at a maximum of 0.3 mg/m^3. Xylene, which is used for formulation, was at a level of 10mg/m^3 air, which is lower by several factors than the maximum workplace concentration of 440 mg/m^3 air.

Workers were examined periodically (in accordance to the requirements of the trade association of the chemical industry (Berufsgenossenschaft-Chemie)) by the internal department of occupational medicine, including effects on skin and lung function as well as for possible health damage expected from exposure to toluene or xylene.

In summary, no substance-related changes in response to fenoxaprop-P-ethyl exposure have been indicated by clinical or laboratory examinations, and no adverse effects on health have been recorded among industrial workers. Sensitisation / allergenicity observations: No dermal allergenic reactions have been detected to date. The racemic fenoxaprop-ethyl (Hoe 033171) had been reported in one event to cause a reversible skin rash by direct skin exposure during production.

High exposure to the active substance or the herbicide may possibly result in non-specific similar to those observed in the animal studies for the most sensitive species as lowering of cholesterol, impairment of liver (non-related to peroxisome proliferation), kidney function and red blood cell parameters.

Reference:	Summary of medical data known for Fenoxaprop-P-ethyl
Author(s). year:	Steffens W., 2016
Report/Doc. number:	M-552833-01-1
GLP:	Not applicable.
Acceptability:	Yes.

This report provides a summary of the data from the first production site as in the report of Caiming (2016), and, of the publication by Zawahir *et al.* (2009), as well as summarized data as in MCA section 5. The information can be found in the following report summary of Caiming (2016) and in remaining sections of 0 Medical data of this document.

Reference:	Summary of medical data known for Fenoxaprop-P-ethyl provided to Bayer CropScience AG.
Author(s). year:	Caiming, 2016
Report/Doc. number:	M-553684-01-1
GLP:	Not applicable.
Acceptability:	Yes.

In this report, observational data from workers in two production sites ([redacted]; [redacted]) are provided.

Production site [redacted]: 15-18 employees (5-6 per shift) handling the product in the production period of 1985-2016 were monitored.
Personal safety measures included work clothing, safety glasses, helmet, safety shoes and chemical protection gloves. Additionally, for charging and filling Tyvek-type suit, dust-mask or airstream helmets were available.

- In-company experience: no known medical problems associated with potential fenoxaprop-P-ethyl exposure were reported.
- Occupational medical experience: Medical examinations for the 18 exposed workers were done annually starting from 2007 (history, work history and clinical examinations). Examinations included full blood count, liver enzymes and urine sediment as well as lung function testing.

Medical assessment: Occupational medical surveillance of workers in the production of fenoxaprop-P-ethyl, performed annually on a routine basis, not directly related to exposures, did not reveal any unwanted effects in the workers. The examinations included the above laboratory parameters and clinical and technical examinations.
During the production period 1985 to 2016 no accidents with fenoxaprop-P-ethyl occurred in the workers and no consultations of the Medical Department due to work or contact with fenoxaprop-P-ethyl were required.

Production site [redacted].: 47 employees handling the product in the production period of 2008-2016 were monitored.
Personal safety measures consisted of personal protective equipment (no details provided).

- In-company experience: No medical problems occurred during fenoxaprop production.
- Occupational medical experience: Medical examinations for the 47 exposed workers were done annually starting from 2008 (medical history, basic examination, toxicological examination, noise examination, dust examination, X-ray examination). Examinations included liver function, blood RT and routine urinalysis. Depending on job tasks in the plant, electric response audiometry and lung function of some workers was analysed.

Medical assessment: all relative workers passed the medical examination.

Reference:	Medical Surveillance of Manufacturing Personnel. Fenoxaprop-P-ethyl Technical Material
Author(s). year:	Dong F., 2016
Report/Doc. number:	CHA Doc. No. 579 FPE / Flag-2016002
GLP:	Not applicable.
Acceptability:	Yes.

In this report, observational data from workers in the production site in [redacted] are provided.

Production period:	starting from 2008
Occupational safety measures:	PPE in the workshop (approved respirator, chemical resistant gloves, eye googles)
Industrial hygiene requirements:	Good industrial hygiene, face shield or googles, elbow-length PVC gloves, cotton overalls buttoned to neck and wrist, washable hat and half-face respirator with dust and vapour cartridge After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.
No. of workers in production:	40-43
Medical examinations:	Yearly Medical history, ENT examination, Laboratory examinations (fasting blood glucose, leucorrhea conventional, blood routine, liver and kidney function, urea routine and carcinoembryonic antigen) Physical examinations (height, weight, blood pressure, heart rate), B ultrasound, X-ray, ECG, inertial examination (basic, gynaecological, andrology) Allergic skin test

Medical assessment: Annual occupational medical surveillance of workers exposed to fenoxaprop-P-ethyl technical has not revealed any adverse effects in the workers.
In-company experience: effects on skin, allergic reactions and eyes are monitored for all the workers potentially exposed to fenoxaprop-P-ethyl on a routine basis. No incidence happened during the production of fenoxaprop-P-ethyl technical.

Conclusion:
No adverse health effects have been reported in the workforce during the production of fenoxaprop-P-ethyl technical.

B.6.9.2. Data collected on humans

The following publication has been submitted, which is about a series of poisoning with a product containing fenoxaprop-P-ethyl:

Reference:	Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: A prospective observational study.
Author(s). year:	Zawahir S. *et al.*, 2009
Report/Doc. number:	M-544633-01-1
GLP:	Not applicable.
Acceptability:	Supplementary, as no information about ingested dose is available.

Eighty-six patients, who had intentionally ingested a mixture of the 3 pesticide active ingredients (fenoxaprop-P-ethyl, ethoxysulfuron and the safener isoxadifen-ethyl), were evaluated. Time to clinical presentation was 4 h on average (median), and the median amount ingested was 22.5 ml. Six patients additionally ingested significant amounts of ethanol. 60 and 6 patients had received forced emesis and gastric lavage, respectively, before arriving at the study hospital.
Symptoms were mostly epigastric pain and vomiting, however, 78% of patients with vomiting had received forced emesis or gastric lavage before.
Ninety-one percent had a normal consciousness level, 9% had a reduced Glasgow coma scale (minimum at 9, non-comatose), which normalized latest 22 hours after ingestion. In single cases (1 each) pulmonary and cardiac findings resolved on the second day. Laboratory parameters were all normal. Admission blood samples were provided by 35 patients. In 7 of these, where serial blood samplings were available, fenoxaprop-P-ethyl was detected with a median admission plasma concentration of 2.24 ng/mL. In the serial samples as well as in the remaining 28 patients fenoxaprop-P-ethyl was below the lowest LOQ of 0.5 ng/mL.
Treatment was supportive and symptomatic, and hospital stay was only 1 day on average. No sequelae were seen.

B.6.9.3. Direct observation

The following statement was made in Tier 2, Annex II, Section 3 Summary:
"*There were no reports of adverse effects and/or poisoning under work-place conditions or under conditions of experimental agricultural use*."
The following statement was presented in the MCA Section 5:
"No poisoning cases with fenoxaprop-P-ethyl have come to the attention of Bayer CropScience."

In the Cheminova report of Dong (2016, see section B.6.9.1) following is reported:
"*In-company experience:*
Effects on skin, allergic reactions and eyes are monitored for all the workers potentially exposed to fenoxaprop-P-ethyl on a routine basis.
No any incidence was happened during the production of fenoxaprop-P-ethyl technical.
Conclusion:
No adverse health effects have been reported in the workforce during the production of fenoxaprop-P-ethyl technical."

B.6.9.4. Epidemiological studies

No epdidemiological studies are available.

B.6.9.5. Diagnosis of poisoning (determination of active substance. metabolites). Specific signs of poisoning. clinical test

The following statement was presented in Section MCA 5, where the publication of Zawahir *et al.* (2009) was cited:
"Signs and symptoms of poisoning:
There is a case series published from Sri Lanka (n = 86 patients) of intentional selfpoisonings with a herbicide containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen (M-544633-01-1). Symptoms were an epigastric burning sensation and vomiting. 8 patients had a reduced level of consciousness resolving without therapy. No patient died. Treatment was symptomatic and supportive (M-544633-01-1; see above)."

B.6.9.5.1. Expected effects of poisoning

The following statement was presented in the report from Kaleja R. (section B.6.9.1):
"*No accidental poisoning resulting from production, formulation and agricultural use of Fenoxaprop-P-ethyl is known to us. Therefore, high exposure to the active substance or the herbicide may possibly result in non-specific signs similar to those observed in the animal studies for the most sensitive species as lowering of cholesterol, impairment of liver (non-related to peroxisome-proliferation), kidney function and red blood cell parameters.*"

B.6.9.6. Proposed treatment: first aid measures. antidotes. medical treatment

The following statement was presented in section 5.9.6 of the summary document KCA 5.9.1-02 (*Steffen W.*, 2016) as well as in MCA Section 5 (*Bomann W.*, 2016):
*"**First aid**:*

- *Remove patient from exposure/terminate exposure.*
- *Thorough skin decontamination with copious amounts of water and soap, if available with polyethyleneglycol 300 followed by water.*
  ***Note**: Most formulations with this active ingredient can be decontaminated with water (and soap), so for formulations polyethylenglycol 300 is not required.*
- *Flushing of the eyes with lukewarm water for 15 minutes.*
- *Induction of vomiting does not seem to be required in regard of the low toxicity. It should only be considered if a large amount has been swallowed, if the ingestion was less than one hour ago, and if the patient is fully conscious. Induced vomiting can remove maximum 50% of the ingested substance.*
  ***Note**: Induction of vomiting is forbidden, if a formulation containing organic solvents has been ingested!*

***Treatment**:*

- *Gastric lavage does not seem to be required in regard of the low toxicity of the compound.*
- *The application of activated charcoal and sodium sulphate (or other cathartic) may be considered in significant ingestions.*
- *As there is no antidote, treatment has to be symptomatic and supportive."*

In the study report of *Caleja (1997)* the following is stated:
"*First aid measures in the case of suicidal intake of Fenoxaprop-P-ethyl should consist of standard hygienic measures, i.e. decontamination and symptomatic treatment of non-specific symptoms. In addition, it is advisable to monitor the lipid status, liver, kidney and red blood cell function*."

Additionally, in the study report of *Caiming (2016*), a list of first aid measures were provided for the production site in China:

- *"If in eyes: immediately flush eyes with large amounts of water or eyewash solution, occasionally opening eyelids, until no evidence of chemical remains. Remove contact lenses after a few minutes and flush again. Get medical attention.*
- *If on skin: immediately remove contaminated clothing and shoes and wash with water and soap. Get medical attention if irritation develops.*
- *If swallowed: inducing vomiting is not recommended. Drink a few glasses of water. Get medical attention immediately.*
- *If inhaled: If experiencing any discomfort, move to fresh air and obtain medical advice if discomfort does not disappear."*

B.6.10. REFERENCES RELIED ON

For fenoxaprop-P-ethyl, its metabolites and appropriate trade names, the search and review of the published literature is presented in MCA Section 9 Literature Data. Information from the report is summarized in the following.

Time window:	From 2005-01-01 to 2016-01-11
Databases used (date of last update):	Agricola (Jan. 2016), Biosis (Jan. 2016), CABA (Jan. 2016), Chemical Abstracts (Jan. 2016), Derwent Drug File (Jan. 2016), EMBASE (Jan. 2016), Esbiobase (Jan. 2016), IPA (Jan. 2016), Medline (Jan. 2016), Pascal (Dec. 2014), PQSciTech (Dec. 2015), Registry (Jan. 2016), Scisearch (Jan. 2016), Toxcenter (Jan. 2016), FSTA (Dec. 2015)
Key words included:	Fenoxaprop-P-ethyl, fenoxaprop-ethyl and chemical names/synonyms thereof, as well as product names including the substances Chemical names/synonyms of metabolites M01, M02, M03, M04, M05, M06, M07, M08, M09, M10, M11, M12, M13, M14, M15 M16

For fenoxaprop-P-ethyl and its relevant metabolites, a total of 1250 references were identified and evaluated for potential relevance. This evaluation was performed according to the EFSA guidance (EFSA Journal 2011;9(2):2092).

Results of the study selection process

Data requirement(s) captured in the search	a.i.	M01	M02	M03	M04	M05	M07	M13	M16
Total no of *summary records* retrieved after all searches of pee-reviewed literature	642	4	23	485	60	16	18	1	1
No of *summary records excluded* from the search results after rapid assessment for relevance	565	4	21	454	57	15	17	1	1
Total no of *full-text documents* assessed in detail	77	--	2	31	3	1	1	--	--
No of *publications excluded* from further consideration after detailed assessment for relevance	57	--	2	27	3	1	1	--	--
No of *publications not excluded* for relevance after detailed assessment (i.e. relevant studies and studies of unclear evidence)	20	--	--	4	--	--	--	--	--
Publications considering human health or animal health	1	--	--	--	--	--	--	--	--

a.i. = active ingredient

Besides references that were clearly out of the scope of the LRR (e.g. publications dealing with chemical synthesis, or efficacy reports), the area of environmental fate and ecotoxicology were most represented in the search results.

According to EFSA guidance 1135 publications have been excluded from further consideration after the rapid assessment. For 115 publications full-text documents have been obtained and assessed in detail. Ninety-one publications have been considered irrelevant after detailed assessment.

In total 24 publications were evaluated as relevant for detailed assessment and classified for relevance according to EFSA guidance.

For fenoxaprop-P-ethyl a publication assessing the degradation behaviour of the two enantiomers of fenoxaprop-ethyl in aerobic soil (*Zhang, Y. et al., 2010*; M-507961-01-1) was identified as relevant after detailed assessment and classified as case a) according to EFSA Guidance Point 5.4.1.

Of the remaining 23 publications that have been identified as studies relevant after detailed assessment and classified in accordance with the EFSA Guidance Point 5.4.1, only one concerned the field of mammalian toxicology, which was classified as case b) according to EFSA Guidance Point 5.4.1. The publication of *Zawahir et al.* (2009) assesses the poisoning cases with a plant protection product including fenoxaprop-P-ethyl in Sri Lanka. The evaluation of 86 intentional ingestion cases revealed that no mortalities occurred and only mild symptoms such as vomiting were seen. Around 9% of the patients had decreased consciousness levels, but were not comatose, which recovered after the first day.

However, none of these studies was considered to have an impact on an EU-agreed endpoint, or would require any adaptation of the risk assessments presented in the fenoxaprop-P-ethyl supplementary (Annex I Renewal) dossier.

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.1.1 /01	[redacted]	1987a	Kinetics in the rat after single oral and intravenous administration of 2 mg/kg body weight Hoe 046360-14C [redacted], Report No.: A37450, Edition Number: M-119157-01-1 Date: 1988-02-15 GLP/GEP: yes, unpublished **...also filed: KCA 5.1.2 /02**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /02	[redacted]	1982	Kinetics and residue determinations following oral and intravenous applications in rats Hoe 33171-14C [redacted], Report No.: A24284, Edition Number: M-096760-01-2 EPA MRID No.: 00130640 Date: 1982-04-22 GLP/GEP: no, unpublished **...also filed: KCA 5.1.2 /01**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /03	[redacted]	1984a	Excretion and residues after oral administration of 2 mg/kg body weight to rats Hoe 033171 (dioxyphenyl-1-14C) [redacted], Report No.: A32611, Edition Number: M-112025-01-1 Date: 1984-11-22 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /04	[redacted].	1987	Kinetics in the rat after single oral administration of 10 mg/kg body weight Hoe 046360-14C [redacted] Report No.: A37448, Edition Number: M-119155-01-1 Date: 1988-02-15 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.1.1 /05	[redacted]	1984b	Kinetics and residue concentrations following oral application of 10 mg/kg body weight in rats Hoe 033171 (chlorphenyl-U-14C) [redacted], Report No.: A30454, Edition Number: M-106502-01-2 EPA MRID No.: 00148478, acc.258971 Date: 1984-11-30 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /06	[redacted]	1984c	Kinetics and residues after oral administration of 10 mg/kg body weight to rats Hoe 033171 (dioxyphenyl-1-14C) [redacted] Report No.: A32612, Edition Number: M-112029-01-1 Date: 1984-12-03 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /07	[redacted]	1987b	Kinetics in the rat after repeated (14 + 1) oral doses of 2 mg/kg body weight Hoe 046360-14C [redacted] Report No.: A37449, Edition Number: M-119156-01-1 Date: 1988-02-15 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /08	[redacted]	1984d	Kinetics and residue concentrations following repeat-ed oral Applications of 2 mg/kg/day in rats Hoe 033171 (chlorophenyl-U-14C) [redacted] Report No.: A30456, Edition Number: M-106503-01-2 EPA MRID No.: 00148479, acc.258971 Date: 1984-12-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.1.1 /09	[redacted]	1987	Metabolism in male and female rats after a single oral administration of 10 mg/kg body weight Hoe 046360-14C [redacted] Report No.: A37324, Edition Number: M-119042-01-1 Date: 1987-10-19 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /10	[redacted]	1985	Metabolism in rats orally administered at two doses, 2 and 10 mg/kg Weight Hoe 033171 - dioxyphenyl-1-14C [redacted] Report No.: A30377, Edition Number: M-106317-01-1 EPA MRID No.: 00148477, acc.258971 Date: 1985-01-03 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /11	[redacted]	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 [redacted] Report No.: A49483, Edition Number: M-138521-01-1 Date: 1993-01-06 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.1 /12	[redacted]	1988	Comparison and evaluation of the metabolism and pharmacokinetics in rats Code: Hoe 033171 and Code: Hoe 046360 [redacted] Report No.: A38647, Edition Number: M-120271-01-1 Date: 1988-07-22 GLP/GEP: no, unpublished **...also filed: KCA 5.1.2 /04**	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.1.2 /01	[redacted]	1982	Kinetics and residue determinations following oral and intravenous applications in rats Hoe 33171-14C [redacted] Report No.: A24284, Edition Number: M-096760-01-2 EPA MRID No.: 00130640 Date: 1982-04-22 GLP/GEP: no, unpublished **...also filed: KCA 5.1.1 /02**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.2 /02	[redacted]	1987a	Kinetics in the rat after single oral and intravenous administration of 2 mg/kg body weight Hoe 046360-14C [redacted] Report No.: A37450, Edition Number: M-119157-01-1 Date: 1988-02-15 GLP/GEP: yes, unpublished **...also filed: KCA 5.1.1 /01**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.2 /03	[redacted]	1992a	Dermal penetration in the rat (final report) 14C-Hoe 046360 [redacted] Report No.: A48898, Edition Number: M-137986-01-1 Date: 1992-10-15 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.1.2 /04	[redacted]	1988	Comparison and evaluation of the metabolism and pharmacokinetics in rats Code: Hoe 033171 and Code: Hoe 046360 [redacted], Report No.: A38647, Edition Number: M-120271-01-1 Date: 1988-07-22 GLP/GEP: no, unpublished **...also filed: KCA 5.1.1 /12**	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.2.1 /01	[redacted]	1992	Testing for acute oral toxicity in the male and female Wistar rat - Fenoxaprop-p-ethyl - Substance, technical - Code: Hoe 046360 00 ZC97 0002 [redacted] Report No.: A47470, Edition Number: M-135864-01-1 Date: 1992-02-28 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.1 /02	[redacted]	1979a	Acute oral toxicity to the male rat of Hoe 33171 0H AT201 active ingredient technical [redacted] Report No.: A24696, Edition Number: M-097667-01-2 EPA MRID No.: acc.71787 Date: 1979-10-09 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.1 /03	[redacted]	1979b	Acute oral toxicity to the female rat of Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24698, Edition Number: M-097668-01-2 EPA MRID No.: acc.71787 Date: 1979-10-02 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.1 /04	[redacted]	1985a	Acute oral toxicity in the male and female NMRI mouse Hoe 046360 active ingredient technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A37268, Edition Number: M-118995-01-1 Date: 1985-12-05 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.2.1 /05	[redacted]	1979a	Acute oral toxicity to the male mouse Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24692, Edition Number: M-097665-01-2 EPA MRID No.: acc.71787 Date: 1979-07-27 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.1 /06	[redacted]	1979b	Acute oral toxicity to the female mouse Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24694, Edition Number: M-097666-01-2 EPA MRID No.: acc.71787 Date: 1979-07-27 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.1 /07	[redacted]	2008	Fenoxaprop-p-ethyl: Acute oral toxicity in the rat - Fixed dose method [redacted] TF- BCS-CHA, Report No.: 271 FPE, Edition Number: M-548211-01-1 Date: 2008-11-26 GLP/GEP: yes, unpublished	Y	Y	Study performed to address data requirements in the EU	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.2.1 /08	[redacted]	2005	Fenoxaprop-p-ethyl technical: Acute oral toxicity in the rat - up and down procedure [redacted] TF- BCS-CHA, Report No.: 127 FPE, Edition Number: M-548055-01-1 Date: 2005-11-02 GLP/GEP: yes, unpublished	Y	Y	Study performed to address data requirements in the EU	TF- BCS-CHA	Submitted for the purpose of Renewal

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.2.2 /01	[redacted]	1985b	Testing for acute dermal toxicity in the male and female Wistar rat - Hoe 046360 - Active ingredient technical (Code: Hoe 046360 OH ZC96 0002) [redacted] Report No.: A36023, Edition Number: M-117843-01-1 EPA MRID No.: 42009614 Date: 1985-12-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.2 /02	[redacted]	1978b	Acute precutaneous toxicity to the female SPF-Wistar rat (vehicle: sesame oil) Code: Hoe 33171 0H AT202 [redacted] Report No.: A24673, Edition Number: M-097654-01-2 Date: 1978-07-25 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.2 /03	[redacted]	1979c	Acute percutaneous toxicity to the female rat of Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24702, Edition Number: M-097670-01-2 EPA MRID No.: 00130018, acc.71795 Date: 1979-10-02 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.3 /01	[redacted]	1991	Acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC50 Fenoxaprop-P-ethyl substance, technical Code: Hoe 046360 00 ZC97 0002 [redacted] Report No.: A46998, Edition Number: M-130946-01-1 Date: 1991-11-18 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCA 5.2.3 /02	[redacted]	1982	Aerosol inhalation in male and female SPF-Wistar rats 4-hour LC50 of Hoe 33171 active ingredient Code: Hoe 33171 0H AT204 [redacted] Report No.: A24752, Edition Number: M-097643-01-2 EPA MRID No.: 00130017, acc.71787 Date: 1982-06-08 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.4 /01	[redacted]	1985d	Testing for primary dermal irritation in the rabbit - Hoe 046360 - Active ingredient technical (Code: Hoe 046360 OH ZC96 0002) [redacted] Report No.: A36061, Edition Number: M-117880-01-1 EPA MRID No.: 42009617 Date: 1985-12-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.4 /02	[redacted]	1979d	Irritance to the rabbit skin and eye mucosa Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24688, Edition Number: M-097663-01-2 EPA MRID No.: acc.71787 Date: 1979-07-11 GLP/GEP: yes, unpublished **...also filed: KCA 5.2.5 /02**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.4 /03	[redacted]	2005	Fenoxaprop-p-ethyl technical: Acute dermal irritation in the rabbit [redacted] TF- BCS-CHA, Report No.: 125 FPE, Edition Number: M-548033-01-1 Date: 2005-11-02 GLP/GEP: yes, unpublished	Y	Y	Study performed to address data requirements in the EU	TF- BCS-CHA	Submitted for the purpose of Renewal

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KCA 5.2.5 /01	[redacted]	1985e	Testing for primary eye irritation in the rabbit - Hoe 046360 - Active ingredient technical (Code: Hoe 046360 OH ZC96 0002) [redacted], Report No.: A36022, Edition Number: M-117842-01-1 EPA MRID No.: 42009616 Date: 1985-12-06 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.5 /02	[redacted]	1979d	Irritance to the rabbit skin and eye mucosa Hoe 33171 0H AT203 active ingredient technical [redacted] Report No.: A24688, Edition Number: M-097663-01-2 EPA MRID No.: acc.71787 Date: 1979-07-11 GLP/GEP: yes, unpublished **...also filed: KCA 5.2.4 /02**	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.5 /03	[redacted]	2005	Fenoxaprop-p-ethyl technical: Acute eye irritation in the rabbit [redacted] TF- BCS-CHA, Report No.: 124 FPE, Edition Number: M-548024-01-1 Date: 2005-11-02 GLP/GEP: yes, unpublished	Y	Y	Study performed to address data requirements in the EU	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.2.6 /01	[redacted]	1986a	Sensitizing properties in the Pirbright-White guinea pig in a Maximisation test Hoe 046360 active ingredient technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A37243, Edition Number: M-118976-01-1 Date: 1986-04-11 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.2.6 /02	[redacted]	1986	Testing for sensitising properties in the Pirbright-White guinea pig according to the technique of BUEHLER - Hoe 046360 - Active ingredient technical (Code: Hoe 046360 OH ZC96 0002) [redacted] Report No.: A36040, Edition Number: M-117860-01-1 EPA MRID No.: 42009618 Date: 1986-05-30 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.6 /03	[redacted]	1992b	Sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Fenoxa-prop-P-ethyl substance technical Code: Hoe 046360 00 ZC97 0002 [redacted] Report No.: A47403, Edition Number: M-135807-01-1 Date: 1992-02-20 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.2.6 /05	[redacted]	2005	Fenoxaprop-p-ethyl technical: Local lymph node as-say in the mouse [redacted] TF- BCS-CHA, Report No.: 123 FPE, Edition Number: M-547997-01-1 Date: 2005-11-02 GLP/GEP: yes, unpublished	Y	Y	Study performed to address data requirements in the EU	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.2.7 /01	Heppenheimer, A.	2014	Fenoxaprop-P-ethyl, technical: Cytotoxicity assay *in vitro* with BALB/c 3T3 cells: Neutral Red (NR) test during simultaneous irradiation with artificial sunlight Harlan Cytotest Cell Research GmbH (Harlan CCR), Rossdorf, Germany TF- BCS-CHA, Report No.: 1637600, Edition Number: M-496758-01-1 Date: 2014-09-01 GLP/GEP: yes, unpublished	N	Y	Data needed to cover requirement according to Reg-ulation (EC) No 1107/2009	TF- BCS-CHA	Submitted for the purpose of Renewal

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KCA 5.3.1 /02	[redacted]	1990	Repeated-dose oral toxicity: 28-day feeding study in rats Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A42820, Edition Number: M-125805-01-1 Date: 1990-02-28 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.1 /03	[redacted]	1980a	Range-finding-test in a 32-day study with SPF-Wistar rats with Hoe 33171 0H AT203 [redacted] Report No.: A26171, Edition Number: M-099056-01-1 EPA MRID No.: 00130025, acc.71788 Date: 1980-06-09 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.1 /05	[redacted]	1980b	Toxicity test in a 32-day study (range-finding-test) with SPF-mice of Code: Hoe 33171 0H AT203 [redacted] Report No.: A26168, Edition Number: M-099053-01-1 EPA MRID No.: 00130029, acc.71790 Date: 1980-06-10 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.1 /06	[redacted]	1981	Toxicity test in a 30-day study (range-finding-test) with SPF-mice (supplement) Code: Hoe 33171 0H AT204 [redacted] Report No.: A26169, Edition Number: M-099054-01-1 EPA MRID No.: 00130030, acc.71791 Date: 1981-06-24 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.3.2 /01	[redacted]	1987	Sub-chronic oral toxicity 13-week feeding study in rats Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36566, Edition Number: M-118342-01-1 Date: 1987-09-01 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /02	[redacted]	1981	Repeated-dose (3 month) oral toxicity study administered in the feed to rats of the active substance Hoe 33171 Code: Hoe 33171 0H AT204 [redacted] Report No.: A35788, Edition Number: M-099057-02-1 EPA MRID No.: acc.71789 Date: 1981-12-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /03	[redacted]	1986	Repeated-dose (3 month) oral toxicity study administered in the feed to rats (supplement) Hoe 033171 active substance Code: Hoe 033171 0H AT204 [redacted] Report No.: A32697, Edition Number: M-112269-01-1 Date: 1986-01-20 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /04	[redacted]	1986	Repeated-dose (3 month) oral toxicity study administered in the feed to rats. Plant protection product levels in small animal diet (addendum to report No. 695/81 document A35788) Hoe 33171 active substance Code: Hoe 33171 0H AT204 [redacted] Report No.: A32985, Edition Number: M-113063-01-1 Date: 1986-04-16 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.3.2 /05	[redacted]	1987a	Sub-chronic oral toxicity 13-week feeding study in nice Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36567, Edition Number: M-118343-01-1 Date: 1987-07-14 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /06	[redacted]	1993a	Subchronic oral toxicity (13-week range finding (feeding) study) in the NMRI mice Hoe 033171 substance, technical Code: Hoe 033171 00 ZD96 0005 [redacted] Report No.: A50244, Edition Number: M-131275-01-1 EPA MRID No.: 49054603 Date: 1993-04-07 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /07	[redacted]	1987b	Sub-chronic oral toxicity 13-week feeding study in beagle dogs Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36617, Edition Number: M-118393-01-1 Date: 1987-07-10 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /08	[redacted]	1981	Repeated-dose (3 month) oral toxicity study in dogs of Code: Hoe 33171 0H AT204 [redacted] Report No.: A24131, Edition Number: M-095576-01-2 EPA MRID No.: 00130031, acc.71793 Date: 1981-11-24 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.3.2 /09	[redacted]	1986	Oral toxicity study in dogs repeated-dose (3-month). Idividual ophthalmologic findings, individual and mean body weights (supplement to document No. A24131) Code: Hoe 33171 0H AT204 [redacted] Report No.: A32690, Edition Number: M-112243-01-1 Date: 1986-01-28 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /10	[redacted]	1984	Toxicological testing by repeated oral administration to Beagle dogs for one year of Hoe 33171 active ingredient, technical Code: Hoe 033171 0H ZC94 0001 [redacted] Report No.: A29692, Edition Number: M-102290-02-1 EPA MRID No.: acc.255852 Date: 1984-07-19 **...Amended: 1987-06-11** GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /11	[redacted]	1985	Toxicological testing by repeated oral administration to Beagle dogs for 2 years of Hoe 33171 - active ingredient, technical Code: Hoe 033171 0H ZC94 0001 [redacted] Report No.: A31854, Edition Number: M-109895-02-1 Date: 1985-01-30 **...Amended: 1987-09-25** GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.2 /12	[redacted]	1987	Repeated oral administration to Beagle dogs for two years (explanatory supplement to report No. 85.0073 Hoe 033171 substance, technical Code: Hoe 033171 0H ZC94 0001 [redacted] Report No.: A37042, Edition Number: M-118806-01-1 Date: 1987-12-01 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.3.3 /01	[redacted]	1989	Subchronic inhalation toxicity (28 applications within 40 days) in male and female Wistar rats Hoe 046360 substance, technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A40799, Edition Number: M-123650-01-1 Date: 1989-04-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.3.3 /02	[redacted]	1988	Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rat Hoe 046360 active ingredient Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A40800, Edition Number: M-123662-01-1 Date: 1988-11-24 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /01	Mueller, W.	1994	Mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli Hoe 046360 substance, technical Code: Hoe 046360 00 ZC97 0002 Hoechst AG, Frankfurt am Main, Germany Bayer CropScience, Report No.: A53077, Edition Number: M-133836-01-1 Date: 1994-09-09 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /03	Edwards, C. N.	1986a	Forward mutation in Schizosaccharomyces pombe P1 Hoe 046360 substance, technical Code: Hoe 046360 0H ZC96 0002 Life Science Research Roma Toxicology Centre, Pomezia, Italy Bayer CropScience, Report No.: A34056, Edition Number: M-114840-01-1 Date: 1986-09-15 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.4.1 /04	Mellano, D.	1982a	"Mutagenic ativity ""*in vitro*"" with Schizosaccharomyces pombe of the compound Code: Hoe 33171 0H AS201 " Istituto di Ricerche Biomediche, Torino, Italy Bayer CropScience, Report No.: A24239, Edition Number: M-097266-01-1 EPA MRID No.: 00130023, acc.71787 Date: 1982-09-10 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /05	Seeberg, A. H.	1986	Gene mutation in Chinese hamster V79 Cells - Hoe 046360 substance, technical Code: Hoe 046360 0H ZC96 0002 Life Science Research Roma Toxicology Centre, Pomezia, Italy Bayer CropScience, Report No.: A34057, Edition Number: M-114841-01-1 Date: 1986-09-18 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /06	Mosesso, P.	1987	Chromosome aberrations in human lymphocytes cultured *in vitro* Hoe 046360 substance, technical Code: Hoe 046360 0H ZC96 0002 Life Science Research Roma Toxicology Centre, Pomezia, Italy Bayer CropScience, Report No.: A35218, Edition Number: M-117024-01-1 Date: 1987-02-06 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /07	Mellano, D.	1982b	Capacity to induce chromosome aberrations in human lymphocytes cultured *in vitro* of the test article Code: Hoe 33171 0H AS201 Istituto di Ricerche Biomediche, Torino, Italy Bayer CropScience, Report No.: A26227, Edition Number: M-099113-01-1 EPA MRID No.: 00144685, acc.255849 Date: 1982-12-23 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.4.1 /08	Edwards, C. N.	1986b	Mitotic gene conversion in S.cerevisiae D4 test substance: Hoe 046360 substance, technical $$Code: Hoe 046360 0H ZC96 0002 Life Science Research Roma Toxicology Center, Pomezia, Italy Bayer CropScience, Report No.: A34058, Edition Number: M-114842-01-1 Date: 1986-09-15 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /09	Mellano, D.; Mondino, A.	1982c	Mutagenic ativity with Saccharomyces cerevisiae of the compound Code: Hoe 33171 0H AS201 Istituto di Ricerche Biomediche, Torino, Italy Bayer CropScience, Report No.: A24238, Edition Number: M-097265-01-1 EPA MRID No.: 00130022, acc.71787 Date: 1982-09-13 GLP/GEP: yes, unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /10	Mellano, D.	1982d	Unscheduled DNA synthesis in cultured hela cells of the capacity of the test article Code: Hoe 33171 0H AS201 Istituto di Ricerche Biomediche, Torino, Italy Bayer CropScience, Report No.: A24582, Edition Number: M-097593-01-1 EPA MRID No.: 00144686, acc.255849 Date: 1982-10-10 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.4.1 /12 *	Mueller, W.	1995	Detection in the unscheduled DNA synthesis test in mammalian cells *in vitro* Hoe 046360 substance, technical Hoechst AG, Frankfurt am Main, Germany Bayer CropScience, Report No.: A54045, Edition Number: M-134646-01-1 Date: 1995-03-20 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.4.1 /13	Sokolowski, A.	2015	Fenoxaprop-P-ethyl (AE F046360): Salmonella typhimurium reverse mutation assay Harlan Cytotest Cell Research GmbH (Harlan CCR), Rossdorf, Germany Bayer CropScience, Report No.: 1698300, Edition Number: M-528795-01-1 Date: 2015-07-08 GLP/GEP: yes, unpublished	N	Y	Study done to support new specification	Bayer CropScience	Submitted for the purpose of Renewal
KCA 5.4.1 /14	Thompson, P. W.	2005	Fenoxaprop-p-ethyl technical: Reverse mutation assay Ames Test using Salmonella Typhimurium Safepharm Laboratories Limited, Derbyshire, United Kingdom TF- BCS-CHA, Report No.: 132 FPE, Edition Number: M-548064-01-1 Date: 2005-11-18 GLP/GEP: yes, unpublished	N	Y	Study done to support new specification	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.4.1 /15	Donath, C.	2011	Reverse mutation assay using bacteria (Salmonella typhimurium and Escherichia coli) with fenoxaprop-p-ethyl technical BSL Bioservice Scientific Laboratories GmbH, Planegg, Germany TF- BCS-CHA, Report No.: 396 FPE, Edition Number: M-548280-01-1 Date: 2011-03-09 GLP/GEP: yes, unpublished	N	Y	Study done to support new specification	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.4.1 /16	Flanders, L.	2006	Fenoxaprop-p-ethyl technical: L5178Y TK +/- mouse lymphoma assay Safepharm Laboratories Limited, Derbyshire, United Kingdom TF- BCS-CHA, Report No.: 175 FPE, Edition Number: M-548098-01-1 Date: 2006-06-28 GLP/GEP: yes, unpublished	N	Y	Study done to support new specification	TF- BCS-CHA	Submitted for the purpose of Renewal

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KCA 5.4.1 /17	Wright, N. P.; Jenkinson, P.	2006	Fenoxaprop-p-ethyl technical: Chromosome aberration test in human lymphocytes *in vitro* Safepharm Laboratories Limited, Derbyshire, United Kingdom TF- BCS-CHA, Report No.: 178 FPE, Edition Number: M-548121-01-1 Date: 2006-07-24 GLP/GEP: yes, unpublished	N	Y	Study done to support new specification	TF- BCS-CHA	Submitted for the purpose of Renewal
KCA 5.4.2 /01	[redacted]	1986	Micronucleus test in male and female NMRI mice after oral administration Hoe 046360 substance, technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A34297, Edition Number: M-115073-01-1 Date: 1986-09-18 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Submitted for the purpose of Renewal
KCA 5.4.2 /02	[redacted]	1986	Mouse micronucleus test with Hoe 033171 substance technical grade Code: Hoe 033171 0H ZD97 0001 [redacted] Report No.: A34294, Edition Number: M-115070-01-1 Date: 1986-08-26 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /01	[redacted]	1983a	Chronic feeding study in rats study No. 688 (interim killing after 6 months) Hoe 33171 active ingredient technical Code: Hoe 033171 0H AS201 [redacted] Report No.: A30803, Edition Number: M-107234-01-1 EPA MRID No.: 00149664, acc.258955 Date: 1983-01-10 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.5 /02	[redacted]	1983b	Chronic feeding study in rats study No. 688 (interim killing after 12 months) Hoe 33171 active ingredient technical Code: Hoe 033171 0H AS201 [redacted] Report No.: A29693, Edition Number: M-102291-01-1 EPA MRID No.: 00145638, acc.258955 Date: 1983-09-11 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /03	[redacted]	1984	Chronic feeding study in rats study No. 688 (interim killing at 12 months) (supplement to report No. 83.0613 of 11 November 1983) Hoe 33171 active ingredient, technical [redacted] Report No.: A29694, Edition Number: M-102292-01-1 EPA MRID No.: acc.255855 Date: 1984-09-24 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /04	[redacted]	1984a	Feeding study (24 months) in rats (study No. 688) Hoe 33171 active ingredient technical Code: Hoe 033171 0H AS201 [redacted] Report No.: A30807, Edition Number: M-107246-01-1 EPA MRID No.: 00149665, acc.258955 Date: 1984-09-19 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /05	[redacted]	1985	Chronic feeding study (24 months) in rats study No.688 determination of residues in organs and tissues report No.331/84 of 3 December 1984 (supplement to report No. 84.0632 of 29 September 1984) Hoe 33171 active ingredient technical [redacted] Report No.: A30804, Edition Number: M-107240-01-1 EPA MRID No.: acc.258955 Date: 1985-02-26 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.5 /06	[redacted]	1985b	Combined chronic toxicity and carcinogenicity study in rats Part II: carcinogenicity study (28-month feeding study) Hoe 33171 active ingredient technical Code: Hoe 33171 0H AS201 [redacted] Report No.: A31878, Edition Number: M-109965-03-1 EPA MRID No.: 00151565 Date: 1985-06-26 **...Amended: 1987-08-15** GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /07	[redacted]	1985c	Cancerogenicity study in mice - 24-month feeding study - Hoe 33171 active ingredient technical - Code: Hoe 033171 0H AS201 [redacted] Report No.: A30816, Edition Number: M-107287-01-1 EPA MRID No.: 00149666, 258955-65 Date: 1985-03-11 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /08	[redacted]	1983c	Chronic feeding study in mice study No. 695 (interim killing after 12 months) Hoe 33171 active ingredient technical Code: Hoe 033171 0H AS201 [redacted] Report No.: A29695, Edition Number: M-102293-01-1 EPA MRID No.: 00145639, acc.255856 Date: 1983-11-25 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /09	[redacted]	1984b	Chronic feeding study in mice (study No. 695, interim killing at 12 months) (supplement to report No.83.0654 of 25 November 1983) Hoe 33171 active ingredient technical Code: Hoe 33171 0H AS 201 [redacted] Report No.: A29696, Edition Number: M-102294-01-1 EPA MRID No.: acc.255856 Date: 1984-10-26 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.5 /10	[redacted]	1987	Historical data of ovarian papillary cystadenomas in 2-year mouse oncogenicity studies Code: Hoe 033171 [redacted] Report No.: A37096, Edition Number: M-118858-01-1 Date: 1987-12-15 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /11	[redacted]	1988	Historical data of ovarian papillary cystadenomas in 2-year mouse oncogenicity studies [redacted] Report No.: A37251, Edition Number: M-118979-01-1 Date: 1988-01-05 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /13	[redacted]	1996	Fenoxaprop-ethyl - Substance technical (Code: Hoe 033171 00 ZD96 0005) - Carcinogenicity study in mice [redacted] Report No.: A57500, Report includes Trial Nos.: 93.0127 Edition Number: M-141216-01-1 EPA MRID No.: 44157402 Date: 1996-10-10 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /14	[redacted]	1996	Carcinogenicity study in mice (supplement to report No.: 96.0880) Fenoxaprop-ethyl substance, technical Code: Hoe 033171 00 ZD96 0005 [redacted] Report No.: A58176, Edition Number: M-141886-01-1 Date: 1996-12-12 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.5 /15	[redacted]	1997	Mouse, carcinogenicity, feeding (addendum) Hoe 033171 (Fenoxaprop-ethyl) [redacted] Report No.: A58838, Report includes Trial Nos.: 93.0127 Edition Number: M-142554-01-1 Date: 1997-02-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /29	[redacted]	1989	Comparison of the toxicological profile of Hoe 046360 and Hoe 033171 substances technical [redacted] Report No.: A40415, Edition Number: M-123029-01-1 Date: 1989-03-13 GLP/GEP: n.a., unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.5 /30	[redacted]	1985a	Combined chronic toxicity and carcinogenicity study in rats (24 and 28 month feeding studies) (summary) and evaluation of the results Hoe 33171 active ingredient technical Code: Hoe 33171 0H AS201 [redacted] Report No.: A31880, Edition Number: M-110046-01-1 EPA MRID No.: 00151564, 258948-58 Date: 1985-06-28 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.5 /31	Klauning, J. E.; Babich, M. A.; Baetcke, K. P.; Cook, J. C.; Corton, J. C.; David, R. M.; DeLuca, J. G.; Lai, D. Y.; McKee, R. H.; Peters, J. M.; Roberts, R. A.; Fenner-Crisp, P. A.	2003	PPAR alpha agonist-induced rodent tumors: Modes of action and human relevance Publisher:Taylor and Francis Inc., Journal:Critical Reviews in Toxicology, Volume:33, Issue:6, Pages:655-780, Year:2003, Report No.: M-556195-01-1, Edition Number: M-556195-01-1 GLP/GEP: n.a., published	Y	N		Public data	Submitted for the purpose of Renewal
KCA 5.6.1 /01	[redacted]	1986a	Multiple generation study in rats (report part I) on Hoe 033171 substance, technical grade Code: Hoe 033171 0H ZD97 0001 [redacted] Report No.: A32781, Edition Number: M-112616-02-1 EPA MRID No.: 00161983, assc. 159920 Date: 1986-02-20 **...Amended: 1987-08-21** GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.1 /02	[redacted]	1986b	Multiple generation study in the rat on Hoe 033171 sbstance, techni- cal grade Code: Hoe 033171 0H ZD97 0001 [redacted] Report No.: A33840, Edition Number: M-114636-01-1 Date: 1986-06-19 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /01	[redacted]	1985a	Embryotoxicity in Wistar rats following oral administration Hoe 046360 active ingredient technical Code: Hoe 046360 0H ZB99 0002 [redacted] Report No.: A33810, Edition Number: M-114591-01-1 Date: 1985-12-19 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.6.2 /02	[redacted]	1988a	Embryotoxicity in Wistar rats following oral administration (supplement to report No. 85.1239) Hoe 046360 Wirkstoff Code: Hoe 046360 0H ZB99 0002 [redacted] Report No.: A37496, Edition Number: M-119197-01-1 EPA MRID No.: 48763002 Date: 1988-01-27 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /03	[redacted]	1990a	Embryotoxicity in Wistar rats following oral administration (supplement to report No. 85.1239) Hoe 046360 Wirkstoff Code: Hoe 046360 0H ZB99 0002 [redacted] Report No.: A42779, Edition Number: M-125765-01-1 EPA MRID No.: 48763001 Date: 1990-03-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /04	[redacted]	1982a	Oral embryotoxicity study in Wistar rats of Hoe 33171 0H AT204 [redacted] Report No.: A26170, Edition Number: M-099055-01-1 EPA MRID No.: 00130032 Date: 1982-10-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /05	[redacted]	1986	Oral embryotoxicity study in Wistar rats (supplement to report No. 613/82 of Hoe 033171 active ingredient, technical grade Code: Hoe 33171 0H AT204 [redacted] Report No.: A32696, Edition Number: M-112263-01-1 EPA MRID No.: 00159924, acc.263034 Date: 1986-01-21 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.6.2 /06	[redacted]	1989	Oral embryotoxicity study in Wistar rats (supplement 2 to report No. 613/82 Code: Hoe 33171 0H AT204 [redacted] Report No.: A41709, Edition Number: M-124791-01-1 Date: 1989-08-07 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /07	[redacted]	1987a	Embryotoxicity and effects on post-natal development in Wistar rats oral administration Hoe 046360 active ingredient Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A35687, Edition Number: M-117538-01-1 Date: 1987-04-01 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /08	[redacted]	1990a	Embryotoxicity and effects on post-natal development in Wistar rats after oral administration (supplement to report No.87.0309) Hoe 046360 active ingredient Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A42781, Edition Number: M-125767-01-1 Date: 1990-03-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /09	[redacted]	1986b	Embryotoxicity and effects on postnatal development in Wistar rats following oral administration Hoe 033171 active ingredient technical Code: Hoe 033171 0H ZD98 0001 [redacted] Report No.: A35783, Edition Number: M-112275-02-1 EPA MRID No.: 00159921 Date: 1986-02-04 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.6.2 /10	[redacted]	1986a	Embryotoxicity in Himalayan rabbits following oral administration Hoe 046360 Wirkstoff Code: Hoe 046360 0H ZB99 0002 [redacted] Report No.: A33302, Edition Number: M-113735-01-2 Date: 1986-04-23 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /11	[redacted]	1990	Embryotoxicity in Himalayan rabbits following oral administration (supplement to report No. 86.0488) Hoe 046360 Wirkstoff Code: Hoe 046360 0H ZB99 0002 [redacted] Report No.: A42780, Edition Number: M-125766-01-1 EPA MRID No.: 48763003 Date: 1990-03-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /12	[redacted]	1982b	Oral embryotoxicity study in Himalayan rabbits of Hoe 33171 active ingredient, technical grade Code: Hoe 33171 0H AT204 [redacted] Report No.: A24756, Edition Number: M-097706-01-1 EPA MRID No.: 00152158, acc.256667 Date: 1982-10-21 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /13	[redacted]	1986	Oral embryotoxicity study in Himalayan rabbits (supplement to report No. 667/82 Hoe 33171 active ingredient, technical grade Code: Hoe 33171 0H AT204 [redacted] Report No.: A32692, Edition Number: M-112250-01-1 EPA MRID No.: 00159940, acc.263034 Date: 1986-01-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.6.2 /14	[redacted]	1989	Oral embryotoxicity study in Himalayan rabbits (supplement 2 to report No. 667/82 Historical control data for diaphragmatic hernia in fetusesof Hoe 33171 active ingredient, technical grade Code: Hoe 33171 0H AT204 [redacted] Report No.: A41707, Edition Number: M-124789-01-1 Date: 1989-08-07 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /15	[redacted]	1983	Embryotoxicity in Himalayan rabbits following oral administration Hoe 033171 active ingredient technical Code: 033171 0H ZC96 0002 [redacted] Report No.: A29690, Edition Number: M-102288-01-1 EPA MRID No.: 00152159, acc.256667 Date: 1983-09-29 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /16	[redacted]	1986	Embryotoxicity in Himalayan rabbits following oral administration (supplement to report No. 83.0516 Hoe 033171 active ingredient technical Code: 033171 0H ZC96 0002 [redacted] Report No.: A32695, Edition Number: M-112260-01-1 EPA MRID No.: 00159922, acc.263034 Date: 1986-01-14 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.6.2 /17	[redacted]	1983	Effect on pregnancy of the mouse of the active ingredient Hoe 033171 technical Code: Hoe 033171 0H ZC96 0002 [redacted] Report No.: A30282, Edition Number: M-106138-01-1 EPA MRID No.: 00152155, acc.256763 Date: 1983-12-14 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.6.2 /19	[redacted]	1984	Oral embryotoxicity study in the Cynomolgus monkey Hoe 033171 technical grade Code: Hoe 033171 0H ZC96 0002 [redacted] Report No.: A38394, Edition Number: M-120039-01-1 Date: 1984-11-12 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.7.2 /01	[redacted]	1993	"Neurotoxic potential- 5.7 ""Neurotoxicity studies"" registration document according to Council Directive 91/414/EEC (statement) Hoe 046360 substance, technical " [redacted] Report No.: A50069, Edition Number: M-131108-01-1 Date: 1993-03-30 GLP/GEP: n.a., unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.8.1 /01	[redacted]	1985	6-Chlorobenzoxazolone: 13 week oral (dietary administration) toxicity study in the rat with a 28 day treatment-free period. [redacted] Report No.: R012455, Report includes Trial Nos.: 4229-198/14 Edition Number: M-186025-01-1 Date: 1985-03-01 GLP/GEP: no, unpublished	Y	N		Bayer CropScience	Submitted for the purpose of Renewal
KCA 5.8.2 /02	[redacted]	1987	13-week dietary toxicity study in rats determinations of mixed function oxidase, catalase and glutathione in liver Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36954, Edition Number: M-118723-01-1 Date: 1986-07-22 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)

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KCA 5.8.2 /04	[redacted]	1987d	13-week dietary toxicity study in mice determinations of mixed function oxidase, catalase and glutathione in liver Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36960, Edition Number: M-118729-01-1 Date: 1986-07-01 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.8.2 /06	[redacted]	1987d	13-week dietary toxicity study in dogs determinations of cytochrome P-450 N-demethylase and glutathione in liver Hoe 046360 technical Code: Hoe 046360 0H ZC96 0002 [redacted] Report No.: A36959, Edition Number: M-118728-01-1 Date: 1986-07-09 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.8.2 /07	[redacted]	1996	13-week oral toxicity (feeding) study in the rat Influence on the coadministration of Hoe 107892 on the toxicological profile of Hoe 046360 with Hoe 046360 + Hoe 107892 (2:1) Code: Hoe 046360 00 ZC97 0002 + Code: Hoe 107892 00 ZC97 000 [redacted] Report No.: A57200, Edition Number: M-140945-01-1 Date: 1996-07-31 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.8.2 /11	[redacted]	2011	Fenoxaprop-P-ethyl - 28-day immunotoxicity study in the female rat by dietary administration [redacted] TF- BCS-CHA, Report No.: SA 10132, Edition Number: M-404362-01-1 EPA MRID No.: 48445201 Date: 2011-03-28 GLP/GEP: yes, unpublished	Y	Y	New GLP study to support the registration in the USA	TF- BCS-CHA	Submitted for the purpose of Renewal

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KCA 5.9.1 /01	Kaleja, R.	1997	Medical data. Medical surveillance of manufacturing plant personnel. Proposed first aid measures Fenoxa-prop-P-ethyl Code: AE F04360 [redacted] Bayer CropScience, Report No.: A58432, Edition Number: M-142114-01-1 Date: 1997-03-03 GLP/GEP: n.a., unpublished	N	N		Bayer CropScience	Yes, in DAR (2007)
KCA 5.9.1 /02	Steffens, W.	2016	Summary of medical data known for Fenoxaprop-P-ethyl. Bayer CropScience, Report No.: M-552833-01-1, Edition Number: M-552833-01-1 Date: 2016-04-18 GLP/GEP: n.a., unpublished	N	N		Bayer CropScience	Submitted for the purpose of Renewal
KCA 5.9.1 /03	Caiming	2016	Summary of medical data known for Fenoxaprop-P-ethyl provided to Bayer CropScience AG [redacted] Bayer CropScience, Report No.: M-553684-01-1, Edition Number: M-553684-01-1 Date: 2016-04-27 GLP/GEP: n.a., unpublished	N	N		Bayer CropScience	Submitted for the purpose of Renewal
KCA 5.9.1 /01	Dong, F.	2016	Medical Surveillance of Manufacturing Personnel. Fenoxaprop-P-ethyl Technical Material [redacted] Cheminova Report No.: CHA Doc. No. 579 FPE Date: 2016-05-05 GLP/GEP: n.a., unpublished	N	N		Cheminova	Submitted for the purpose of Renewal
	Bomann W.	2017	Fenoxaprop-P-ethyl, AE F046360 – Response to a request of the RMS Austria within the EU-re-approval process Crop Science Division, Bayer S.A.S., Francee Date: 2017-10-09 GLP/GEP: n.a., unpublished	N	N		Bayer CropScience Cheminova	Submitted on request of RMS for the purpose of Renewal