4/24/84 00-1099 TR-3792

Rev. 4/14/82 Toxicology Branch/HED Review

Caswell No(s).: 431 C

To: Mountfort 003792

Registration No(s).:

Pesticide Petition No(s).: 8340-EUP-1, 4G3035

Chemical(s): Fenoxaprop-ethyl

Requested Action(s): EUP on rice and Temporary tolerance in rice of 0.020 ppm.

Recommendation: Request is toxicologically supported. Concerning registration see comments below.

Inert(s) cleared 180.1001: Non-phytotoxic carboxylic acids

% of ADI occupied: Existing: 5.74 Resulting: 7.12

Resulting % increase in TMRC: 0.0002

Data considered in setting the ADI: 3-month dog oral NOEL: 2.5mg/kg/day

Attached (?): ADI printout: YES/NO; TOX "one-liner": YES/NO; DER: YES/NO

Existing regulatory actions against registration:

RPAR status:

New Data: See attached reviews.

Data gaps & Comments: See attached excerpts from previous fenoxaprop-ethyl actions.

Comments:

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Reviewer: W Thomas Edwards 4-24-84 Date: 1/25

Section Head: William H. Dutton 4/25/84 Branch Chief:

File last updated 4/19/84

003792

ACCEPTABLE DAILY INTAKE DATA

	DOG mg/kg	NOEL ppm	S.F.	RADI mg/kg/day	MPI mg/day(60kg)
	0.400	16.00	2000	0.0002	0.0120

Unpublished,Tox Approved 362940

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	0.050	0.92	0.00069

MPI	TMRC	% ADI
0.0120 mg/day(60kg)	0.0007 mg/day(1.5kg)	5.74

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Current Action 433035

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Rice(137)	0.020	0.55	0.00017

MPI	TMRC	% ADI
0.0120 mg/day(60kg)	0.0005 mg/day(1.5kg)	7.12

****

DRAFT

0[illegible]92

[illegible]
DATA [illegible]

[illegible] Type: [illegible]

[illegible] Number: [illegible]

[illegible]: [illegible]

[illegible]: Hoechst Aktiengesellschaft, report No. 83.0484

Cont[illegible]ing Lab:

Data: 9-16-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy) -propanoate, Fenoxaprop-ethyl, Whip 0.75 EC, 9.8 % a.i (Hoe 033171 OH EC10 A710)

Protocol:

Dose levels and animals per group are shown in the lethality table in the results section.

"The emulsifiable concentrate was diluted in water and administered to fasted animals by gavage. After treatment, the course of intoxication, the lethality rate and the times of death were recored. During the 14-day observation period the animals were weighed weekly. Lethally intoxicated animals were dissected and the macroscopic findings recorded. At the end of the observation period the surviving animals were killed by carbon dioxide asphyxiation, dissected and examined for macroscopically visible changes."

"The LD50, the 95 % limts of confidence and the equation of the probit lines were established on the basis of the death rates by probit analysis (according to the method of LINDER and WEBER); confidence limits were calculated by the method of FIELLER or SIDAK (program supplied by the Department Praktische Mathematik of HOECHST AG). LD50 values are calculated for male and female animals separately."

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Dose in mg/kg bw.			Number of dead animals	
			males	females
2000	25	[illegible]	3	0/5
2120	25	[illegible]	-	0/5
2200	25	8.8	-	3/5
2240	25	8.96	-	3/5
2500	25	10.0	1/5	-
2800	25	11.2	-	5/5
3150	25	12.6	4/5	5/5

The lethally intoxicated animals died between 2 hours and 3 days after administration.

The following median lethal doses (LD 50) were calculated:

Males

LD 50	:	2810 mg/kg bw.
Limits of confidence P = 0.05	:	2410 and 3270 mg/kg bw.
Equation of probit lines	:	y = 25.1x - 81.6

Females

LD 50	:	2260 mg/kg bw
Limits of confidence P = 0.05	:	2120 and 2580 mg/kg bw.
Equation of probit lines	:	y = 25.1x - 79.3

Clinical signs of intoxication

"During the first few minutes after adminstration all animals treated with the test substance showed hypoactivity, followed by contracted abdomen and flanks together with uncoordinated and staggering gait. About 30 minutes after administration the animals had abdominal and lateral position, mydriasis and pilo-erection. After 2 -4 hours there was an inhibition of the corneal, placing and paw-pinch reflexes; in a number of animals the placing reflex was no longer obtainable.

After 2 - 4 hours the animals showed increased lacrimation, hyperaemia, decreased respiratory rate and jerk breathing. In a number of animals, wheezing respiratory sounds were heard. Some of the animals in the higher dose groups were in a state of stupor. Lethally intoxicated animals died between 2 hours and 3 days after administration. On day 1 after administration, squatting postion, high-legged posture, piloerection, contracted abdomen and flanks, jerky breathing, blood-encrusted eyelid margins, staggering gait and splaying of extremities were observed in some of the animals. The animals were in poor general condition. In the surviving animals, general health conditions subsequently improved. 3 days after administration almost all surviving animals were free of clinical signs of intoxication. There was no decrease in bodyweight gains."

Autopsy findings

"Macroscopic examination of the male and female animals which died during the study showed the following abnormalites: Lungs discoloured greyish-red to greyish, bleeding from the nose, and urinary bladder taut with clear, light-yellow urine. Remnants of the test substance were found in the gastro-intestinal tract. Also, in some animals the lungs were congested, the liver partly lighter in colour (up to ochre) and with accentuated markings, the kidneys were speckled light-brown, the adrenals discoloured dark-brown, the small intestine partly of glassy appearance and with yellowish mucus, sometimes filled with clotted blood. The animals killed at the end of the observation period were free of macroscopically visible changes."

Conclusions:

Acute oral LD50 (males):2810 (2410-3270) mg/kg
Acute oral LD50 (female):2260 (2120-2580) mg/kg

Acute oral toxicity Catergory: III

Core Classification:

Minimum

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute dermal toxicity, rat

Accession Number: 072309 (2)

MRID Number:

Sponsor: Hoechst Aktiengesellschaft, report No. 83.0459

Contracting Lab:

Data: 8-24-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy) -propanoate, Fenoxaprop-ethyl, Whip 0.75 EC, 9.8 % a.i (Hoe 033171 OH EC10 A710)

Protocol:

Dose level and animals used are shown in the lethality table in the results section.

"24 hours before dermal treatment the hair was mechanically removed from the dorsal skin of the test animals over an area of about 30 cm^2. The undiluted test substance Hoe 033171 OH EC10 A710 was applied as uniformly as possible once over the shaved, intact dorsal skin. The treated skin area was covered with an aluminium foil (6 x 8 cm) and fixed with an elastic plaster bandage fixed around the animal's body (Elastoplast^R, 8 cm width). After a dermal exposure period of 24 hours the bandage was removed and the treated skin area washed with warm water to remove any remaining test substance. After dermal application, the course of intoxication and the lethality rate were recored. During the 14-day observation period the animals were weighed weekly. At the end of the observation period the animals were killed by carbon dioxide asphyxiation, dissected and examined for macroscopically visible changes."

Results:

Lethality and LD 50

"Under the test conditions described above, the following lethality was recorded:

Dose in mg/kg bw.	Concentration in % (w/v)	volume applied in ml/kg bw.	Lethality males	females
2000	undiluted	2.08	0 / 5	0 / 5

Following application of 2000 mg/kg bodyweight no deaths occurred among either males or females during the 14-day observation period. Based on the present acute dermal toxicity testing of [illegible] OH EC10 A710 in Wistar rats, the median lethal dose (LD 50) for both male and female animals is greater than 2000 mg/kg bodyweight."

Clinical signs of intoxication

"Immediately after application of the occlusive bandage, the animals showed increased motor activity for several minutes. Throughout the observation period no clinical signs of intoxication were observed. Application of the undiluted [illegible] concentrate were tolerated without signs of irritation of the treated skin areas. When the bandages were removed at the end of the 24-hour exposure period, no unresorbed remnants of substance could be detected on the skin.

The females showed inhibited bodyweight gains."

Autopsy Findings

"The animals killed at the end of the observation period showed no macroscopically visible changes."

Conclusions:

Acute dermal LD 50 (males): more than 2000 mg/kg
Acute dermal LD 50 (females): more than 2000 mg/kg

Acute dermal toxicity Category: III

Core Classification:

Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Aerosal inhalation Toxicity, rat

Accession Number: 072309 (3)

MIRD Number:

Sponsor: Hoechst Aktiengesellschaft, report No. 83.0600

Contracting Lab:

Date: 11-14-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy) -propanoate, Fenoxaprop-ethyl, Whip 0.75 EC, 9.8 % a.i (Hoe 033171 0H EC10 A710)

Procedure:

"The rats were placed individually in cylindrical plastic tubes and exposed to specified aerosol concentrations for 4 hours. The plastic tubes leading into the exposure cylinder are so arranged that only the noses of the animals are inside the cylinder. The inhalation chamber itself consists of a stainless-steel and glass cylinder with a volume of 60 l, standing in a vent pipe with a volume of ca. $4m^3$. Particles of test substance ecaping from the exposure chamber into the vent pipe are drawn off and neutralized by gas-cleaning equipment. After passing through an oil separation filter and an absolute filter, air is pumped at a pressure of 4 bar into a special nozzle with a welded-in supply pipe for the test substance. The air supply at the nozzle is maintained at 800 l/h by means of an air-calibrated rotameter. Hoe 033171 0H EC10 A710 was injected into nozzle at a constant speed by means of a continuous infusion apparatus. The primary aerosol formation took place in a 10-litre four-necked round-bottomed flask. Smaller aeosol particles (secondary aerosol) entered the inhalation chamber through a rising tube. A suction device at the bottom of the inhalation chamber drew off the aerosol at rate of 1100 l/h through a cotton-wool filter and 10% aqueous sodium hydroxide. The difference between the introduction of air through the nozzle at 800 l/h and its extraction at 1100 l/h ensures the necessary slight negative pressure in the inhalation chamber. Additional extraneous air was drawn in through the animal tubes."

"During the exposures the behaviour of the animals was carefully observed and recorded. After the exposures the animals were kept under observation for a further 14 days and weighed on days 2, 3, 4, 7 and 14 after inhalation; behaviour checks were also carrid out. Lethally intoxicated animals were dissected and examined macroscopically. At the end of the observation period the surviving test animals were killed by carbon dioxide asphyxiation, dissected and examined macroscopically. During the exposures CO, CO_2, O_2, atmospheric humidity and temperature in the exposure chamber were measured continuously by means of air-monitoring equipment manufactured by Hartmann & Braun. Determination of the aerosol particle size distribution was performed with the Model 225 Particle Counting System manufactured by Kratel GmbH, Gerlingen 2, Stuttgart."

Results:

Lethality and LC 50

"Under the present test conditions the following lethality rates were recored:

Actual cons. in exp. chamber in mg Hoe 033171 OH EC10 A710 / l air	Lethality Males	females	Total
2.49	0/5	0/5	0/10
4.29	0/5	0/5	0/10
6.12	0/5	1/5	0/10
7.14	4/5	3/5	7/10
Blank formulation (Hoe 033171 OH EC00 A301)			
45 ml/h	3/5	3/5	6/10

Lethally intoxicated animals died between 4 hours and day 3 after inhalation. Exposure to the blank formulation resulted in a similar death profile, indicating that the active ingredient is probably not the cause of death.

The following median lethal concentration (LD 50) was calculated

Male : Calculation of an LC 50 for the males was impossible owing to the lethality rate. The data indicate an LC 50 6.12 and 7.14 mg Hoe 033171 H0 EC10 A710 /1 air.

Females

LC 50 : 6.39 mg Hoe 033171 0H EC10 A710 /1 air

Equation of probit lines : y = 16.5 x - 8.87"

Particle size distribution in %

"Particle size	Concentration of Hoe 033171 0H EC10 A710 in mg/1 air			
	2,49	4,29	6,12	7,14
	Particle size distribution in %			
0,37 um - 0,49 um	16,2	17,7	19,2	16,5
0,5 um - 1,49 um	28,8	32,6	34,7	25,0
1,5 um - 2,01 um	17,6	16,0	16,7	16,8
2,02 um - 2,99 um	13,8	14,3	11,5	14,5
3,0 um - 3,99 um	6,4	6,8	6,8	7,8
4,0 um - 4,99 um	5,9	4,5	5,4	6,2
5,0 um - 5,99 um	3,7	3,0	2,6	4,3
> 6,0 um	7,6	5,1	3,1	8,9 "

These are respirable size particles.

Clinical signs of intoxication

"The following clinical signs of intoxication were observed:

Irregular, jerky breathing, reduced respiratory rate, gasping, noisy breathing (inspiratory medium rale) and whistling respiratory sounds, disequilibrium, crawling or cowering posture, abdominal position, blood-coloured encrustation around the nose, increased salivation, hyporeflexia, corneal opacity, sneezing and pilo-erection. A concentration- related decrease in body-weight gains was observed between days 3 and 14 after inhalation in both males and females."

Autopsy findings

"Autopsy of the animals which died during the study revealed lungs with dark-red foci, and dark-red lungs containing foamy-sanguineous fluid. Autopsy of the animals killed at the end of the study revealed no macroscopically conspicuous findings, except for one male with dark-red foci on the lung, and one female with a swollen gastro-intestinal tract."

Conclusions:

Acute 4 hours inhalation LC 50 (males):
more than 6.12 and less than 7.14 mg fenoxaprop, EC/l air

Acute 4 hours inhalation LC 50 (females):
6.89 mg/l air.

Acute inhalation Category: III

Core Classification:

Minimum

003792

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Primary dermal irritation, rabbit

Accession Number: 072309 (4)

MRID Number:

Sponsor: Hoechst Aktiengesellschaft, report No. 83.0449

Contracting Lab:

Date: 8-19-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy) -propanoate, Fenoxaprop-ethyl, Whip 0.75 EC, 9.8 % a.i (Hoe 033171 0H EC10 A710)

Procedure:

"About 24 hours before the start of the study the hair in the dorsal to lateral region of the body was removed with an electric clipper over an area of about 25 cm^2. Only animals with intact skin were used. At the start of the study 0.5 ml of the undiluted test substance Hoe 033171 0H EC10 A710 was applied to each of the 2.5 x 2.5 cm cellulose patches of surgical plaster (specially manufactured by Baiersdorf AG, Hamburg). The patches were fixed in place on the shaved skin areas and then covered over with a semi-occlusive bandage. The exposure period was 4 hours. After the exposure period any remnants of the test substance were carefully removed from the skin. A first evaluation took place 30 - 60 minutes after removal of the patches and further evaluations took place 24, 48 and 72 hours after removal. Since there were still skin findings after 72 hours, a further evaluation took place after 7 days. Erythema and oedema formation was evaluated numerically according to the technique" of Draize. All other toxicologically significant findings were recorded."

Results:

Slight irritation persisted 72 hours but not 7 days.

Conclusions:

Primary irritation Catergory: III

Core Classification:

Guideline

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003792

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Primary eye irritation, rabbits

Accession Number: 072309 (5)

MRID Number:

Sponsor: Hoechst Aktiengesellschaft, report No. 83.0115

Contracting Lab:

Date: 5-9-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy)-propanoate, Fenoxaprop-ethyl, Whip 0.75 EC, 9.8 % a.i (Hoe 033171 OH EC10 A710)

Protocol:

"About 24 hours before the start of the study the test eyes of all animals were examined under UV light for corneal lesions following instillation of one drop of a 0.01% fluorescein-soduim solution. Only animals without ocular findings were used for the study. 0.1 ml of the undiluted test substance Hoe 033171 OH EC10 A701 was applied once to the conjunctival sac of the left eye of each of the 9 rabbits. The untreated eye served in each case as a control. 1 minute after application of the test substance the treated eyes of 3 animals were washed out for 1 minute with physiological saline at a temperture of about 37°C. The treated eyes of the other 6 animals were washed out after 24 hours. The findings were evaluated in accordance with the grading scale set out in the EPA Guideline, and all toxicologically relevant finding were recored. The eyes were examined with a magnifying glass 1, 7, 24, 48 and 72 hours and 7, 14 and 21 days after application of the test substance. 24 and 72 hours after application of the test substance the eyes were also exmained under UV light for corneal lesions following administration of one drop of a 0.01% fluorescein-sodium solution."

Results:

In the eyes which were unwashed before 24 hours, "the corneal findings (opacity with vascularization) in 4 out of 6 animals were not completely reversible 21 days after application of the test substance. A moderate irritant effect also occurred in the eyes washed out 1 minute after application of Hoe 033171.0H EC10 A701." The corneal effects in these animals were reversed within 14 days.

Conclusion:

Primary eye irritation Category: I

Core Classification:

Guideline

003792

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Primary eye irritation, rabbit
(5% solution (w/v) in deionized water)

Accession Number: 072309 (6)

MRID Number:

Sponsor: Hoechst Aktiengesellschaft, report No. 83.0126

Contracting Lab:

Data: 3-25-83

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy)
-propanoate, Fenoxaprop-ethyl EC, Whip 0.75 EC,
(Hoe 033171 OH EC10 A710), 5% solution in
deionized water.

Protocol:

"About 24 hours before the start of the study the test eyes of all animals were examined under UV light for corneal lesions following instillation of one drop of a 0.0% fluorescein-sodium solution. Only animals without ocular findings were used for the study. 0.1 ml of the test substance, Hoe 033171 OH EC10 A70% (5%) was applied once to the conjunctival sac of the left eye of each of the 6 rabbits. The untreated eye served in each case as a control. The treated eyes of the 6 animals were washed out after 24 hours. The findings were evaluated in accordance with the grading scale set out in the EPA Guideline, and all toxicologically relevant findings were recored. The eyes were examined with a maginifying glass 1, 7, 24, 48 and 72 hours after application of the test substance, and the reversibility or irreversibility of the findings were taken into account. 24 and 72 hours after application of the test substance the eyes were also examined under UV light for corneal lesions following Administration of one drop of a 0.01% fluorescein-sodium solution."

Results:

"The treated eyes of rabbits yielded a maximum irritance index of 11 after 1 hour. The individual data at the scheduled observation intervals are given in Table 1. Findings occurred mainly in iris and conjuctivae. In the fluorescein test one animal showed a slight translucence of the cornea 24 hours after application, but this was no longer present 72 hours after application. 1 hour after application, 5 of the 6 animals showed diffuse redness of the conjunctivae.

In 4 of 6 the animals conjunctival chemosis was only slight, in 2 of the 6 animals more strongly pronounced (part... eversion of the lids). 1 hour after application, 5 of the 6 animals showed a slight to marked discharge. The observation period was 72 hours. During this period the signs of irritation had largely receded and are to be considered reversible."

"INDIVIDUAL DATA, TABLE 1

Time after appl.	Animal No.	Fluorescein area	Cornea opacity area	Iris	Conjunctiva redness	Conjunctiva chemosis	Conjunctiva discharge	Index
1 h	1		0	1	2	2	2	
	2		0	1	2	1	1	
	3		0	0	2	2	2	
	4		0	0	2	1	1	11
	5		0	1	1	1	1	
	6		0	0	2	1	0	
7 h	1		0	0	2	2	2	
	2		0	0	1	1	1	
	3		0	0	1	2	2	
	4		0	0	2	1	1	7
	5		0	0	1	1	0	
	6		0	0	1	1	0	
24 h	1	2 mm*	0	0	2	2	2	
	2	0	0	0	1	1	0	
	3	0	0	0	2	1	0	
	4	0	0	0	1	0	0	6
	5	0	0	0	2	0	0	
	6	0	0	0	2	1	1	
48 h	1		0	0	1	1	0	
	2		0	0	1	0	0	
	3		0	0	1	0	0	
	4		0	0	1	1	0	3
	5		0	0	1	0	0	
	6		0	0	1	0	0	
	1	0	0	0	1	0	0	
	2	0	0	0	1	0	0	
	3	0	0	0	1	0	0	
	4	0	0	0	0	0	0	1
	5	0	0	0	0	0	0	
	6	0	0	0	0	0	0	

Notes: * = punctiform"

[illegible]:

A moderate eye irritant

Primary eye irritation Category of 5% water solution: III

[illegible] Classification:

[illegible]

MAR 14 1984

Caswell No(s).: 431C 003792

To: Mountfort acc nos. 071786-071795 + 07185

Registration No(s).:

Pesticide Petition No(s).: (1) 8340-EUPT, (2) 3G2940

Chemical(s): Fenvalerate, Esfenvalerate

Requested Action(s): EUP and temporary tolerance for use on soybeans

Recommendation: Request is supported toxicologically.

Inert(s) cleared 180.1001: yes

% of ADI occupied: Existing: Non-chronic Resulting:

Resulting % increase in TMRC:

Data considered in setting the ADI:

Attached (?): ADI printout: ~~YES~~/NO; TOX "one-liner": ~~YES~~/NO; DER: ~~YES~~/NO

Existing regulatory actions against registration:

RPAR status:

New Data: See reviews attached.

Comments: See conclusions on 90 day rat study. Also see comments on mouse oncogenicity study, an acceptable chromosome aberration analysis in vivo or in vitro and a gene mutation in mammalian cells in culture will be needed for registration. See attached comments for metabolism.

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Reviewer: [illegible] Date: MAR 14 1984

003792

Comments on benfuracarb-ethyl metabolism studies.

The metabolism studies to support evaluation of this new chemical varied from EPA guideline procedures in several important respects. These studies are useful but more information is needed for registration.

Each study was performed at only one dose level. The dose levels for the two studies were different (about 2 mg/kg and 40 mg/kg) other suggestions are to be found in the attached current EPA guidelines.

Also it would be helpful to follow metabolite distribution storage (at peak) and distribution with the other ring tagged.

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TOXICOLOGY BRANCH DATA REVIEW

Study Type: 3-months feeding, rat

Accession Number: 071789 (A18)

MRID Number:

Sponsor: American Hoechst Corporation

Contracting Lab: Hoechst Aktiengesellschaft, report no. 695/81

Date: 12-4-81

Test Material: ethyl-2-(4-(6-chlorobenzoxazolyloxy)-phenoxy)-propanoate, 96%, Fenoxaprop-ethyl (Hoe 33171 OH AT204)

Protocol:

"Fenoxaprop-ethyl was administered to rats (30 males and 30 females per group) in the daily feed for 3 months at concentrations of 0, 20, 80 and 320 mg/kg diet/day (ppm). 10 male and 10 female animals per group were kept for a 4-week recovery period."

"Behavior and general state of health were assessed daily. Once a month the rats were examined for neurological disorders, cloudiness of ocular media, disorders in dental growth and changes of the oral mucosa."

"The body weight was recorded once a week."

"The food consumption was checked together with the body weight."

The water consumption was determined at 14-day intervals. The indicated values represent the 16-hour consumption.

"Haematological examinations were made prior to the beginning of the study at week 6 and 13 of the study."

The blood samples of 10 ♂ / 10 ♀ non-fasted rats were withdrawn from the retroorbital venus plexus.

The following parameters were examined:

[illegible]
[illegible]ytes
[illegible]
[illegible]ytes
[illegible]ties

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Leucocytes
Thrombocytes
Coagulation time
Differential blood count

*Examined only at the end of the study."

"Further parameters were calculated by data processing:

MCV = median cell volume
MCH = median corpuscular haemoglobin content
MCHC = median corpuscular haemoglobin concentration.

The Met-haemoglobin (1.11.) of 10 ♂ / 10 ♀ rats in test group 4 was determined at week 6 and 13 of the study."

"Serum analyses were made in 10 non-fasted rats per group and sex prior to the beginning of the study. The following parameters were determined:

Glucose
Urea-N
SGOT
SGPT
alkaline phosphatase"

"The following parameters were determined in 10 ♂/ 10 ♀ non-fasting rats at week 6 of the study (intermediate values):

Sodium
Potassium
Inorg. phosphorus
Uric acid
Total bilirubin
Glucose
Creatinine
Urea-N
Calcium
Chloride

"The following examination was made during week 6 of the study in 10 ♂ 10 ♀ rats.

SGOT
SGPT
Alk. phosphatase
Total protein
Total lipids
Cholesterol
LDS
Bilirubin direct
Electrophoresis

(Protein, α_1 -, α_2 -, α_3 -Globuline
β -, δ_1 -Globuline

"At week 13 of the study (final value) the above mentioned parameters were determined in the serum of 20 ♂ / 20 ♀ animals obtained from exsanguination."

"The remaining animals were examined accordingly after a 4-week follow-up period."

"After the animals were deprived of food and drinking water, their urine was collected overnight in diuresis cages. The urine of 10♂/10♀ animals per group was analyzed prior to the beginning of the study (initial value), at week 6 (intermediate value) and at week 13 of the study (final value)."

"The following parameters were determined:

Appearance
Color
Protein
Glucose
Haemoglobin
Bilirubin
pH-value
Sediment
Specific weight
Ketone bodies
Urobilinogen

"3 months after the beginning of the study 20♂ / 20♀ rats were killed 24 hours, the remaining animals 4 weeks after withdrawal of the test substance under Pentobarbital-sodium-anaesthesia (50 mg/kg i.p.) and exsanguinated after severing of the Vena cava cranialis."

"Integument, orifices, eyes and viscera were gross-examined on dissection. Findings deviating from normal were registered in the autopsy records."

"The following organs were removed, weighed and conserved in fixative:

Heart
Lungs
Liver
Kidneys
Spleen
Brain
Both testes/ovaries
Adrenals
Pituitary
Seminal vesicle
Thyroid"

"The remaining organs or parts of these organs were conserved without indication of weight:

Thymus
Salivary glands (Parotis and Mandibularis)
Trachea, oesophagus
Stomach (fundus and prepyloric region)
Intestine (duodenum, jejunum, ileum, coecum, colon, rectum)
Urinary bladder, prostate, epididymes, uterus
Pancreas
Abdominal aorta
Diaphragm
Eyes with optic nerves
Skeletal muscle
Marrow of the femur
Lumbar vertebra
Lymph nodes (Hilus and Iliacus)
Skin with mammary gland
Tumors (if any)
Spinal marrow with sciatic nerve.

"The organs or parts of organs removed on dissection were conserved in fixative and submitted to histological examination.

Results:

"All animals survived to the scheduled end of the study."

"The behavior of the rats was not influenced by the test-substance throughout the study.

Neurological disorders, cloudiness of ocular media, disorders in dental growth or changes of the oral mucosa, attributable to the oral administrtion of Hoe 33171 were not observed."

"The body weight gains were normal and not influenced by the test-substance."

"The food consumption showed no differences between treated and untreated animals."

"The relative water consumption of the male rats and the female animals in the 320 ppm group was slightly lower throughout the study than that of the untreated animals."

"The haematological examinations revealed no harmful influences of the test substance."

"The results of clinical chemistry indicate a substance-induced change in the lipid status manifesting itself in the serum cholesterol of the males (80 and 320 ppm group) and in the cholesterol (320 ppm group) and total lipid content (20, 80, 320 ppm) in the serum of the females."

A significant increase in alkaline phosphatase-values in the male rats (320 ppm-group) was observed.

"The urinalyses were not indicative of any adverse effect of the test-substance." Increased turbidity was seen in urine of high dose level.

"During the study the following relative organ weights were increased as compared to the values of the controls." Changes marked with an asterisk were statistically significant.

Organ	Sex	Percent increases of dosage groups 20	80	320
Liver	male	-0.15	0.10	15.5*
Kidney	male	0.69	1.73	10.7*
Thyroids	male	10.6	14.9	21.3*
Kidney	female	1.99	4.59	6.29*
Adrenals	female	10.1	15.2*	19.5*
Ovaries	female	15.0*	11.5	13.0

Changes appear to be dose related at all dosage levels in male kidneys and thyroids and in female kidneys and adrenals.

"No substance-induced macroscopic organ changes were seen. The changes - particularly in the kidneys - indicated under individual findings are considered spontaneous alterations and appear in treated and untreated rats."

"From the groups dosed with 20 and 80 ppm only the liver and the organs with macroscopic findings were examined histologically."

"The histological examinations revealed that the administration of the high dosage of 320 ppm in the daily feed produced moderate enlargement of the centrobular hepatocytes in the male rats. The cytoplasm of these cells was eosinophilic and finely granulated."

"The administration of 20 and 80 ppm produced no lesions in the livers of male and female rats."

"After the 4-week follow-up period all organ weights were inconspicious except for the significantly decreased weights of the liver of the female rats of the 80 ppm group and the males of the 20 ppm dosage group."

Concinsions:

Although the above apparent organ weight increases at the 20 ppm level are not confirmed statistically they indicate cause for concern. 20 ppm has been accepted as the NOEL for use to support the EUP, but a clearer NOEL is neeed from the 2-year study to support registration. The issues raised by the apparent effects should be addressed in the report on the two year study.

NOEL: 20 ppm

LEL: 80 ppm (relative organ weight changes)

Core Classification:

"Minimum"