2-13-86 EUP-1395 TXR-1166

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004963

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fenoxaprop-ethyl, WHIP, ACCLAIM, Hoe 033171

FROM: Thomas Edwards, Pharmacologist Thomas Edwards
Hazard Evaluation Division (TS-769) 2-13-86

TO: Richard Mountfort
Registration Division (TS-767)

THRU: Clint Skinner, Section Chief Clint Skinner 2-13-86
Review Section III

and

Theodore Farber, Chief
Toxicology Branch, HED (TS-769)

Chemical: Fenoxaprop-ethyl

Caswell No.:431C

EPA Registration Nos.:8340-EUP-7, 3G2940, 8340-EUP-8, 4G3035, 8340-EG, 8340-EE, 6F3316, 8340-RI.

Accession Nos.: 255848-255858, 256666-256667, 256763, 073961-073973, 258947-258972.

Requested Actions: Review data and comment on adequacy for EUP and for registration.

Comments:

Attached is a summary of status of submitted or needed testing studies. One-liners and DERs are also attached.

Conclusions

1. The acute studies for inhalation toxicity and eye irritation must be replaced.

2. The mutagenicity studies (Micronucleus, UDS) must be replaced.

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3. The two hepatic enzyme studies (rat and mouse) included assays made after one year only. The studies showed dosage related lipid effects. There are also indications in short term studies, including dermal and inhalation studies, that effects on lipid enzymes and other enzymes is considerably larger than shown by longer term studies. Clarification of the nature and extent of these effects is needed. It is suggested protocols be submitted to EPA for suggestion before studies are begun. Determinations of other blood and urine changes should be included. Also, as appropriate, histopathology should be performed.

4. The NOEL (15 mg/cu m) for repeated dose inhalation is equivocal. It is noted that histopathology was not conducted for the animals given 15mg/cu m or for recovery animals at any dosage level. Clarificationis needed additional pathology and study of lipid metabolism is need.

5. A NOEL was not demonstrated in the repeat dermal study. Also the data suggests that dermal absorption may be greater than gastrointestinal absorption.

6. The ADI based tentatively on dog NOEL of 3ppm (0.075 mg/kg/day) with a safety factor of 100 is ~~0.00075~~ 0.0008 mg/kg/day. Unpublished TOX. appears plus the current action ratio is 2.45% of the ADI. RR

7. A fetal NOEL was not determined in the 2- generation study (LDT, 5 ppm). Decreased survival and body weight of offsprings and significant changes in kidney and liver weights were found F2a and F2b litters. Decreased survival of offsprings were significant at all dosage levels but apparently not dose related. A new study must be submitted prior to issuance of permanent tolerances.

8. Consideration of need for repeating the mouse oncogenicity study is attached as a separate presentation.

In summary, it appears from the conclusions that the data received ~~perhaps~~ marginally justifies the issuance of an EUP, or an extension of a temporary exemption, but not a permanent tolerance or full registration.

The various data gaps need to be filled and equivocal findings clarified before further decisions can be made.

Free Standing Summary of Current Status of Submitted Studies useful for Registration of Fenoxyoxaprop-ethyl, Whip, Acclaim, Hoe C33171,Technical

Acute oral toxicity

LD 50 (rat):2357 mg/kg. Toxicity category, III. Core guideline.

Acute dermal toxicity

LD 50 (rabbit): >1000 mg/kg. Toxicity category, II. Core minimum. A category indicating less hazard might be justitied if a study using a higher exposure is submitted.

Acute inhalation toxicity

INVALID study only.

Eye irritation

INVALID study only.

Dermal sensitation.

Not sensitizing. Core minimum.

42-Day repeated dose inhalation toxicity, rat

NOEL: 15 mg/cu m. (provisionally accepted)
LEL: 75 mg/cu m. (Clinical changes found in both sexes and ketonuria in males indicate disturbances in lipid metabolism). Other studies may clarify concerns.

Repeated dose dermal toxicity,rat (30 days)

A NOEL was mot found. LEL was 2 mg/kg (LDT). Clinical changes were found in both sexes. ketonurea in males was found at all dosage levels. Sodium levels for high dosage males did not return to normal levels during the 4 weeks recovery period.

Ames test

Not mutagenic. Acceptable.

Chromasome Abberation

Not mutagenic. Acceptable.

Micronucleus test

Unacceptable. A replacement is required.

Unscheduled DNA synthesis

Unacceptable. A replacement is needed.

Hepatic enzyme assays in rat and mouse

Assays were only made after 12 months. Some indication of dose related lipid effects were found. Earlier assays are needed.

Chronic toxicity, rat (6-,12-,24-months)

NOEL: 30ppm. LEL:180ppm (decreased serun cholesterol especially in males).

Oncogenicity, rat (28-months)

Not oncogenic at 180 ppm (HDT).

Oncogenicity/chronic toxicity, mouse (24)

A MTD was not found at 40ppm (HDT). Toxicity LEL:more than 40 ppm. The study was not adequate for oncogenicity determination because a minimum effective dose was not found.

See attached statement of consideration of need for repeating this study because of no MTD.

Chronic toxicity, dog (2-years)

NOEL: 3 ppm. LEL: 15 ppm (reduced body weight).

Metabolic studies, rat

A 10 mg/kg single dose, labled in the chlorophenyl ring, was excreted rapidly. Biphasic. Greater storage was in fat. 98% was eliminated in 7 days from males. 100%, females.

Similar results were obtained when labeled dose followed 14 daily doses of unlabled material. 3 to 4% remained in tissue after 168 hours. Mostly in kidney, liver, blood, and fat. Other tissues contained less than 0.1 ppm.

When in a 24 months study 2 rats were sacrificed at 6, 12, 18, and 24 months,it was found that dose related increases were not sex related. Lack of increase with time suggested steady state metabolism.

These studies are acceptable.

Metabolism studies pregnant, rat, rabbit, and monkey

The radioactivity in fetus was small compared to other tissues.

Faster tissue absorption in rat than in mouse was found. There was slightly faster elimination in rat than in mouse. Monkey data was not comparable. Different dosing. Only one monkey (which was not killed) was used.
Acceptible supplimental.
These studies are acceptable.

Tissue residues

Dosage related residues were found. Accumulations with time or or sex related differences were not found.

Metabolism studies pregnant, rat, rabbit, and monkey

The radioactivity in fetus was small compared to other tissues.

Faster tissue absorption in rat than in mouse was found. There was slightly faster elimination in rat than in mouse. Monkey data was not comparable. Different dosing. Only one monkey (which was not killed) was used.
Acceptible supplimental.

2-Generation reproduction, rat

Maternal NOEL: 30 ppm. LEL: 180 ppm (increased liver and kidney weight; nephrocalcinosis)

Fetal NOEL: Not determined. LEL: 5 ppm (LDT) (decreased survival and body weight of offsprings and significant changes in kidney and liver weights for F2a and F2b litters.

Teratogenicity, rabbit

Maternal NOEL: 12.5 mg/kg. LEL: 50 mg/kg (decreased food consumption and weight gain).
Fetal NOEL: 50 mg/kg. LEL: 200 mg/kg (increased incidence of rib anomalies. decreased fetal weight).

Teratogenicity NOEL: 50 mg/kg. LEL: 200 mg/kg (diaphragmatic hernia).

The teratogenic margin of safety based the NOEL of 50 mg/kg/day for one serving of rice per day was calculated to be 740,000. One serving of soybean oil, 260,000. If it were assumed that 4 servings would be eaten per day, the MOS's would be 180,000 for rice and 66,000 for soybean oil.

Teratogenicity, rat

Maternal NOEL: 32 mg/kg. LEL: 100 mg/kg (reduced body weight increase).

Fetal NOEL: 32 mg/kg. LEL: 100 mg/kg (delayed ossification and slightly impaired growth).

Teratogenicity NOEL: more than 100 mg/kg (HDT).

The maternal LEL of 100 mg/kg appeared to be borderline but was accepted, both fetal and maternal effect (even though slight) were noted at 100 mg/kg.

Teratogenicity, monkey

Fetotoxicity and maternal toxicity LEL's: 10 mg/kg (LTD), the only dosage having an adequate number of survivors. No controlls were used. Teratogenicity was not adequately accertainable. Supplimental (not required).

Teratogenicity,dermal application, rabbit.

Teratogenicity, tetotoxity, and maternal toxicity NOEL: 1000 mg/kg (HDT). The amount of absorption was not determined.

Supplimental (not required).

Teratogenicity, dermal application, rat

Teratogenicity, fetotoxicity, and maternal toxicity NOEL: 1000 mg/kg (HDT). The amount of absorption was not determined.

Supplimentary (not required).

Consideration of the Need for repeating the Mouse Oncogenicity Study

Because no MTD was found, there is concern relating to the adequacy of the study. In compliance with a proposed branch policy, the following conciderations are offered.

There were no 90 day mouse feeding studies for determining an MTD.

A 32 day study mouse study reported increased absolute and relative liver weights at all dosages. Lesions in liver and kidney were found at 80 ppm the lowest dosage tested.

A 30 day mouse study study reported increased liver and kidney weight gains at 10 ppm.

There were two other rodent (rat) studies (24 and 28 months). The LEL was found to be 9 mg/kg/day whereas the HDT for mouse was 6 mg/kg/day. The rat LEL was 50% higher than the mouse HDT.

Only two types of acceptable mutation tests were available, the Ames test and a chromosome abberation test. These were negative, but other mutagenicity testing is required.

No structural analogue was shown by a search of CIS sources to be an oncogen.

Following are Margin of Safety calculations for diet exposure, which are usefull in Toxicology Branch consideration of the need for additional testing.

$$\text{MOS} = \frac{\text{NOEL (mg/kg/day)}}{\text{daily intake (mg/kg/day)}}$$

Residue in rice = 0.02
Single serving portion of rice = 202 gms.
Residue in soybean oil = 0.05
Single serving portion of soybean oil = 227.
HDT used as NOEL = 40 ppm = 6 mg/kg/day.

Daily intake of rice (asuming one serving per day).

$$\frac{202 \times 0.05}{1000 \times 60} = 0.00017 \text{ mg/kg/day for a 60 kg person.}$$

$$\text{MOS for rice} = \frac{6}{0.00017} \quad 35{,}000$$

Daily intake of soybean oil (assuming one serving per day).

$$\frac{227 \times 0.05}{1000 \times 60} = .000189 \text{ mg/kg/day for a 60 kg person.}$$

$$\text{MOS for soybean oil} = \frac{6}{0.000189} = 31{,}000$$

If it were assumed that a person would eat 4 servings each day instead of one, the calculated margin of safety would be 8,700 instead ot 35,000 for rice and 7,900 instead of 31,000 for soybeans.

Although concern remains regarding the adequacy of the oncogenicity testing in mouse because of lack of MTD, the above calculations suggest that the margin of safety for dietary exposure is large.

Calculations of ap licator exposure have been requested but not yet received.

A final determination regarding the requirement for an additional mouse oncogenicity study needs tc be defer-ed until additional mutagenicity data and applicator exposure studies are reviewed.

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File last updated: 4/5/95

DRAFT

mg/kg			mg/kg/day	mg/day(60kg)	
0.075	3.00	100	0.0009	0.0450	

VDEL change not recorded ss

Unpublished, Tox approved 372940,433035

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(140)	0.50	0.92	0.00034
Rice(137)	0.20	0.55	0.00017

TPI	TMRC	% ADI
0.0450 mg/day(60kg)	0.0009 mg/day(1.5kg)	1.50

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Current Action 372940,433035 [Rev Sec 7]

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(140)	0.030	0.92	0.00050
Rice(137)	0.030	0.55	0.00025

TPI	TMRC	% ADI
0.0450 mg/day(60kg)	0.0011 mg/day(1.5kg)	2.5

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Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology oral - rabbit; Two studies combined Hoechst No. A245756, 11-21-82 and Hoechst No. G2K0400, 9-29-83. Each alone was supplimental.	Fenoxaprop-ethyl, Technical (WHIP)	256667	Fetotoxicity NOEL: 50 mg/kg. LEL: 200 mg.kg (increased incidence of rib anomalies). Maternal NOEL: 12.5 mg/kg. LEL: 50 mg/kg (decreased weight gain and food consumption). Teratogenicity NOEL: 50 mg/kg. LEL: 200 mg/kg (diaphragmatic hernias).		Minimum
Teratogenicity, rat. Hoechst No.613/82 (A26170),10-4-82. and including consideration of the supplimental study, Huntington Research Centre, No. 223/89691, 11-12-83.	Technical	256666	Teratogenicity NOEL; >100 mg/kg (HDT). Fetotoxicity NOEL: 32 mg/kg. LEL: 100 mg/kg (slightly impaired growth and delayed ossification) Maternal NOEL: 32 mg/kg. LEL:100 mg/kg (reduced weight increase)		Minimum
Teratogenicity - monkey; Hazleton Laboratories, West Germany; #245-16916; November 12, 1984	Technical (96.2%)	256667	Fetotoxicity and maternal toxicity LEL's 10 mg/kg (LDT), the only dosage level having an adequate number of survivors. No controls were used. Teratogenicity not adequately accessible. 50 mg/kg was HDT.		Supplemental (not required)

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Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratogenicity (dermal application) - rabbit; Research and Consulting Co., AG, Switzerland, #028776; October 3, 1984	Technical (96.5%)	256667	Teratogenicity, fetotoxicity, and maternal toxicity NOEL: 1000 mg/kg (HDT). Determination of absorption was not included.		Supplemental (not required)
Teratogenicity (dermal application) - rat; Research and Consulting Co., AG, Switzerland; #028765; October 17, 1984	Technical (96.5%)	256667	Teratogenicity, fetotoxicity, and maternal toxicity NOEL: 1000 mg/kg (HDT). Determination of absorption was not included.		Supplimental (not required)
Teratogenicity - mouse; Huntingdon Research Centre; #221/222-R/83666; December 14, 1983	Technical (96.2%)	256763	No effects seen at 50 mg/kg (HDT). Other objections to completeness of study stated in review.		Supplemental (not required)
Metabolic study in pregnant monkey, rabbit, and rat; Hoechst Aktiengesellschaft; #A29711; October 1, 1984	Technical (last doses were 14 C radiolabeled also first dose in monkey)	256667	Faster tissue absorption was found in rats than in rabbits. Also rat eliminated slightly faster. The one monkey was not killed. Its data were not comparable because of difference in dosing.		Supplemental
Dermal sensitization - guinea pig; Hoechst Aktiengesellschaft; #24449 (573/82); September 24, 1982	Technical	071787	Not dermally sensitizing.		Minimum

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Unscheduled DNA synthesis, hela cells; Ricerche Biomediche "Antoine Marxer"; #A24582; October 10, 1982	Technical (94.0%)	255849	Cytotoxic dose response relationship was not demonstrated. Sensitivity of assay was comprised by presence of S-phase cells.		Unacceptable
Chromosome aberration, cultured human lymphocytes; Istituto DiRicerche Biomediche "Antoine Marxer" RBM; #A26227; December 23, 1982	Technical (94.0%)	255849	No clastogenic or mutagenic response (dosages 1 to 1000 ug/mL) with or without activation.		Acceptable
Micronucleus test - mice; Hoechst Aktiengesellschaft; #29691; November 26, 1984	Technical (93.0%)	255849	Clastogenic potential not determined because sampling intervals were insufficient for assessing the entire hematopoetic cycle.		Unacceptable

Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Repeated dose inhalation toxicity; Research and Consulting Co., AG; #028697 and #034233; October 1984	Technical (96.5%)	255851	NOEL: 15 mg/cu m (probably borderline). LEL: 75 mg/cu m (absolute and relative liver and kidney weight increases, clinical chemistry changes related to lipid metabolism, eye opacity. Testicular effects were seen at higher dosages. Concern is abetted by lack of histopathology data for the 75 mg/cu m recovery animals or for the 15 mg/cu m animals. This study is acceptable provided the above concerns are adequately clarified. It is possible that chronic feeding results will suffice.		Provisionally acceptable
Repeated dose dermal (30 days) toxicity - rat; Research and Consulting Co., AG; #A29704; October 2, 1984	Technical (96.5%)	255851	NOEL: < 20 mg/kg (LDT). LEL: 20 mg/kg (decreased total lipids and total cholesterol and also hetonurea in males at all treatment levels. Several clinical changes were seen in both sexes at 100 and 500 mg/kg dosage levels. Increased sodium levels did not return to normal during 4 weeks recovery.		Supplemental
1-year feeding - dog; Hoechst Aktiengesellschaft; #719; July 19, 1984	Technical (94.0%)	255852	No toxic effects at 75 ppm (HDT).		Minimum

Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
1-year feeding - dog; Hoechst Aktiengesellschaft; #719; July 19, 1984	Technical (94.0%)	255852	No toxic effects at 75 ppm (HDT).		Minimum
Hepatic enzyme levels, rat. Hoechst No. A29694. 9-24-84	Technical	255856	Assays were made after 12 months treatment only. Carnitine acetyltransferase and lactic dehydrogenase increases may have been dosage related. These and aminopyrine N-demethylase were significantly increased at the highest level tested, 180 ppm. To draw conclusions, more assays including shorter treatment times would be needed. Dose levels were 0, 5, 30, and 180 ppm. 10 rats/sex/dosage level.		Supplimental
Hepatic enzyme levels, mouse. Hoechst Aktiengesellschaft; #A29696; October 11, 1984	Technical	255856	Because assays were made after 12 months only, the potential cannot be adequately assessed. Some enzymes appeared to be significantly elevated at all dosage levels. There was only 5 mice/sex/dosage level. Dosages were 0, 2.5, 10, and 40 ppm.		Supplimental

Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Generation reproduction rat. Life Sciences Research, Nos. A 30806 and A 31073. 5-13-85.	Fenoxaprop-ethyl, technical 94.0 %	258965-258970	Parental NOEL: 30 ppm (increased liver and kidney weights and increased incidences of nephrocalcinosis. LEL for progeny: 5 ppm (LDT), based on significant changes in kidney and liver weights for F2a and F2b litters at all dietary levels.		Minimum
Oncogenicity (28 months) / chronic toxicity (24 months), rat. Combined feeding studies. Hoechst, No. A 30807. 9-19-84. Hoechst, No. A 31880. 6-28-85.	Fenoxaprop-ethyl, technical 94 %	258948-258958 and 073961-073971	NOt oncogenic to rat at 180 ppm (HDT) Systemic NOEL: 30 ppm. LEL: 180 ppm (decreased serum lipids and cholesterol). Doses tested were 0, 5, 30 and 180 ppm.		Minimum
Oncogenicity, mouse. Hoechst, No. A 30816. 3-11-85.	Fenoxaprop-ethyl, technical, 94 %	258955-258965	A MTD was not found at 40 ppm (HDT). The study was not adequate for oncogenicity determination. A LEL was not found. See cover letter for comments on on need for repeat study.		Inadequate
Chronic toxicity, dog (2-years). Hoechst, No. 693.	Fenoxaprop-ethyl, technical, 94 %	073972-073973	NOEL: 3 ppm. LWEL: 15 ppm (reduced body weight).		Minimum

Tox Chem No. 431C Fenoxaprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism, rat (single oral dose) 10 mg/kg). Hoechst, No. A 30453. 11-30-84.	Fenoxaprop-ethyl, labeled in chlorophenyl ring.	258971	98 % was eliminated in 7 days from males. 100 % from females.		Acceptable
Metabolism, rat. Hoechst, No. A 30455. 12-4-84.	Fenoxaprop-ethyl, unlabeled and labeled 14 C in the chlorophenyl ring. Both 98 %.	258971	Results from 2 mg/kg single labeled dose alone was similar to that of 14 daily unlabeled doses followed by a single labeled 2 mg/kg dose. Residue was found mostly in kidney, liver, blood, and fat. Other Other tissues contained less than 0.1 ppm.		Acceptable
Metabolism, rat. (single dose. males 10 mg/kg. Females 2 or 10 mg/kg) Hoechst No. A 30377. 1-3-85	Fenoxaprop-ethyl, (1-14 C dioxaphenyl) 96 %	258971	Radiolabel was eliminated in urine and feces within 24 hours. Sex and dose related differences in metabolism were demonstrated. After dose of 10 mg/kg to males, 99 % of urine radioactivity was 2-(4-hydroxy-phenoxy)-propionic acid (HPP acid). After the same dose to females, the major metabolites were HPP acid and 2(4-(6-chloro-2-benzoxalyloxy)-phenoxy)-propionic acid, the free acid of fenoxaprop-ethyl.		Acceptable
Metabolism rat (single oral doses of 2 or 10 mg/kg. Also 15 daily doses of 2 mg/kg/day. Hoechst, No. 30490. 2-11-85	Fenoxaprop-ethyl, 14 C chlorophenyl labeled. 97 %	258971	Percentages of renal and fecal elimination were in the same order of magnitude for males and females but when rats were given 10 mg/kg, males eliminated 24 % in feces unchanged , females 6 %.		Acceptable

Tox Chem No. 431C Fenoxyprop-ethyl File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Tissue residues, rat Hoechst, No. A 30804. 2-26-85	Fenoxaprop-ethyl, technical 95.8 and 94 %	258955	Dosages were 0, 5, 30, and 180 ppm in diet. 2 rats per sex per dosage were analysed for tissue residue after 6, 12, 18, and 24 months. Dosage related residues were found Accumulations with time or sex related residues were not found.		Acceptable

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CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

EPA: 68-01-6561
TASK: 114
September 24, 1985

DATA EVALUATION RECORD

HOE 33171 OH AS201

Dermal Sensitization Study in Guinea Pigs

STUDY IDENTIFICATION: Jung and Weigand. Test for sensitizing properties of HOE 33171 OH AS201 in the guinea pig according to Buehler. (Unpublished study No. A24449 by and for Hoechst Pharma Research Toxicology, 6230 Frankfurt (M) 80, Postlach 800320, Federal Republic of Germany; dated September 24, 1982.) EPA Accession Numbers 071787 through 071795; Report No. 573/82.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 9-24-85

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1. CHEMICAL: HOE 33171 OH AS201, ethyl 2[4(6-chloro-2-benzoxazolyloxy-)-phenoxy-]-propanoate.

2. TEST MATERIAL: HOE 33171 OH AS201, in the form of a yellow powder.

3. STUDY/ACTION TYPE: Dermal sensitization study in guinea pigs.

4. STUDY IDENTIFICATION: Jung and Weigand. Test for sensitizing properties of HOE 33171 OH AS201 in the guinea pig according to Buehler. (Unpublished study No. A24449 by and for Hoechst Pharma Research Toxicology, 6230 Frankfurt (M) 80, Postiach 800320, Federal Republic of Germany; dated September 24, 1982.) EPA Accession Numbers 071787 through 071795; Report No. 573/82.

5. REVIEWED BY:

William Butler, M.S.
Principal Author
Dynamac Corporation
Signature: William Butler
Date: 9-24-85

Paul Wennerberg, D.V.M., M.S.
Independent Reviewer
Dynamac Corporation
Signature: James P. Blaut for PW
Date: September 24, 1985

6. APPROVED BY:

Finis L. Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation
Signature: Finis Cavender
Date: 9/24/85

W. T. Edwards
EPA Reviewer
Signature: W. Thomas Edwards
Date: 10-7-85

Clint Skinner, Ph.D.
EPA Section Head
Signature: Clint Skinner
Date: 10-24-85

7. SUMMARY:

The test substance, HOE 33171 OH AS201, a yellow powder, was dissolved in polyethylene glycol 400.

Ten female Pirbright white guinea pigs were used for the dermal sensitization test. The guinea pigs ranged in body weight from 247 g to 320 g. The flanks of the animals were shorn and exposed to three applications weekly of the 10 percent concentration of HOE 33171 in polyethylene glycol 400 for 3 weeks. Polyethylene glycol 400 was applied by patch to five guinea pigs as the control group. Each patch was removed after 6 of hours exposure, and dermal reactions were determined after 24 hours. Following the last treatment, the animals were held for 16 days. A first and a second challenge application of 0.5 ml of a 5 percent dilution was made at intervals 48 hours apart. Dermal reaction was observed at 6, 24, and 48 hours postapplication. Each of five control animals received 0.5 ml of the 5 percent dilution of test material in polyethylene glycol 400 at the time of challenge.

In the dermal sensitization test, the 10 percent concentration in polyethylene glycol 400 resulted in a slight to marked reddening of the treated flanks, which was transient. The vehicle control results varied from no reaction to isolated slight erythema.

The first or second challenge applications with 5 percent test material did not elicit an irritation response. The control groups were also free of any irritation when challenged with the 5 percent vehicle control.

Body weight gains of the animals were unaffected. At necropsy no adverse macroscopic findings were revealed.

The study authors concluded, that "HOE 33171 OH AS201 produced no indication of any allergenic effect in the dermal sensitization test."

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The design and conduct of the study were acceptable. The reporting would have been more complete with the inclusion of individual animal data sheets.

A quality assurance statement was included and dated, but unsigned.

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EPA: 68-02-4225
DYNAMAC No. 24G
November 27, 1985

DATA EVALUATION RECORD

HOE 033171 (WHIP)

Repeated Dose Dermal (30 Days) Study in Rats

OK

STUDY IDENTIFICATION: Ullman, L., Sacher, R., Luetkemeier, H., Chavalier, J., Terrier, C. H., and Sachsse, K. Subchronic (21 applications in 30 days) repeated dose dermal toxicity study in rats. (Unpublished study No. A29704 by Research and Consulting AG, Itingen, Switzerland, for Hoechst AG, Frankfurt/Main, West Germany; dated October 2, 1984.) Accession No. 255851.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-27-85

9. CLASSIFICATION:

Core Classification: Core minimum.

Toxicity Category: IV.

Sensitization Results: Not a dermal sensitizer.

1. CHEMICAL: HOE 033171 (Whip).

2. TEST MATERIAL: Technical grade HOE 033171, Lot HOE 033171 OH ZD96 0001, purity 96.5 percent. Vehicle: Sesame oil (Siegfried AG, Zofingen, Switzerland).

3. STUDY/ACTION TYPE: Repeated Dose Dermal (30 Days) Study in Rats.

4. STUDY IDENTIFICATION: Ullman, L., Sacher, R., Luetkemeier, H., Chavallier, J., Terrier, C. H., and Sachsse, K. Subchronic (21 applications in 30 days) repeated dose dermal toxicity study in rats. (Unpublished study No. A29704 by Research and Consulting AG, Itingen, Switzerland, for Hoechst AG, Frankfurt/Main, West Germany; dated October 2, 1984.) Accession No. 255851.

5. REVIEWED BY:

Robert J. Weir, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Robert J. Weir
Date: 11/27/85

Charles Rothwell, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Charles Rothwell
Date: 11-27-85

6. APPROVED BY:

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Subchronic Toxicology
Technical Quality Control
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Date: 11/27/85

W. T. Edwards
EPA Reviewer

Signature: W. Thomas Edwards
Date: 1-22-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 1-24-86

7. CONCLUSIONS:

A NOEL has not been demonstrated. The lowest dosage level produced effects in clinical chemistry parameters in male rats. These parameters included decreased total lipids and total cholesterol. Also, ketonuria was seen in the males at all doses, sodium levels were significantly increased in the high-dose males, and the sodium level did not return to normal after a 4-week recovery. In the females a 20 mg/kg NOEL was demonstrated. There was an increased relative liver weight at the mid-dose which was meaningful in that absolute and relative liver weights were seen at the high dose.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

A copy of the materials and methods section of the final report is included in Appendix A.

1. The test material used in this study was technical grade HOE 033171, lot No. HOE 033171 OH ZD96 001, with a purity of 96.5 percent. Sesame oil (Siegfried AG, Zofingen, Switzerland) was used as a vehicle.

2. The test animals used in this study were outbred, SPF Wistar rats purchased from Kleintierfarm Madcerin AG, Fuellinsdorf, Switzerland.

3. The dosing mixture was prepared daily in sesame oil. Doses of 20, 100, and 500 mg/kg were administered by applying evenly to the shaved skin 6 hours/day, 5 days/week, for 21 applications over a 30-day period. The vehicle control was sesame oil only. An occlusive dressing was used in all groups to prevent loss or ingestion. At the end of the 30-day dosing period, five animals of each sex from the two high-dose and control groups were monitored during a recovery phase of the study.

4. Univariate one-way analysis of variance and the Student's t-test were used to assess intergroup differences. Williams' test was used to determine the lowest dose group that was significantly different from the control. The difference of the overall mean of the dosed groups from the control group was tested for significance ("significance as a whole"). The median test was used to assess significance of intergroup differences. Fisher's exact test for 2 x 2 tables was used if variables could be dichotomized without information loss.

[1]Only items appropriate to this DER have been included.

B. Protocol:

No separate protocol was provided in the report.

12. REPORTED RESULTS:

A. No deaths nor topical and systemic signs of toxicity were observed during the dosing and recovery period. Starting on day 12 of the recovery period a palpable mass was found in the right flank of a female rat administered 100 mg/kg. No ophthalmologic alterations were observed.

B. Body weight gain (Table 1) was significantly ($p \leq 0.05$) reduced in high-dose male animals during weeks 2 to 4. No other differences in body weights were observed. Food consumption (Table 2) was significantly ($p \leq 0.05$) reduced in the high-dose male rats during weeks 1 to 4; however, female food consumption was not different from controls at any dosage level.

C. The hematologic data for test animals were not different from controls with regard to the parameters measured; however, those values (sporadically observed) with statistically significant differences were considered incidental and of normal biological variance. Data from clinical chemistry determinations on dosed animals (Table 3) differed from the control group as follows:

- Slight increase in glucose levels of males in the high-dose group.
- Decrease in total lipids and total cholesterol for males in the mid- and high-dose groups.
- Increase in triglycerides for females in the mid- and high-dose groups.
- Increase in alkaline phosphatase activity for high-dose males.
- Decrease in calcium and phosphorus levels for high-dose males.

No morphologic changes were associated with any of these changes, and they were reversible in the recovery period. Other values found to be statistically significant were considered incidental and to have resulted from normal biological variation. Urinalysis at 4 weeks revealed ketonuria in male rats of mid- and high-dose groups as the only adverse effect; however, this finding was reversed after 4 weeks of recovery.

TABLE 1. Body Weight (g) for Male Rats Dosed Topically with HOE 033171 for 4 Weeks. Body Weights are also Presented for a 4-Week Post-Dosage Period (Recovery)

Dosage Group (mg/kg)	Study Weeks: Treatment 1	2	3	4	Recovery 5	6	7	8	9
Vehicle control	282	298	315	322	349	371	389	402	406
20	268*	285	309	318	--	--	--	--	--
100	272	285	301	303	319	346	369	380	386
500	265*	281	292*	294	311*	336	355	367	369

* Significantly different from control by ANOVA followed by Duncan's test for multiple comparison ($p \leq 0.05$).

TABLE 2. Food Consumption (g) for Male Rats Dosed Topically with HOE 033171 for 4 Weeks. Food Consumption is also Reported for a 4-Week Post-Dosage Period

Dosed Group (mg/kg)	Study Weeks: Treatment 1	2	3	4	Recovery 5	6	7	8
Vehicle control	24.6	24.8	25.4	23.3	30.4	28.2	26.2	26.0
20	23.0	23.3	24.8	23.0	--	--	--	--
100	22.0*	22.6*	23.9	22.0	28.6	28.8	26.6	25.8
500	20.0*	22.6*	22.5*	20.6*	28.4	27.4	25.4	24.6

* Significantly different from control by ANOVA followed by Duncan's test for multiple comparison ($p \leq 0.05$).

TABLE 3. Clinical Chemistry Values for Male and Female Rats following 4 Weeks (21 doses) of Dermal Dosing with HOE 033171

Dosage Group (mg/kg)	Glucose (mmol/L)	Total Lipids (g/L)	Total Cholesterol (mmol/L)	Triglyceride (mmol/L)	ALAT[a] (SGPT) (ukat/L)	Phosphorus (mmol/L)	Ca (mmol/L)	K (mmol/L)	Na (mmol/L)	Alk.[a] Phos. (µkat/L)
					MALES					
Vehicle control	5.46	2.7	1.48	0.29	0.75	3.40	2.52	2.16	141.8	3.40
20	5.58	2.4*	1.24*	0.30	0.67	3.78	2.50	2.16	143.6**	3.78
100	5.87	1.9**	1.14**	0.30	0.59**	3.83	2.46*	1.99*	143.8**	3.83
500	6.27**	1.4**	1.01**	0.30	0.59**	4.61**	2.41**	1.87**	144.3**	4.61**
					FEMALES					
Vehicle control	5.26	2.8	1.81	0.24	0.54	1.45	2.54	1.55	142.0	1.45
20	5.12	2.9	2.05	0.25	0.56	1.50	2.56	1.78	142.6	1.50
100	5.31	2.4	1.64	0.30**	0.41**	1.56	2.52	1.59	143.8	1.56
500	5.47	2.6	1.34*	0.31**	0.52	1.53	2.54	1.63	143.1	1.53

[a] ALAT: alanine aminotransferase
SGPT: serum glutamate pyruvic transaminase
Alk. Phos.: alkaline phosphatase

* Significantly different from control value, $p \leq 0.05$.

** Significantly different from control value, $p \leq 0.01$.

D. Liver weights were significantly higher than control values in males of the high-dose group and females of the mid- and high-dose groups. Liver-to-body weight values were significantly higher in both sexes of the mid- and high-dose animals. Absolute and relative kidney weights were significantly higher in high-dose rats of both sexes.

E. No gross lesions were found in rats killed at the termination of dosing. Microscopic examination of the tissues indicated acanthosis and/or hyperkeratosis in one control and in three low-, one mid-, and one high-dose animal. Other occasional lesions of various organs were similar in type, incidence, and severity in all groups.

F. No chemical analysis for exposure validation was conducted for this study. Stability and homogeneity were not addressed by the laboratory; the sponsor had found the test material to be stable in the vehicle if mixed daily.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The NOEL for HOE 033171 in this subchronic dermal study is 20 mg/kg body weight. The LOEL is 100 mg/kg based on decreased total lipids, decreased cholesterol level, increased triglycerides, increased alkaline phosphatase activity, decreased calcium and phosphorus levels, and increased liver and kidney weights.

B. The conduct of the study was subjected to four inspections during the course of the study, and the report was audited by the quality assurance unit.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Dermal dosing of male and female rats with up to 500 mg/kg of HOE 033171 produced no mortality, topical or systemic effects, or changes in hematology. Using Duncan's test for multiple comparison, body weight (Table 1) interpretation differs from the authors' interpretation. At weeks 1, 3, and 5 the high-dose male body weights were significantly lower than controls ($p \leq 0.05$). The low-dose male body weights were also lower than controls in week 1. Food consumption (Table 2) was lower than controls in males at mid and high doses for weeks 1 and 2 and at high doses for weeks 3 and 4 only. Food consumption was lower in high-dose females at w 4 of treatment. Urinalysis at 4 weeks revealed ketonuria in male rats of all dose groups. Females were not affected. This finding was reversed after 4 weeks of recovery. Clinical chemistry values (Table 3) were significantly different than controls in a number of parameters; for example, increased glucose in high-dose males and decreased total lipids and total cholesterol for all three test compound doses in the

males. In the females there was no difference in the total lipids but total cholesterol was decreased at high doses. Triglycerides were increased in the females at mid- and high-doses but unchanged in the males. These alterations in lipid metabolism were reflected in the ketonuria in the male rats in all dose groups found in the 4-week urinalysis. Alanine aminotransferase (ALAT) was significantly decreased for males at mid- and high-doses but only the 100 mg/kg group was affected in the females. Lowered ALAT values, however, have little biological meaning. In high-dose males there was increased alkaline phosphatase activity. Calcium and phosphorus levels were decreased in the mid- and high-dose males, but there were no effects for these three clinical chemistry parameters in the females at all doses. Sodium values were significantly increased at all doses in the males, but the females were unaffected.

All effects except the calcium and sodium values for the high-dose males were reversed in the recovery study.

Liver and kidney weights were increased in high-dose males. In the females, liver weights were increased in high-dose females. Liver-to-body weight ratios were increased in the mid- and high-dose animals of both sexes; the kidney-to-body weight ratios were also increased in the high-dose groups of both sexes.

Microscopic examination of tissues revealed acanthosis and/or hyperkeratosis of equal incidence and severity in all dosage groups. No microscopic alteration was found that would account for the clinical chemical values cited above.

A NOEL has not been demonstrated for the test material, HOE 033171; all doses produced dose-related clinical chemical effects in male rats including significantly decreased total lipids and total cholesterol. Also, sodium levels were significantly increased in the high-dose males and these levels did not return to normal after a 4-week recovery.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 12-24.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 31 through 43 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-01-6561
TASK: 114
August 15, 1985

DATA EVALUATION RECORD

WHIP

Mutagenicity-Chromosome Aberration Assay in
Cultured Human Lymphocytes

OK

STUDY IDENTIFICATION: Mondino, A., Mellano, D., and Berruto, G. Study of the capacity of the test article HOE 33171 OH AS 201 to induce chromosome aberrations in human lymphocytes cultured in vitro. (Unpublished study No. A26227 prepared by Istituto Di Ricerche Biomediche "Antoine Marxer" RBM, Torino, Italy for Hoechst Aktiengesellschaft, Frankfurt am Main, Germany). Accession No. 255849.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 9-14-85

41

1. CHEMICAL: HOE 33171 (WHIP).

2. TEST MATERIAL: HOE 33171, batch No. OH AS 201, a brownish crystal, stable at 20°C and in DMSO, with a purity of 94 percent.

3. STUDY/ACTION TYPE: Mutagenicity-Chromosome Aberration Assay in Cultured Human Lymphocytes.

4. STUDY IDENTIFICATION: Mondino, A., Mellano, D., and Berruto, G. Study of the capacity of the test article HOE 33171 OH AS 201 to induce chromosome aberrations in human lymphocytes cultured in vitro. (Unpublished study No. A26227 prepared by Istituto Di Ricerche Biomedicne "Antoine Marxer" RBM, Torino, Italy for Hoechst Aktiengesellschaft, Frankfurt am Main, Germany). Accession No. 255849.

5. REVIEWED BY:

Brenda Worthy, M.T.
Principal Reviewer
Dynamac Corporation

Signature: Brenda Worthy
Date: August 14, 1985

Nancy McCarroll, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Nancy M. Carroll
Date: 8/14/85

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Genetic Toxicology
Technical Quality Control
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 8-14-85

W. Thomas Edwards, Ph.D.
EPA Reviewer

Signature: W. Thomas Edwards
Date: 10-7-85

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 10-21-85

7. CONCLUSIONS:

A. Under the conditions of the assay, HOE 33171 OH AS 201 did not induce a clastogenic/mutagenic response in human lymphocytes at doses ranging from 1 to 1000 µg/ml with or without S9 activation. However, the authors showed the test system was capable of detecting mutagenicity because the positive controls, Mitomycin C and cyclophosphamide, induced a significant increase in chromosome aberrations in human lymphocytes.

B. The study is acceptable.

8. RECOMMENDATION:

It is standard procedure that all slides should be coded and randomized before they are scored in order to prevent bias. This procedure is recommended by Evans and O'Riordan.[1]

Items 9 and 10 - see footnote 2.

11. MATERIALS AND METHODS (PROTOCOL):

A. Materials and Methods:

See Appendix A for details.

(1) The test material, HOE 33171 batch No. OH AS 201, was described as a brownish crystal, which is stable at 20°C in dimethylsulfoxide (DMSO), the solvent. The test material had a purity of 94 percent.

(2) Fresh heparinized blood was obtained from a healthy male volunteer who had not taken any drugs for 30 days prior to the start of study.

(3) The S9 fraction was prepared from the livers of adult male Sprague-Dawley rats injected ip with Aroclor 1254. The S9 homogenate was assayed for protein concentration and for its activation capacity in Salmonella typhimurium strains TA1538, TA98, and TA100 with the promutagen, 2-aminofluorene. The S9 mix was prepared according to the method of Ames et al.[3]

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[1] H. J. Evans and Maureen L. O'Riordan, "Human Peripheral Blood Lymphocytes for the Analysis of Chromosome Aberrations in Mutagen Tests," in Handbook of Mutagenicity Test Procedures, ed. B. J. Kilbey (New York: Elsevier/North Holland, Inc. 1979), p. 261-274.

[2] Only items appropriate to this DER have been included.

[3] B. N. Ames et al., "Methods for Detecting Carcinogens and Mutagens with Salmonella/Mammalian-Microsome Mutagenicity Test," Mutation Research 31 (1975): 347-364.

(4) The positive controls used in the assay were cyclophosphamide in the S9 activated system and Mitomycin C in the nonactivated system.

(5) Cytogenetic Assay:

Lymphocyte Preparation - Stimulation of lymphocytes was achieved by mixing heparinized human blood with culture medium containing the mitogen, phytohemagglutinine. The cultures were incubated for 48 hours at 37°C.

Exposure - Prepared cultures were incubated with 1, 10, 100, and 1000 µg/ml of the test material, positive controls or solvent control for three hours at 37°C with and without S9 activation. The cultures were centrifuged, and the pellets were resuspended in fresh culture medium and incubated for 23 hours; colchicine was added and the cultures were incubated for an additional three hours. Cells were recovered as pellets and suspended in 0.5 ml of a cold fixing mixture, placed onto slides, dried, and stained.

Slide Analysis - Two slides each per dose level of the test material, positive controls, or solvent control were prepared. Each was labeled with experiment number, number indicating the treatment/dose level, and an identification letter. At least 100 metaphases per dose level, positive controls or solvent control were photographed, and analyzed. Only those metaphases having well distributed and morphologically identifiable chromosomes were examined. Chromosome aberrations were analyzed according to the classification criteria of Evans and O'Riordan[1] and Killian et al.[5]

Statistical significance ($p \leq 0.05$) was assessed, using the chi-square method to compare the incidence of chromosome aberrations in the test material doses or the positive control to the solvent control.

12. REPORTED RESULTS:

The positive controls, cyclophosphamide and Mitomycin C (both at 34.5 µg/ml), caused statistically significant increases in the percentage of chromosome aberrations, either including or excluding gaps, with or without S9 activation (Table 1).

The test material, with S9 activation, was cytotoxic at 1000 µg/ml.

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[5] P. J. Killian et al., "A Collaborative Study to Measure Interlaboratory Variation with the In Vivo Bone Marrow Metaphase Procedure," Handbook of Mutagenicity Test Procedures, ed. B. J. Kilbey (New York: Elsevier/North Holland, Inc., 1979), p. 243-260.

TABLE 1. Representative Results of Chromosome Aberrations in Human Lymphocytes with HOE 33171 OH AS 201

Substance	Dose (µg/ml)	S9 Activation	No. of Metaphases Counted	Total Aberr. (%) Including Gaps	Total Aberr. (%) Excluding Gaps	Damaged Metaphases
Solvent Control						
DMSO		-	113	2(1.77)	1(0.88)	0
		+	125	0	0	0
Positive Controls						
Mitomycin C	34.5	-	83	19(22.9)*	14(16.9)*	4
Cyclophosphamide	34.5	+	59	10(169)*	8(13.6)*	0
Test Material						
HOE 33171	1	-	84	1(1.19)	1(1.19)	0
		+	79	1(1.27)	0	0
	1000	-	103	0	0	0
		+	16[a]	0	0	0

[a] Decreased metaphases indicate cytotoxicity.

* Significantly different from control value at $p < 0.001$.

The test material did not induce a significant increase in chromosome aberrations at any dose level with or without S9 activation; therefore, a linear regression was not calculated. Table 1 shows the results using the lowest and highest dose of test material; results for the positive and negative control are also presented.

13. STUDY AUTHORS' CONCLUSION/QUALITY ASSURANCE MEASURERS:

A. The authors concluded that "the results of this study show that the test article HOE 33171 OH AS 201 did not induce statistically significant increases in chromosome aberrations, in cultured 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 the concentration of 100 µg/ml."

B. A quality assurance statement was present, signed, and dated January 21, 1983.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

It is our assessment that HOE 33171 OH AS 201 did not induce a clastogenic/mutagenic response at the doses tested (1 to 1000 µg/ml) with or without S9 activation.

We concluded the test material was toxic at 1000 µg/ml dose with S9 activation as stated by the authors because of the decreased number of metaphases reported for this dose level, i.e., sixteen metaphases versus 125 metaphases for the solvent control (Table 1).

The positive controls, nonactivated Mitomycin C and S9 activated cyclophosphamide, both at 34.5 µg/ml, caused statistically ($p < 0.001$) significant increases in chromosome aberrations over the solvent control, demonstrating that the assay systems were appropriately sensitive to detect a clastogenic response (Table 1).

Item 15 - see footnote 2.

16. CBI APPENDIX:

Appendix A, Materials and Methods (Protocol), CBI pp. 3-9.

APPENDIX A

(Materials, Methods, and Protocol)

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 51 through 56 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
TASK: 024-L
November 22, 1985

DATA EVALUATION RECORD

WHIP

Determination of Hepatic Enzyme Levels

STUDY IDENTIFICATION: Donaubauer, H. H., Schütz, E., Kramer, M., and Beyhl, F. E. Carcinogenicity study with Hoe 33171 OHAS 201 in mice. Hepatic enzymes after 12 months. (Unpublished study No. A29696 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forchung Toxikologie, Frankfurt, West Germany; dated October 11, 1984.) Accession No. 255856.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-22-85

1. CHEMICAL: Hoe 33171; Whip.

2. TEST MATERIAL: Hoe 33171 OH AS 201, active ingredient, was used; no further description was reported.

3. STUDY/ACTION TYPE: Determination of hepatic enzyme levels.

4. STUDY IDENTIFICATION: Donaubauer, H. H., Schütz, E., Kramer, M., and Beyhl, F. E. Carcinogenicity study with Hoe 33171 OHAS 201 in mice. Hepatic enzymes after 12 months. (Unpublished study No. A29696 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forchung Toxikologie, Frankfurt, West Germany; dated October 11, 1984.) Accession No. 255856.

5. REVIEWED BY:

Brenda T. Worthy, M.T.
Principal Reviewer
Dynamac Corporation

Signature: Brenda T. Worthy for
Date: 11-22-85

Nicolas Hajjar, Ph.D.
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Date: Nov. 22, 1985

6. APPROVED BY:

William L. McLellan, Ph.D.
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Technical Quality Control
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Signature: Jim Cavender for
Date: 11/22/85

W. Thomas Edwards
EPA Reviewer

Signature: W Thomas Edwards
Date: 1-22-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 1-24-86

7. CONCLUSIONS:

A. Under the conditions of the assays, Hoe 33171 OH AS 201 did not cause lipid peroxidation in the livers of mice fed the test material at concentrations ranging from 2.5 to 40 ppm for 12 months. However, enzyme induction studies are normally conducted following repeated dosing over a short time span (1-2 weeks) since adaptation to the test material may occur. Therefore, additional determinations over the course of this study should have been performed to determine the enzyme induction potential of the test material.

B. The study provides supplementary information.

Items 8-10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Hoe 33171 OH AS 201, active ingredient, was used; no further description was reported. However, in report No. 83.0654, accession Nos. 255855-255856, the test material was indicated to be 94 percent pure.

2. Test Animals: Ten male and 10 female mice received diets containing the test material, Hoe 33171, at concentrations of 0 (control), 2.5, 10, or 40 ppm for 12 months. The animals were then sacrificed, and the livers were removed, frozen in liquid nitrogen, and then sent to the laboratory of Dr. Beyhl for hepatic enzyme determinations.

3. Enzyme Induction Assays:

a. Five livers/sex from each dose group were homogenized separately in isotonic potassium chloride. Aliquots of these raw homogenates were used to determine the enzyme activities of catalase and alkaline phosphatase. The remaining homogenates were centrifuged at 1300 x g and the supernatants were obtained and used to determine the enzyme levels of anisic acid ester O-demethylase, aminopyrine N-demethylase, and cytochrome c reductase (with $NADPH_2$). In addition, the activities of lactate dehydrogenase, glycerophosphate dehydrogenase, and malate enzyme were measured by the Warburg optic test.

b. From the five remaining livers of each dose group, the microsomes were extracted by the calcium chloride

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[1] Only items appropriate to this DER have been included.

precipitation method and used to measure the activity levels of ethoxycoumarin O-deethylase and glucuronyltransferase I and II and the extent of microsomal lipid peroxidation.

4. The reference methods used to determine the levels of various enzyme activities are in Appendix A.

5. The results were analyzed statistically by means of a computer program from the Standard Operating Procedure of the Department Praktische Mathematik.

B. Protocol: No protocol was submitted.

12. REPORTED RESULTS:

There was a statistically significant ($p < 0.05$) increase in cytochrome C reductase in male mice fed Hoe 33171 at the two highest dose levels (10 and 40 ppm) and in female mice at the highest dose level (40 ppm) (Table 1); the reasons for these increases were not clear.

A statistically significant increase in glucuronyltransferase I activity compared to control was observed in the male mice receiving 2.5 and 40.0 ppm, and glucuronyltransferase II activity was significantly increased in females at all dose levels. However, these increases were not dose related and were not considered relevant (Table 1).

The activity of lactate dehydrogenase was significantly increased in females at the lowest dose level and significantly decreased in males at all dose levels. However, these effects were not dose related and were not attributed to the test material.

There were no statistically significant changes in the activity of the other enzymes tested (aminopyrine N-demethylase, anisic acid ester O-demethylase, ethoxycoumarin O-deethylase, alkaline phosphatase, glycerophosphate dehydrogenase, or malate enzyme). There was no peroxisomal proliferation because the levels of catalase were not increased in dosed animals and there was no increase in lipid peroxidation in dosed animals compared to controls.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that "The results confirm that the test substance Hoe 33171, active ingredient, did not induce biosynthesis of enzymes of foreign substance metabolism, or cause peroxisomal proliferation, or produce any other effect on the general metabolism."

B. A quality assurance statement was not presented.

TABLE 1. Selected Results of Hepatic Enzyme Activity Determination of Mice Fed Hoe 33171 for 12 Months

Dose Group (ppm)	Cytochrome c Reductase (U/g liver)	Glucuronyl-transferase I (U/g liver)	Glucuronyl-transferase II (U/g liver)
Males			
Control	0.84 ± 0.13	0.182 ± 0.067	0.406 ± 0.112
2.5	3.28 ± 1.28	0.253 ± 0.037*	0.430 ± 0.083
10.0	3.99 ± 0.44*	0.230 ± 0.028	0.470 ± 0.056
40.0	4.29 ± 0.71*	0.221 ± 0.017*	0.473 ± 0.037
Females			
Control	4.65 ± 0.51	0.281 ± 0.023	0.429 ± 0.022
2.5	4.28 ± 0.58	0.296 ± 0.032	0.636 ± 0.040*
10.0	4.83 ± 0.25	0.289 ± 0.020	0.603 ± 0.067*
40.0	6.24 ± 1.02*	0.294 ± 0.007	0.613 ± 0.036*

*Significantly different from control value ($p < 0.05$).

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

It is our assessment based on the limited data presented that Hoe 33171 did not cause lipid peroxidation in the livers of mice fed diets containing 2.5, 10, or 40 ppm of the test material for 12 months. However, enzyme induction studies are usually performed at several intervals of time to determine if, following induction, there is an adaptation to the test material. Therefore, in this study the enzyme induction potential of the test material was not adequately tested and may have been missed due to adaptation.

The authors reported a significant ($p < 0.05$) increase in cytochrome c reductase in male mice at the highest dose levels. It also appears that the enzyme activity in the low-dose group may be elevated; however, we are not able to evaluate the significance of this result or validate those at the higher doses because individual data were not reported. Since the number of samples analyzed in each group was small ($n = 5$), the reliability of the statistical analysis to evaluate toxicologic importance is weak.

The authors also reported that glucuronyltransferase II was significantly increased in the female mice at all doses, whereas the male dose groups were comparable to their respective control. However, the standard deviation of the male control group was 1.3 to 3.3 times greater than the dose groups. Individual data are required to determine if it was due to an outlier value, which could have been censored in performing the statistical analysis. It was reported that glucuronyltransferase I was significantly increased in the males at the low and high doses, and it also appears increased in the mid-dose group; however, since no individual data were reported the significance of the results cannot be determined.

Another point of concern was the activity levels for cytochrome c reductase and glucuronyltransferase obtained for the male control group. The results seem somewhat lower than would be expected; however, no historical data were reported and no baseline studies were conducted.

Item 15--see footnote.1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3-4, 12-13.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 64 through 67 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
DYNAMAC No. 1-024-J
January 27, 1986

DATA EVALUATION RECORD

WHIP

Determination of Hepatic Enzyme Levels

STUDY IDENTIFICATION: Donaubauer, H. H., Schütz, E., Kramer, M., and Beyhl, F. E. Carcinogenicity study with Hoe 33171 OH AS 201 in rats. Hepatic enzymes after 12 months. (Unpublished study No. A29694 prepared and submitted by Hoechst Aktiengesellschaft, Pharma Forchung, Toxikologie, Frankfurt, West Germany; dated September 24, 1984.) Accession No. 255856.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

1. CHEMICAL: Whip; Hoe 33171.

2. TEST MATERIAL: Hoe 33171 OH AS 201 active ingredient was used; no further description was reported.

3. STUDY/ACTION TYPE: Determination of hepatic enzyme levels.

4. STUDY IDENTIFICATION: Donaubauer, H. H., Schütz, E., Kramer, M., and Beyhl, F. E. Carcinogenicity study with Hoe 33171 OH AS 201 in rats. Hepatic enzymes after 12 months. (Unpublished study No. A29694 prepared and submitted by Hoechst Aktiengesellschaft, Pharma Forchung, Toxikologie, Frankfurt, West Germany; dated September 24, 1984.) Accession No. 255856.

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7. CONCLUSIONS:

A. Due to the design of this study, a definitive conclusion regarding the potential of Hoe 33171 (administered in the diet at concentrations ranging from 5 to 180 ppm for 12 months) to induce hepatic enzymes of rats cannot be determined. Additional assays at several intervals over the course of this study should have been performed (particularly early in the study) to assess the enzyme induction potential of the test material.

There was no evidence to indicate that the test material caused peroxisome proliferation or that there was any damage to microsomal membranes.

B. The study is inconclusive.

8. RECOMMENDATIONS: The study should be repeated measuring enzyme induction earlier in the study.

Items 9 and 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Hoe 33171 OH AS 201 active ingredient was used; no further description was reported.

2. Test Animals: Ten male and 10 female rats received diets containing Hoe 33171 in concentrations of 0 (control), 5, 30, or 180 ppm for 12 months. The animals were then sacrificed, and their livers were removed and divided into three aliquots, frozen in liquid nitrogen, and sent to the laboratory for hepatic enzyme determinations.

3. Enzyme Induction Assays: The activities of the hepatic enzymes were determined to establish whether induction of foreign substance metabolism or peroxisomal proliferation had occurred. Carnitine acetyltransferase and catalase activities were used as indicators of peroxisome proliferation, and the other enzymes were used to assay effects on metabolic

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[1] Only items appropriate to this DER have been included.

processes. The three liver aliquots were processed as follows:

Aliquot 1: Livers from each animal were homogenized separately in isotonic potassium chloride. Aliquots of these raw homogenates were used to determine the enzyme activities of catalase and alkaline phosphatase. The remaining homogenates were centrifuged at 13,000 x g, and the supernatants were used to determine the enzyme activities of anisic acid ester O-demethylase, aminopyrine N-demethylase, cytochrome C reductase (with $NADPH_2$), lactate dehydrogenase, glycerophosphate dehydrogenase, and malate enzyme.

Aliquot 2: From these liver aliquots, microsomes were isolated, and the activity levels of ethoxycoumarin O-deethylase and glucuronyltransferase I and II and the extent of microsomal lipid peroxidation were measured.

Aliquot 3: These liver aliquots were used to determine carnitine acetyltransferase activity.

4. Referenced methods used to determine the various enzyme levels are presented in Appendix A.

5. The results were analyzed statistically by means of a computer program from the Standard Operating Procedure of the Department Praktische Mathematik.

B. Protocol: No protocol was submitted.

12. REPORTED RESULTS:

Of the enzymes assayed to determine induction of foreign substance metabolism, only aminopyrine N-demethylase activity was markedly increased in the females receiving 180 ppm; the activity in males receiving 180 ppm was slightly but significantly ($p \leq 0.05$) increased (Table 1). There were other statistical increases ($p \leq 0.05$) reported for dosed groups that were considered marginal and did not indicate an induction of foreign substance metabolism. Anisic acid ester O-demethylase activity was slightly increased in males receiving 5, 30, or 180 ppm and females receiving 180 ppm, and ethoxycoumarin O-deethylase was slightly increased in females receiving 30 ppm but not 180 ppm. There were some slight but significant decreases ($p \leq 0.05$) in inducible enzymes; cytochrome C reductase was slightly decreased compared to control in all dosed groups of males and females receiving 5 and 30 ppm, and ethoxycoumarin O-deethylase was slightly decreased compared to control in males receiving 30 or 180 ppm.

Catalase and carnitine acetyltransferase activities were measured to determine if there was peroxisomal proliferation. Catalase activity was not increased in dosed rats. Carnitine acetyltransferase was increased in both male and female rats receiving 180 ppm (Table 1). This could possibly indicate peroxisomal proliferation or enhancement

TABLE 1. Selected Results of Hepatic Enzyme Activity Determination in Rats Fed Hoe 33171 for 12 Months

Dose Group[a] (ppm)	Aminopyrine N-demethylase (U/g liver)	Carnitine acetyltransferase (E/g liver)	Lactate dehydrogenase (U/g liver)
Males			
Control	0.503±0.0732	0.00351±0.00166	277±49
5	0.539±0.034	0.00465±0.00208	313±62
30	0.533±0.059	0.00606±0.00152	333±56
180	0.597±0.051*	0.01888±0.00440*	400±54*
Females			
Control	0.0395±0.0192	0.00821±0.00184	147±35
5	0.0642±0.0345	0.00848±0.00196	160±28
30	0.0586±0.0224	0.01146±0.00240	157±12
180	0.0883±0.0232*	0.03309±0.00482*	205±55*

[a]Number = 10 rats/group.

*Statistically significant from control ($p < 0.05$).

of mitochondrial biosynthesis. The authors noted that this liver enzyme occurs also in the mitochondria at a high level of activity, and the increase following administration of the peroxisome proliferator, clofibrate, was attributed mainly to the increased biosynthesis of the mitochondrial enzyme. "In this process, mitochondrial proliferation occurs either not at all or only to a marginal extent. Thus it is perfectly possible to interpret the increase of carnitine acetyltransferase observed following administration of Hoe 33171 as resulting from an increase of mitochondrial enzyme, although this was not specifically investigated." The fact that there was no increase in malate enzyme activity in dosed rats was further evidence that no peroxisomal proliferation had taken place.

There was no increase of microsomal lipid peroxidation; therefore, it was considered unlikely that the test material caused any damage to the microsomal membrane. Furthermore, there was no increase in alkaline phosphatase activity.

Of the intermediate metabolism enzymes assayed, only lactate dehydrogenase was increased in both male and female rats at the high-dose level. The assay conducted to determine glucuronyltransferase I and II was successful in the females only; a repeat assay in the male rats was impossible (the authors did not report why a repeat assay could not be performed). Glucuronyltransferase II was increased in the high-dose females. The authors made no comments on the possible biological significance of this change.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that dietary administration of Hoe 33171 active ingredient to rats over a 12-month period at concentrations up to 180 mg/kg did not lead to induction of xenobiotic metabolism or to peroxisomal proliferation.

B. No quality assurance statement was presented.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

It is our assessment, based on the limited data presented, that the ability of Hoe 33171 to induce hepatic enzymes of rats fed diets containing 5, 30, or 180 ppm of the test material for 12 months was not adequately demonstrated; the authors only performed the enzyme determinations at one interval (12 months) of the study. To clearly determine the potential of the test material to induce the hepatic enzymes of rats, enzyme assays should have been performed earlier in the study (it is normally performed after 2 or 3 weeks of dosing).

The increases reported in carnitine acetyltransferase in both the male and female high-dose groups also appear to be dose related; however, because no individual data were reported this observation cannot be evaluated.

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It is our assessment that the test material probably did not induce peroxisome proliferation; adaptation does not normally occur in this process. Peroxisome proliferation is normally assayed by examination of electron micrographs of liver sections and quantitation of observed microbodies and mitochondria.[2] An increase in the ratio of microbodies (peroxisomes) to mitochondria indicates an effect. The use of marker enzymes is a less precise measure particularly since (as pointed out by the report authors) carnitine acetyltransferase activity can be increased by enhanced mitochondrial biosynthesis. The fact that no increase in catalase and no increase in peroxidation of lipids were noted in livers of dosed rats supports the authors' conclusions. Also, there was no increase in alkaline phosphatase, which would be expected if microsomal membranes were damaged directly or indirectly (lipid peroxidation) by the test compound.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3, 4, 12-14.

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[2] Moody, D. E., and J. K. Reddy, Hepatic peroxisome (microbody) proliferation in rats fed plasticizers and related compounds. Toxicol. Appl. Pharmacol. 45(1978): 497-504; and Reddy, J. K., J. R. Warren, M. K. Reddy, and N. D. Lalwani, Hepatic and renal effects of peroxisome proliferators: Biological implications. Ann. N.Y. Acta. Sci. 386(1982): 81-110.

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APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 76 through 80 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

EPA: 68-02-4225
DYNAMAC No. 1-128,G
January 27, 1986

004963

DATA EVALUATION RECORD

ACCLAIM

Oncogenicity/Chronic Toxicity Study in Rats

STUDY IDENTIFICATION: Donaubauer, Schutz, Weigard, and Kramer. Hoe 33171-active ingredient technical (code: Hoe 33171 OH AS201) chronic feeding study (24 months) in rats. (Unpublished study No. A30807 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated September 19, 1984.) Accession Nos. 258948-258954.

AND

Donaubauer, Schutz, Leist, and Kramer. Hoe 33171-active ingredient technical (code: Hoe 33171 OH AS201) combined chronic toxicity and carcinogenicity study (24 and 28 month feeding studies) in rats. (Unpublished study No. A31880 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated June 28, 1985.) Accession Nos. 073961-71.

APPROVED BY:

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Signature: I. Cecil Felkner

Date: 1-27-86

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1. CHEMICAL: Acclaim; Hoe 33171; Whip; fenoxaprop-ethyl; ethyl 2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propanoate.

2. TEST MATERIAL: Hoe 33171, active technical ingredient, was from batch Nos. 11123 and 11283 and codes Hoe 33171 OH AT 206 and Hoe 33171 OH AS 201, respectively. Purities for batch Nos. 11123 and 11283 were 95.8 and 94 percent, respectively.

3. STUDY/ACTION TYPE: Oncogenicity/chronic toxicity study in rats.

4. STUDY IDENTIFICATION: Donaubauer, Schutz, Weigard, and Kramer. Hoe 33171-active ingredient technical (code: Hoe 33171 OH AS201) chronic feeding study (24 months) in rats. (Unpublished study No. A30807 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated September 19, 1984.) Accession Nos. 258948-258954.

AND

Donaubauer, Schutz, Leist, and Kramer. Hoe 33171-active ingredient technical (code: Hoe 33171 OH AS201) combined chronic toxicity and carcinogenicity study (24 and 28 month feeding studies) in rats. (Unpublished study No. A31880 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated June 28, 1985.) Accession Nos. 073961-71.

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7. CONCLUSIONS:

Under the conditions of the studies, Hoe 33171 was not oncogenic when administered to Wistar rats for 24 or 28 months at dietary levels of 5, 30, or 180 ppm. There were no effects of dosing on survival, body weights, food consumption, hematology, or urinalysis. All clinical chemistry parameters were similar in dosed and control groups with the exception that there was a decrease in serum cholesterol and total lipids in high-dose males ($p \leq 0.05$) and high-dose females ($p > 0.05$). Kidney and liver functions were not affected nor did dosing cause any toxicologically important effects on organ weights or organ-to-body weight ratios. Gross and histopathologic findings were similar in dosed and control groups. Although rats may have tolerated a higher dose, the LOEL based on decreased serum lipids and cholesterol is 180 ppm and the NOEL is 30 ppm Hoe 33171.

Core Classification: The study is classified Core Minimum for oncogenicity and chronic toxicity; summary tables on histopathology did not indicate the numbers of tissues examined microscopically.

8. RECOMMENDATIONS: The summary tables on histopathologic findings should be amended to indicate the numbers of tissues examined microscopically.

9. BACKGROUND: Dose selection for this study was based on a 90-day feeding study in rats (Accession No. 071789) in which administration of Hoe 33171 at a dietary level of 320 ppm caused increased liver weights and serum alkaline phosphatase in males and a decrease in cholesterol and total serum lipids in both sexes.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

Although this is a combined chronic toxicity/oncogenicity study and 116 animals/sex/group were initiated at the same time, data were presented in several reports as is indicated below:

	Animals/ Sex/Group	Document No.	EPA Accession No.	Data Presented[a]
Chronic toxicity				
6-month interim sacrifice	10	A30803*	258948	1, 2, 3
12-month interim sacrifice; hepatic enzyme levels	10	A29693 A29694	258853-4	1, 2, 3 others
24-month treatment	20	A30807*	258948-54	1, 2, 3
BSP/BSP function tests (26 months)	6	"		others
Carcinogenicity--28 months	60	A31878*	073961-71	1, 3

*Reviewed in this DER.

[a] 1. Body weights, food consumption, mortality, and clinical observations.
2. Hematology, clinical chemistry, and urinalysis.
3. Organ weights, gross pathology, and histopathology.

II. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for complete details.)

1. Hoe 33171, active ingredient technical, was the test compound. Batch No. 11123 (code OH AS206) used in the first three weeks was 95.8 percent pure; batch No. 11283 (code OH AS201), used thereafter, was 94.0 percent pure.

2. Wistar rats of the Hoe WIS K_f (SPF 71) strain, approximately 4 weeks old, were acclimated to laboratory conditions for approximately 1 week and randomized into four groups of 116 rats/sex. Initial group mean body weights for males and females were approximately 130 and 115 g, respectively. Groups of 116 rats/sex received diets containing 0, 5, 30, or 180 ppm Hoe 33171.

3. Animals were individually caged in temperature- and humidity-controlled rooms under pathogen-free barrier conditions with a 12-hour dark/light cycle. Food (Altromin 1321) and water were available ad libitum except during collection of samples for urinalysis. Diets were prepared weekly and samples taken for content and homogeneity analyses.

4. Animals were observed daily for general health and behavior; detailed physical examinations were performed monthly. Beginning at 6 months, palpation for masses was performed twice monthly. Body weights and food consumption were recorded weekly. Water consumption was measured for a 16-hour period after 6, 12, and 24 months for 10 animals/sex/group.

5. Animals were separated into groups so that 56 animals/sex/group were used for chronic toxicity testing and 60/sex/group for carcinogenicity testing; data were presented in several reports as indicated in section 10.

6. Hematologic and clinical chemistry determinations and urinalyses were performed at termination on all animals in the 6- and 12-month studies and in the 24-month study on 10 animals/sex/group at weeks 26, 54, and 79 and on all surviving animals at week 106.

   Urinary parameters included appearance, color, pH, specific gravity, glucose, ketone bodies, bilirubin, urobilinogen, hemoglobin, and ascorbic acid.

   Hematologic parameters included erythrocytes, hemoglobin, hematocrit, Heinz bodies, reticulocytes, platelets, coagulation time, and total and differential leukocyte counts.

   Clinical chemistry parameters included sodium, potassium, calcium, chloride, inorganic phosphorus, total bilirubin, glucose, uric acid, creatinine, urea nitrogen, glutamic oxaloacetic transaminase, alkaline phosphatase, and cholesterol determinations and serum electrophoresis. A terminal sacrifice value was also determined for total lipids, lactic dehydrogenase, and total lipids (10 animals/sex/group in the 6- and 12-month studies and 20/sex/group in the 2-year study at week 107). In addition, liver and kidney function tests (bromsulfophthalein (BSP) and phenolsulfonphthalein (PSP)) were performed after 6, 12, 18, and 24 months on six rats/sex/group in the 24-month study.

   At each sacrifice organ weights were determined for heart, lung, liver, kidney, spleen, brain, prostate, adrenals, pituitary, thyroid, thymus, testes, and ovaries. Each animal received a complete gross examination and approximately 32 tissues were fixed for histologic examination.

   Statistical analyses were performed on body weight data, water consumption data, hemoglobin, hematocrit, erythrocytes, reticulocytes, leukocytes, platelets, coagulation time, all clinical chemistry parameters, urinalysis findings, and absolute and relative organ weights. The parametric methods of Dunnett or Sidak or the distribution-free method of Nemenyi/Dunnett were employed. In the carcinogenicity study neoplasm data were analyzed using the Fisher exact test.

B. Protocol: A protocol was not provided.

12. REPORTED RESULTS:

Dietary Analysis: Table 1 presents results of dietary analysis. Two batches of diet were analyzed twice monthly. The results indicate a large standard deviation and a wide range at each dose level even though the mean levels were 91 to 102 percent of nominal. Analytical data indicated that the test material was stable in the diets for 14 days. No homogeneity data were provided.

TABLE 1. Results of Dietary Analysis--Hoe 33171
24-Month Feeding Study in Rats

Nominal Level (ppm)	No. of Samples	Analyzed Levels (ppm) Mean ± S.D.	Range
5	95	4.55± 0.73	2.88 - 6.28
30	95	29.06± 3.92	16.2 - 40.0
180	95	185±22.3	136 - 230

Clinical Observations: It was reported that there were no effects on behavior, neurologic activity, dental growth, or oral mucosa attributable to the administration of Hoe 33171. Individual data or summary tabulations of findings were not presented.

Body Weights and Food Consumption: Body weights and food and water consumption were similar in dosed and control groups for males and females. Table 2 presents mean body weight data at selected intervals for all animals in the study (includes 6-month study, chronic toxicity study, and oncogenicity study).

Mortality:

A. 6-Month Study: There was one death, a male receiving 5 ppm; this was not considered compound related.

B. Chronic Study: There was no significant effect of dosing on survival; survival in control males (96 percent) was greater than in dosed groups of males (73-88 percent) (Table 3).

C. Oncogenicity Study: There was no effect of dosing on survival. Mortality in females receiving 30 and 180 ppm was greater than in control females in the last 4 months of the study, but this could not be attributed to dosing (Table 3).

TABLE 2. Mean Body Weights (g) at Selected Intervals in Rats Fed Hoe 33171[a]

Sex/Dietary Level (ppm)	Mean (±S.D.) at the end of study week					
	0	26	52	78	104	121
Males						
0	131 (±9)	457 (±41)	512 (±49)	533 (±52)	541 (±48)	507 (±46)
5	128* (±11)	465 (±46)	523 (±59)	542 (±70)	534 (±73)	498 (±62)
30	127* (±9)	461 (±42)	516 (±53)	538 (±63)	547 (±60)	531 (±70)
180	125* (±12)	467 (±43)	526 (±53)	543 (±61)	552 (±63)	524 (±65)
Females						
0	118 (±7)	252 (±23)	290 (±35)	318 (±46)	344 (±49)	341 (±44)
5	115* (±7)	249 (±22)	288 (±37)	321 (±48)	347 (±54)	332 (±56)
30	114* (±6)	248 (±21)	285 (±31)	315 (±40)	333 (±39)	324 (±39)
180	112* (±9)	249 (±22)	288 (±34)	326 (±44)	343 (±54)	332 (±51)

[a]Includes animals in the 6- and 12-month studies, the chronic study, and the oncogenicity study (initially 116/sex/group).

*Significantly different from control value ($p < 0.05$).

TABLE 3. Mortality and Percent Survival in Rats Fed Hoe 33171

Sex/Dietary Level (ppm)	Mortality and (Percent Survival)				
	At Week[a]		At Week[b]		
	78	106	78	104	123
Males					
0	0(100)	1(96)	5(92)	10(83)	19(68)
5	0(100)	7(73)	1(98)	8(87)	21(65)
30	1(100)	3(88)	0(100)	10(83)	17(72)
180	2(96)	5(81)	0(100)	5(92)	16(73)
Females					
0	5(100)	10(62)	5(92)	14(77)	21(65)
5	3(88)	9(65)	6(90)	13(78)	20(67)
30	3(100)	10(62)	1(98)	10(83)	25(58)
180	1(100)	7(73)	5(92)	14(77)	27(55)

[a]Chronic study; percent survival based on 26 rats/sex/group.

[b]Oncogenicity study; percent survival based on 60 rats/sex/group.

Hematology:

A. 6-Month Study: There was a slight, but significant increase ($p \leq 0.05$), in total leukocyte count in females receiving 180 ppm ($5.5 \pm 1.4 \times 10^9$/L) when compared to controls ($4.1 \pm 1.0 \times 10^9$/L); this was not accompanied by any changes in differential counts. Other hematologic parameters were, in general, similar in dosed and control groups.

B. Chronic Study: There were no effects of dosing on hematologic parameters. The only significant ($p \leq 0.05$) deviations were a decrease in clotting time in males receiving 180 ppm after 26 weeks only and a slight decrease in erythrocyte counts in females receiving 5 ppm after 26 and 54 weeks; these were considered random occurrences.

Clinical Chemistry:

A. 6-Month Study: There was a dose-related decrease in cholesterol in males (significant at $p < 0.05$ in 30- and 180-ppm groups) and a significant decrease ($p \leq 0.05$) in females receiving 30 ppm when compared to controls (Table 4). Total lipids were significantly decreased ($p < 0.05$) in both males and females receiving 5 ppm but there were no effects at higher doses. The authors attributed the changes in lipids to the pharmacodynamic lipid-lowering action of the test compound and did not consider them of toxicologic importance. There was a significant ($p \leq 0.05$) lowering of total serum protein in males receiving 30 and 180 ppm and females receiving 30 ppm and nondose-related changes in some electrolyte values, but these changes were not considered related to dosing.

B. Chronic Study: There were no changes in clinical chemistry parameters considered of toxicologic significance. There were sporadic values for calcium, inorganic phosphorus, glucose, and uric acid that were significantly ($p \leq 0.05$) increased or decreased compared to controls; however, the changes were slight and not consistent over time nor with dose. There was an apparent dose-related decrease in serum cholesterol and total serum lipids (Table 5); however, it was stated that all values were within the normal range of physiological variation for the strain of rat. Decreases in cholesterol were significant ($p \leq 0.05$) in males receiving 180 ppm at 26, 54, and 107 weeks.

Hepatic and renal function tests, BSP and PSP clearance, respectively, did not reveal any functional disturbances at 6, 12, 18, or 25 months of dosing.

Urinalysis: The results of urinalyses did not indicate any adverse effect from dosing. In the chronic study, ketone bodies were occasionally detected in urine of some dosed rats. Ascorbic acid was detected in the urine of three males and one female receiving 180 ppm at 12 months, one male and three females receiving 180 ppm at 18 months, and two females receiving 180 ppm at 24 months.

TABLE 4. Mean Serum Cholesterol and Total Lipid in Rats Fed Hoe 33171 for 6 Months

Dietary Level (ppm)	Cholesterol (mmol/L)		Total lipid (g/L)	
	Males	Females	Males	Females
0	2.14±0.35	2.10±0.45	3.47±0.60	3.18±0.44
5	1.86±0.44	1.79±0.27	2.49±0.28*	2.59±0.39*
30	1.66±0.31*	1.59±0.24*	2.81±0.27	3.04±0.57
180	1.46±0.28*	1.78±0.28	3.07±0.67	3.55±0.88

*Significantly different from control value ($p \leq 0.05$).

TABLE 5. Cholesterol and Total Serum Lipids in Rats Fed Hoe 33171 for 106 Weeks

Dietary Level (ppm)	Cholesterol (mmol/L) at Week				Total Lipids (g/L) at Week 107
	26	54	79	107	
Males					
0	2.41±0.39	3.43±0.38	3.46±0.49	4.92±1.34	6.66±1.68
5	2.71±0.42	3.74±0.64	4.38±1.76	4.84±1.66	6.10±1.84
30	2.52±0.29	3.58±0.40	4.03±0.63	4.36±0.87	5.70±1.72
180	1.96±0.26*	2.69±0.42*	3.14±0.66	3.85±1.15*	5.05±1.69*
Females					
0	2.67±0.42	3.53±0.99	2.88±0.63	3.58±1.00	5.25±1.36
5	2.65±0.43	3.03±0.48	2.54±0.51	3.08±0.78	5.55±1.52
30	2.64±0.59	2.90±0.73	2.97±0.85	3.35±0.91	4.75±0.73
180	2.38±0.50	2.89±0.69	2.76±0.96	3.33±0.93	4.76±1.82

*Significantly different from control value ($p < 0.05$).

Organ Weights:

A. 6-Month Study: It was reported (CBI, vol. 1, p. 5) that absolute and relative liver weights were increased in females receiving 180 ppm; however, the data do not support a statistically significant increase (Table 6). Relative weights of kidney, spleen, and thymus were significantly ($p \leq 0.05$) increased in females receiving 180 ppm (Table 7), but no corresponding effect was found on the absolute weights of these organs.

   Changes in relative kidney weights in high-dose females were accompanied by histologic findings (see below) whereas the other changes were not.

B. Chronic Study: Slight, but significant, decreases in liver weight ($p < 0.05$) and liver-to-body weight ratio ($p < 0.01$), were noted in males receiving 180 ppm Hoe 33171 (Table 8); the changes were not considered toxicologically important since there were no correlating histologic changes. Other absolute and relative organ weights were similar in control and dosed groups.

C. Oncogenicity Study: Results were similar to those found in the chronic study (see Table 8).

Gross Pathology:

A. 6-Month Study: Dilatation of the renal pelvis was noted in two males and one female receiving 180 ppm, two males and two females receiving 30 ppm, but only in one male in the control and 5-ppm groups. Swelling of the liver was noted in two males and one female receiving 180 ppm; similar findings were not seen in other groups. All other findings were similar among groups and considered incidental.

B. Chronic Study: Macroscopic findings were similar in dosed and control groups, and no findings were considered compound related. Several animals exhibited lobular markings of the liver (e.g., 12/20 control and 11/20 high-dose males and 5/20 control and 7/20 high-dose females at 24 months) but there were no histologic correlates. Individual gross findings were present but there was no summary tabulation of results.

C. Oncogenicity Study: Gross findings were not summarized or discussed in the report; findings for individual animals were recorded.

TABLE 6. Mean Liver Weights and Liver-to-Body Weight Ratio (±SD) in Rats Fed Hoe 33171 for 6 Months[a]

Dietary Level (ppm)	Males		Females	
	Liver Weight (g)	% Body Weight	Liver Weight (g)	% Body Weight
0	12.42±1.57	2.86±0.19	8.09±0.98	3.14±0.33
5	12.35±1.68	2.86±0.19	7.55±0.54	2.97±0.18
30	12.55±1.60	2.76±0.32	7.72±0.53	3.17±0.13
180	13.89±0.93	2.93±0.20	8.10±1.75	3.29±0.55

[a]There were no statistically significant differences ($p > 0.05$).

TABLE 7. Mean Organ Weights and Organ-to-Body Weight Ratios (±SD) in Female Rats Fed Hoe 33171 for 6 Months

Organ/Parameter	Dietary Level (ppm)	
	0	180
Kidney		
Weight (g)	1.52 ±0.18	1.72 ±0.21
% Body Weight	0.594±0.052	0.707±0.085*
Spleen		
Weight (g)	0.46 ±0.07	0.53 ±0.09
% Body Weight	0.179±0.016	0.216±0.041*
Thymus		
Weight (g)	0.273±0.062	0.361±0.115
% Body Weight	0.106±0.022	0.146±0.039*

*Significantly different from control value ($p \leq 0.05$).

TABLE 8. Mean Liver Weights and Liver-to-Body Weight Ratios (±SD) in Rats Fed Hoe 33171 for 106 or 121 Weeks

Dietary Level (ppm)	Chronic Study (106 Weeks) Liver Weight (g)	Chronic Study (106 Weeks) % Body Weight	Oncogenicity Study (121 Weeks) Liver Weight (g)	Oncogenicity Study (121 Weeks) % Body Weight
Males				
0	16.78±2.72	3.168±0.314	16.40± 2.17	3.306±0.388
5	16.51±1.84	3.039±0.173	15.84± 2.49	3.194±0.359
30	15.47±1.67	3.023±0.323	19.13±51.95*	2.903±0.426*
180	14.89±1.48*	2.844±0.255**	15.38± 1.88	2.960±0.297*
Females				
0	11.25±2.60	3.251±0.412	11.40±2.05	3.411±0.441
5	11.83±3.55	3.320±0.477	10.93±1.71	3.362±0.358
30	10.01±1.52	3.129±0.316	10.86±1.84	3.395±0.453
180	10.32±1.44	3.196±0.290	10.66±1.77	3.231±0.263

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

Histopathology:

A. Six-month Study: In males receiving 180 ppm Hoe 33171 there was an increase in calcareous precipitates and gravelly deposits in the subepithelial region of the kidney, which extended into the lumen of the renal pelvis. This was accompanied by foci of hyperplasia in the renal pelvis. In the liver there was "peripherolobular" glycogen liberation and deposition of periodic-acid Schiff (PAS) positive substance in Kupffer cells; there was some increase in incidence and severity of the finding in males and females receiving 30 or 180 ppm (Table 9). Other findings were incidental.

B. Chronic Study: Table 10 summarizes the observed neoplastic lesions. This includes findings for the main group of animals (20/sex/group) and those sacrificed at 26 months after BSP and PSP testing (6/sex/group). There was no evidence for an increase in any neoplastic lesion in any group of dosed animals.

Nonneoplastic lesions occurred at similar frequency in control and dosed groups. Summary tabulation of incidence was not provided. Cortical atrophy in the kidney and calcareous foci and concrements and epithelial thickening of the renal pelvis were frequent, but occurred at a similar incidence in both control and dosed groups. Bile duct proliferation was found in 11/20 males and 5/20 females in the control groups compared to 7/20 males and 7/20 females in the high-dose group. Adrenal dilation was found in three females in each of the control and high-dose groups (24-month sacrifice).

C. Oncogenicity Study: Table 11 summarizes neoplastic lesions in rats fed Hoe 33171 for 121 weeks. There was no evidence of an increase in the incidence of any tumor. The authors noted that the concurrent control incidence of Leydig cell tumors of the testes and granulosa tumors of the ovaries was abnormally low in comparison to laboratory historical data. There were no compound-related increases in nonneoplastic lesions in dosed rats (Table 12). The histologic lesions found were considered by the report authors to be age-related changes.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Under the conditions of the studies, Hoe 33171 was not oncogenic in male or female Wistar rats when fed for up to 28 months at dietary levels of 5, 30, or 180 ppm.

There were no effects of dosing on behavior, general health, mortality, body weight gains, and food or water consumption. Hematologic values were within the normal range. There was a slight increase in leukocytes at 6 months in high-dose females but this did not occur subsequently. There were changes in lipid status (lowering of serum cholesterol and total lipids), particularly

TABLE 9. Histologic Findings in Rats Fed Hoe 33171 for 6 Months[a]

Organ/Finding	Males/ Dietary Level (ppm) 0	5	30	180	Females/ Dietary Level (ppm) 0	5	30	180
Kidney								
Calcification of renal pelvis, unilateral	4	2	1	7	2	1	2	3
bilateral	(1)	-	-	(1)	(1)	-	-	(2)
Liver								
PAS-positive Kupffer cells								
slight	3	3	6	5	5	3	3	8
moderate	1	0	2	2	2	1	0	6
marked	0	0	2	3	1	2	0	1

[a]Tissues from 10 rats/group/sex were examined.

TABLE 10. Neoplastic Lesions in Rats Fed Hoe 33171 for 106 Weeks[a]

Organ/Neoplasm	Males/ Dietary Level (ppm) 0	5	30	180	Females/ Dietary Level (ppm) 0	5	30	180
Lungs	(26)[b]	(26)	(26)	(25)	(26)	(26)	(26)	(26)
Adenoma	1	2	0	0	0	0	0	0
Adrenals	(26)	(26)	(26)	(25)	(25)	(25)	(25)	(25)
Cortical adenoma	0	0	0	0	2	0	0	1
Medullary tumor	2	1	0	0	0	0	0	0
Testes	(26)	(26)	(26)	(26)				
Leydig cell tumor	1	2	1	0				
Ovaries					(26)	(26)	(26)	(26)
Theca granulosa cell tumor					0	4	1	0
Pancreas	(26)	(26)	(26)	(25)	(25)	(25)	(25)	(25)
Islet cell adenoma	0	1	1	3	0	1	0	0
Pituitary	(26)	(26)	(24)	(25)	(26)	(26)	(25)	(26)
Adenoma	5	9	7	8	14	13	11	16
Thyroid	(26)	(26)	(26)	(26)	(26)	(26)	(26)	(26)
Follicular adenoma	1	0	0	1	0	1	1	0
Parafollicular adenoma	1	3	0	0	0	1	0	0
Papillary adenoma	0	2	0	0	0	0	0	1
Mammary gland					(26)	(26)	(25)	(26)
Fibroadenoma					3	2	4	1
Adenocarcinoma					4	3	0	1

[a] Includes six rats/sex/group sacrificed after RSP and PSP tests (at 110 weeks) and not included in the summary tables of the report. If a tumor occurred only once in any group it was not included in this table.

[b] Numbers in parentheses are the numbers of tissues examined histologically, determined by our reviewers.

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TABLE 11. Neoplasms in Rats Fed Hoe 33171 for 121 Weeks[a]

Organ/Neoplasm	Males/Dietary Level (ppm)				Females/Dietary Level (ppm)			
	0	5	30	180	0	5	30	180
No. of animals examined[b]	60	60	60	60	59	60	60	59
Skin								
Fibroma	0	2	0	0	0	0	0	1
Fibromyxoma	2	0	0	0	0	0	1	0
Sarcoma	2	2	3	1	1	0	0	0
Carcinoma	0	1	0	1	1	0	0	1
Pituitary								
Adenoma	12	10	15	7	31	23	33	33
Thyroid								
Follicular cell adenoma	2	5	3	2	1	0	1	2
Follicular cell carcinoma	1	0	1	0	0	0	1	0
Parafollicular cell adenoma	4	2	2	4	1	1	1	2
Parafollicular cell carcinoma	0	1	0	0	0	1	0	0
Adrenal								
Adenoma	3	4	2	4	5	2	1	2
Pheochromocytoma	3	1	2	6	0	1	1	1
Pancreas								
Islet cell adenoma	5	6	8	3	5	4	4	1
Testes								
Leydig cell tumor	0	2	2	5				
Ovaries								
Theca granulosa tumor					0	3	1	4
Thymus								
Thymoma, lympho-epithelial	0	1	0	1	1	2	4	1
Lymphosarcoma	1	0	0	0	0	0	2	0

(Continued)

[a]A neoplasm was not tabulated if it occurred in only one animal in any group and could not be combined with other tumors in the organ for statistical analysis.

[b]The number of tissues examined histologically was not presented.

TABLE 11. Neoplasms in Rats Fed Hoe 33171 for 121 Weeks[a] (Continued)

Organ: Neoplasm	Males/Dietary Level (ppm)				Females/Dietary Level (ppm)			
	0	5	30	180	0	5	30	180
No. of animals examined[b]	60	60	60	60	59	60	60	59
Lymph node								
Lymphoma	2	0	1	1	1	2	0	0
Mammary gland								
Adenoma/fibroadenoma					4	9	4	4
Carcinoma					7	6	12	3
Uterus								
Fibroadenomatous polyp					10	6	11	10
Sarcoma					1	1	1	2
Carcinoma					4	1	3	0
Adenocarcinoma								
Brain								
Granular cell tumor	3	1	2	1	3	0	0	0
Lungs								
Alveolar carcinoma	2	1	0	1	0	1	0	1
Bone								
Osteosarcoma	1	0	0	2	0	0	0	0

(Concluded)

[a] A neoplasm was not tabulated if it occurred in only one animal in any group and could not be combined with other tumors in the organ for statistical analysis.

[b] The number of tissues examined histologically was not presented.

TABLE 12. Frequently Occurring Nonneoplastic Lesions in Rats Fed Hoe 33171 for 121 Weeks

Lesion	Males/Dietary Level (ppm)				Females/Dietary Level (ppm)			
	0	5	30	180	0	5	30	180
No. of animals examined[a]	60	60	60	60	59	60	60	60
Nephropathy	36	32	26	18	19	19	11	5
Concrements in renal pelvis	10	18	15	23	22	23	33	43
Cardiomyopathy	16	21	22	30	18	22	21	18
Dystrophy, sciatic nerve	31	29	34	33	16	16	20	13
Dystrophy, femoral muscle	24	23	29	30	8	15	23	11

[a]The number of tissues examined histologically was not presented.

in animals receiving 180 ppm. Other significant changes in serum parameters in dosed groups when compared to controls were considered within the normal physiological range and were random occurrences.

After 6 months there was an increase in absolute and relative kidney weight in females receiving 180 ppm but not at other intervals and there was an increase in absolute liver weight in males receiving 180 ppm. After 12 months there was a dose-related increase in absolute and relative adrenal weights in dosed males and a slight decrease in liver-to-body weight ratio in males receiving 30 ppm. There were significant decreases in liver weights after 24 months (180-ppm males) and 28 months (30- and 180-ppm males), but no correlated pathologic findings indicated by hepatic function tests, clinical chemistry findings, or histologic examinations.

There were isolated cases of increased calcification in the renal pelves of males and females of the 180-ppm group after 6 months and histologic changes in adrenals after 12 months, but these abnormalities were not detected at subsequent sacrifices; hence they were not considered compound related. The NOEL was considered to be 30 ppm Hoe 33171.

B. A quality assurance statement for the combined chronic and carcinogenicity study was dated June 28, 1985; quality assurance statements for the 6-month and 2-year studies were dated January 10, 1983 and September 19, 1984, respectively.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The results of the 2-year chronic toxicity study, the 28-month oncogenicity study, and the 6-month (this DER) and 12-month (DER 1141) sacrifices will be integrated in this discussion.

There was no effect from Hoe 33171 dosing on mean body weights when males or all animals in the combined studies were evaluated. The significant increase ($p < 0.05$) in mean body weights in 10 males receiving 180 ppm in the 6-month study and slight but nonsignificant ($p > 0.05$) increase in mean body weights in high-dose males (13, 26, and 58 weeks) in the 12-month study (10/sex/group) are therefore not considered related to dosing.

Previous 30- and 90-day studies (see Section 9) indicated that the liver was a possible target organ, the effects being hepatomegaly. In the 6- and 12-month studies there were no significant ($p > 0.05$) effects of dosing on mean liver weights or liver-to-body weight ratios; in the 2-year study, liver weights (absolute and relative) were decreased in male and female rats receiving 180 ppm Hoe 33171 ($p \leq 0.05$ in males) when compared to controls (Table 8); and in the 28-month study liver-to-body weight ratios were decreased ($p \leq 0.05$)

in males receiving 30 or 180 ppm (Table 8). Changes in the liver were interpreted by the authors to be adaptive and not of toxicologic importance, since no induction of microsomal or peroxisomal enzymes was noted after 12 months of dosing (DER 114J). We do not agree with the study authors' conclusion (CBI, Summary of Toxicology, Vol. 1, p. 5) that there was an increase in absolute and relative liver weight at 6 months in females receiving 180 ppm (see Table 6). No histologic changes were noted in the livers of dosed rats at the 6-, 12-, 24-, or 28-month sacrifices. We agree with the study authors that there were no toxicologically important effects on liver. The authors may have missed microsomal enzyme induction; the enzymes were only assayed at 12 months and adaption could have occurred.

We assess that there were no toxicologically important changes in clinical chemistry parameters with the possible exception of decreases in cholesterol and total lipids. In the 12-month study (DER 114J) there were increases in bilirubin and creatinine in females receiving 30 or 180 ppm Hoe 33171 when compared to controls. However, no comparable changes were seen in the 6-month study or at any interval (26, 54, 79, or 106 weeks) in the 2-year study. There were no effects consistent with time or dose for inorganic phosphorus or calcium when data for all the studies were examined. Although significant changes in these electrolytes were noted in some dosed groups in the 12-month study as well as at various intervals in the 2-year study, we consider these values to be within the normal physiological range.

Decreases in serum cholesterol and total serum lipid levels in dosed rats were noted in all of the studies, but the authors considered these due to the pharmacologic lipid-lowering effect of Hoe 33171 and did not consider the decreases a toxicologic effect. In the 6- and 12-month studies there were dose-related decreases in the cholesterol level in both males and females. The decreases were significant ($p \leq 0.05$) in males receiving 30 or 180 ppm and females receiving 30 ppm at 6 months and in females receiving 30 ppm and males receiving 180 ppm at 12 months. In the 2-year study, cholesterol levels were significantly lower ($p \leq 0.05$) than control at 26, 54, and 107 weeks in the male group receiving 180 ppm Hoe 33171. Mean serum lipid levels were significantly decreased ($p \leq 0.05$) compared to control at 6 months in males and females receiving 5 ppm, at 12 months in males receiving 5 or 180 ppm and in females receiving 180 ppm, and at 24 months in males receiving 180 ppm. We assess that the changes in the lipid status should be considered of possible toxicologic importance.

A mild leukocytosis was observed in females receiving 180 ppm in the 6-month study. However, since a corresponding effect was not seen at any interval in the 2-year study, this occurrence can be considered incidental.

At the 6-month sacrifice, there was an apparent compound-related increase in the incidence of calciferous deposits in the renal pelvis (Table 9). In the chronic toxicity study, this finding was rather

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common but there was no apparent relationship to dosing; in addition, there were no effects on renal function testing at any interval in the chronic study. In the oncogenicity study, there was an apparent increase in "concrements in the renal pelvis" in both males and females receiving 180 ppm when compared to controls, but this was not accompanied by histologic nephropathic changes (Table 12).

In both the 24-month study and 28-month study, the incidence and distribution of neoplasms were similar. There were no indications of an oncogenic effect of Hoe 33171.

The study design was adequate, and the reporting was acceptable with the exceptions that no summary tables of nonneoplastic lesions were presented in the chronic study. In both the chronic toxicity and oncogenicity studies, the summary tables of neoplastic lesions did not indicate the number of tissues examined histologically. A check of the individual pathology data sheets for control and high-dose males (oncogenicity study) indicated that the summary incidence tables of neoplasms were accurate and for major organs, tissues from all animals were examined. In control males, six pituitaries were missing and in high-dose males three pituitaries were missing. This does not affect conclusions on oncogenic potential of Hoe 33171.

Based on decreases in serum cholesterol and total lipids in males receiving 180 ppm the LOEL can be established at 180 ppm and the NOEL at 30 ppm Hoe 33171. However, it is possible that the rats may have tolerated a higher dose since there was no liver disease or thyroid changes accompanying the effect. The rationale for dose selection was adequate, however.

Item 15--see footnote 1.

16. CBI APPENDIX: Materials and Methods, CBI pp. 13-22 (study No. A30807) and CBI pp. 4-7 (study No. A31880).

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 105 through 118 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

EPA: 68-02-4225
DYNAMAC No. 1-012D
January 27, 1986

004063

DATA EVALUATION RECORD

ACCLAIM (HOE 33171)

Carcinogenicity Study in Mice

STUDY IDENTIFICATION: Donaubauer, Schütz, Leist, and Kramer. HOE 33171-active ingredient technical (code: HOE 33171 OH AS 201) carcinogenicity study in mice 24-month feeding study. (Unpublished study No. A30816 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxicologie, West Germany; dated March 11, 1985.) Accession No. 258955-258965.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

004963

1. CHEMICAL: Acclaim; Hoe 33171; Whip; fenoxapropethyl; ethyl 2-(4-(6-chloro-2-benzoxazolyloxy)phenoxy)propanoate.

004963

2. TEST MATERIAL: Hoe 33171, active technical ingredient (code: HOE 33171 OH AS 201), batch No. 11283, Op. 6 + 7 + 6/81, was 94% pure.

3. STUDY/ACTION TYPE: Carcinogenicity study in mice.

4. STUDY IDENTIFICATION: Donaubauer, Schütz, Leist, and Kramer. HOE 33171-active ingredient technical (code: HOE 33171 OH AS 201) carcinogenicity study in mice 24-month feeding study. (Unpublished study No. A30816 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxicologie, West Germany; dated March 11, 1985.) Accession No. 258955-258965.

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7. CONCLUSIONS:

A. A ~~NOEL~~ MTD could not be established from this study. The administration of Hoe 33171 in the diet of mice for 24 months did not produce an effect; a maximum tolerated dose (MTD) was therefore not used. No conclusion can be made with regard to oncogenicity, and the LOEL could not be established.

B. This study is considered inadequate to provide information on oncogenicity in the absence of dosing with an MTD. It was also poorly controlled from the standpoint of diet preparation and analysis. The study is therefore classified Core Supplemental.

Item 8--see footnote 1.

9. BACKGROUND: A prior subchronic study is referred to without further identification. Based on the subchronic study, the study authors indicate an anticipated MTD of 40 ppm.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The mice used in this study were obtained from the Hoechst SPF breeding colony and were designated as HOE: NMRKf (SPF71) strain.

2. The animals were housed individually in Makrolon cages in an environmentally controlled room. Temperature was 18-24°C and humidity was 32-67%. Lighting was cycled on a 12-hour basis. Feed and water were available ad libitum.

3. The basal diet was Altromin R1321 to which Hoe 33171 was added to make a premix. The premix was prepared to the final concentration (0, 2.5, 10, and 40 ppm) by dilution with basal feed and mixing in a Loedige FM/D mixer. Diets were prepared fresh weekly. Content of Hoe 33171 in the diet and stability were determined by weekly analysis. The Hoe 33171 was extracted with acetone, concentrated, and analyzed using gas chromatography (GLC/MS).

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[1] Only items appropriate to this DER have been included.

4. During the course of the study observations were made on behavior, general health, and mortality twice daily. Monthly observations were made on the opacity of the eyes, dental growth, oral mucosa, and neurobiological response. Body weight and food consumption were determined weekly.

5. Blood was taken from 10 male and 10 female mice at interim sacrifice (52 weeks) and just before termination (105 weeks) for hematology (nine parameters) and clinical chemistry (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], alkaline phosphatase, and gamma-glutamyl transpeptidase). Hepatic enzymes were evaluated on the livers of mice killed at 12 months.

6. On completion of the first 12 months of the study 10 male and 10 female mice were killed. At the end of 24 months all surviving animals were killed. Necropsies were performed on all of the above animals as well as those that died prior to termination. The following organs were weighed: heart, lungs, liver, kidneys, spleen, brain, and testes/ovaries. Approximately 35 organs were preserved for histopathologic examination.

7. Statistical evaluation was performed on body weight, hematology, clinical chemistry, liver enzymes, and relative organ weights. The methods used were distribution-free method of Nemenyi/Dunnett or Nemenyi/Sidak or the parametric method of Dunnett or Sidak. No references were provided. The level of significance calculated was $p = 0.05$.

B. Protocol: A protocol was not provided.

12. REPORTED RESULTS:

A. Dietary Analysis: The study authors presented data on stability and diet content based on chemical dietary analysis. No data on homogeneity were presented; the authors did not comment on these data. Inspection of the data indicates that the variation between added and found diet content may vary over 30 percent. We provide an analysis of mean diet content (Table 1); wide ranges and high standard deviations indicate the variations found.

B. Clinical Observations and Mortality: It was reported that there were no behavioral changes or toxic signs that could be associated with the administration of Hoe 33171. However, individual animal data and summary incidence data were not presented. Mortality (Table 2) was increased in the males at all dose levels and in the females at 2.5 and 10 ppm for the last 6 months only.

TABLE I. Analytical Results[a] of Test Substance in the Diet

Nominal[b] Level (ppm)			Analyzed Level (ppm) Mean ± SD	Range	N
2.5			2.33±0.30	1.70 - 3.20	96
	Day	1[c]	2.32±0.41	1.60 - 2.74	9
		7	2.23±0.42	1.63 - 2.72	9
		14	2.32±0.45	1.33 - 2.88	9
10			9.52±1.25	5.93 - 12.0	96
	Day	1	10.26±1.22	8.37 - 11.9	9
		7	9.98±1.92	6.7 - 13.7	9
		14	9.24±1.06	7.77 - 11.2	9
40			39.41±4.80	24.2 - 48.5	96
	Day	1	39.89±4.68	30.6 - 44.3	9
		7	40.64±3.13	36.3 - 45.1	9
		14	41.09±2.88	36.8 - 44.9	9

[a] Calculated by our reviewers and expressed as parts per million test substance.

[b] Does not include stability data.

[c] Stability analyses were conducted 3 times for each dose level during study.

TABLE 2. Mortality and Percent Survival[a] of Mice Fed Hoe 33171 for 104 Weeks

Dose Group[b] (ppm)	Mortality (Percent Survival) at Week				
	13	26	52	78	104
Males					
Control	0 (100)	1 (98)	5 (90)	8 (84)	14 (72)
2.5	0 (100)	1 (98)	6 (88)	10 (80)	21 (58)
10	0 (100)	1 (98)	3 (94)	6 (88)	21 (58)
40	0 (100)	0 (100)	5 (90)	10 (80)	19 (62)
Females					
Control	0 (100)	0 (100)	2 (96)	8 (84)	21 (58)
2.5	0 (100)	1 (98)	2 (96)	8 (84)	30 (40)
10	0 (100)	0 (100)	0 (100)	3 (94)	26 (48)
40	0 (100)	0 (100)	2 (96)	6 (88)	20 (60)

[a]Calculated by our reviewers on the basis of animals found dead and killed moribund.

[b]Fifty mice/sex/group.

This effect is not considered compound related due to the lack of a dose-effect relationship. At 104 weeks, survival in male groups ranged from 58 to 72% and in female groups from 40 to 60%.

C. Body Weight and Food Consumption: Selected mean body weight values are presented in Table 3. The mean body weights of males receiving 40 ppm were occasionally significantly ($p \leq 0.05$) higher than those of the control males. No consistent effects were seen in the females at high dose nor in either sex at the mid and low doses. Food consumption was unaffected by the feeding of Hoe 33171.

D. Hematology: Leucocyte values were significantly different ($p < 0.05$) from the control in the low-dose female group. This was considered spontaneous variation and not related to administration of the test material because no dose-effect relationship was apparent. Hemoglobin was significantly ($p < 0.05$) elevated in the high-dose females. No alterations in any hematologic values were associated with the test substance.

E. Clinical Chemistry: SGOT, SGPT, and alkaline phosphatase were not affected by the administration of Hoe 33171 regardless of dose. Gamma-glutamyl transpeptidase (GGT) was significantly ($p < 0.05$) lower for the high-dose females when compared to the controls (Table 4). There were anomalously high values in four control females; accordingly, no biological significance was attached to the GGT results. Nevertheless, reduced GGT values have no biological significance.

F. Necropsy and Organ Weights: It was reported that no gross findings were observed at necropsy that could be related to the test compound; however, no summary tables of incidence of gross findings were presented to support this statement. In the individual organ weight tables an "F" (finding) appears beside the weight. This implies a gross change but the nature of the finding is not given. The absolute and relative kidney weights were slightly increased in both sexes at the 12-month interval kill. The kidney-to-body weight ratio in females receiving 40 ppm was the only value significantly ($p \leq 0.05$) different from controls, and this finding was considered of questionable biologic significance. There were no effects on the kidney in either sex at termination. As seen in Table 5, liver-to-body weight ratios in female mice receiving 10 and 40 ppm Hoe 33171 were significantly ($p \leq 0.05$) lower than the controls. According to the authors, examination of the individual data revealed that the above-noted effect was due to the control values being unusually high. It was concluded that the administration of Hoe 33171 resulted in no compound-related effects on organ weights.

TABLE 3. Selected Mean Body Weights for Male and Female Mice Fed Hoe 33171 for 104 Weeks

Dose Group (ppm)	Body Weight (g) at Week			
	0	26	52	104
Males				
Control	21±1	34±3	35±3	36±3
2.5	22±1	35±2	36±3	36±3
10	22±1	36±3*	36±3	36±3
40	22±1	37±3*	37±3*	36±3
Females				
Control	19±1	29±2	31±2	33±3
2.5	19±2	29±2	30±3	34±3
10	19±1	30±2	31±2	34±4
40	19±1	29±2	31±2	33±3

* Significantly different from controls ($p < 0.05$) by the Nemenyi/Sidak method.

TABLE 4. Clinical Chemistry Data in Mice Fed Hoe 33171 for 104 Weeks

Dose Group (ppm)	γ-Glutamyl transpeptidase (U/L)	
Males	Males	Females
Control	4.40± 2.55	7.40± 5.08
2.5	3.40± 3.69	2.50± 2.76
10	2.30± 2.79	3.90±11.64*
40	3.80± 3.58	1.30± 1.64*[b]

[a]Data from 10 mice/sex/group.

[b]One value in this series of 10 animals is 32, all the other values are 0.

*Significantly different from control value ($p < 0.05$) by Nemenyi/Dunnett's method.

TABLE 5. Absolute and Relative Liver Weights in Mice Fed Hoe 33171 for 104 Weeks

Dose Group (ppm)	Liver Weight	
	Grams	% of Body Weight
Males		
Control	1.73±0.34	4.773±0.701
2.5	1.72±0.27	4.729±0.659
10	1.72±0.24	4.651±0.587
40	1.83±0.29	4.933±0.707
Females		
Control	2.01±0.52	5.841±1.260
2.5	1.76±0.41	5.186±1.104
10	1.69±0.20	4.959±0.650*
40	1.71±0.31	5.017±0.705*

* Significantly different from control value ($p < 0.05$) by the Nemenyi/Sidak method.

G. Liver Enzyme Activity: The livers from the 12-month interim sacrifice were examined with regard to enzyme activity. Feeding Hoe 33171 to mice for 12 months was stated to have had no effect on foreign substance metabolism or liver enzyme activity. However, no data were presented to support the statement.

H. Histopathology: The incidence of nonneoplastic lesions in mice fed Hoe 33171 for 104 weeks is summarized in Table 6. None of the recorded changes were considered to demonstrate a dose-related effect, and the findings were considered fortuitous in their occurrence by the study authors. Table 7 summarizes the neoplastic lesions reported. An apparent increase in ovarian papillary cystadenomata was noted (1/45, 4/50, 2/48, and 7/49 for 0, 2.5, 10, and 40 ppm, respectively). The pathologist and the study authors considered it appropriate to combine the ovarian papillary cystadenomata with the incidence of cysts lined by hyperplastic epithelium since both lesions are characterized by a cyst lined by proliferative epithelium, the only difference between the diagnosis depended on a projection into the cystic cavity. Depending on the plane of section the projection could be present or absent. The incidence of cysts lined by hyperplastic epithelium was 4, 2, 0, and 1 with the combined incidence being 5/45, 6/50, 2/48, and 8/49 for 0, 2.5, 10, and 40 ppm, respectively.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that Hor 33171 did not affect behavior, clinical findings, body weight gains, absolute and relative food consumption, hematology, clinical chemistry, liver enzyme, biochemistry, and gross or histopathologic findings. Absolute and relative increases in kidney weights seen in both sexes at 12 months were absent at 24 months. Absolute and relative liver weights were lower than the controls at 10 and 40 ppm after 24 months. An increase in mortality among the 2.5- and 10-ppm groups over the last 6 months was not attributed by the authors to feeding Hoe 33171. There were no indications of oncogenic properties in mice fed the test substance for 24 months.

B. A signed and dated (March 11, 1985) quality assurance statement was included in the report; inspection was performed at least 12 times during the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

We agree with the study authors' interpretation of results. Feeding Hoe 33171 to mice for a period of 24 months produced no effect on animal behavior, clinical signs, mortality, body weight, food consumption, hematology, clinical chemistry, liver enzyme activity, organ weights, and histopathology. Accordingly, neither a NOEL nor LOEL can be established from this study. We do not agree with the

TABLE 6. Nonneoplastic Lesions in Mice Fed Hoe 33171 for 104 Weeks

Organ/Lesion	Males/Dose Level (ppm) 0	2.5	10	40	Females/Dose Level (ppm) 0	2.5	10	40
Lungs	(50)[a]	(49)	(49)	(30)	(46)	(50)	(49)	(49)
Pneumonia/pneumonitis	1	2	5	0	3	4	2	2
Bronchopneumonia	1	0	0	1	0	0	0	0
Adenomatosis	4	0	1	1	2	2	1	0
Perivascular lymphoid aggregations	1	2	0	2	1	0	0	0
Vascular congestion	0	1	0	2	0	2	0	0
Leucocytosis	0	0	0	0	1	0	1	1
Pleurisy	1	0	0	0	0	1	1	0
Alveolar macrophages	0	0	0	1	0	0	0	2
Thymus	(40)	(44)	(34)	(38)	(38)	(38)	(40)	(35)
Hyperplasia	1	0	2	0	4	6	7	7
Regression	0	1	2	1	1	0	1	1
Lymph Nodes	(48)	(46)	(43)	(45)	(43)	(45)	(47)	(47)
Hyperplasia	8	8	11	6	9	11	9	13
Sinus histiocytosis	1	0	1	1	2	1	0	1
Liver	(50)	(49)	(49)	(50)	(47)	(50)	(49)	(49)
Hepatocyte enlargement	12	3	2	4	5	1	3	0
Leucocytosis	1	0	3	0	4	2	2	6
Hepatocyte vacuolation	0	1	1	0	2	0	0	0
Hepatocyte necrosis	0	1	3	0	0	1	4	6
Extramedullary hemopoiesis	1	0	1	1	1	2	4	7
Spleen	(48)	(48)	(48)	(50)	(47)	(50)	(47)	(48)
Extramedullary hemopoiesis	3	7	5	4	6	12	7	12
Hyperplasia	7	5	8	3	8	6	13	11
Kidneys	(50)	(49)	(49)	(50)	(45)	(50)	(49)	(49)
Glomerulonephritis	2	0	0	2	5	3	3	1
Perivascular lymphoid aggregations	13	12	11	15	13	8	10	8

(continued)

[a]Numbers in parentheses indicate number of tissues examined.

TABLE 6. Nonneoplastic Lesions in Mice Fed HOE 33171 for 104 Weeks (Continued)

Organ/Lesion	Males/Dose Level (ppm) 0	2.5	10	40	Females/Dose Level (ppm) 0	2.5	10	40
Kidneys								
Cortical cysts	5	2	2	1				
Seminal Vesicles	(50)[a]	(48)	(48)	(49)				
Distended with colloid	6	8	10	9				
Fibrosis	7	6	5	4				
Testes	(50)	(48)	(49)	(49)				
Reduced spermatogenesis	9	10	4	14				
Spermatocele	5	3	0	6				
Mineral deposits in seminiferous tubules	2	3	3	4				
Uterus					(45)	(50)	(50)	(49)
Cystic endometrial hyperplasia					29	24	27	34
Endometritis					2	1	1	1
Polyps					4	1	2	4
Distended lumen					1	2	4	2
Hyalinization					2	2	1	3
Ovaries					(45)	(50)	(48)	(49)
Cysts					8	9	10	7
Hemorrhagic cysts					6	1	1	5
Periarteoritis					6	4	4	4
Tubular hyperplasia					3	1	6	8
Adrenals	(48)	(48)	(48)	(49)	(44)	(48)	(47)	(49)
Cortical cell vacuolation	1	0	2	1	7	1	4	4
Ceroid cells	0	2	0	1	1	0	0	2
Cortical cell hyperplasia	9	17	15	15				
Medullary hyperplasia	1	1	0	1	0	0	1	0
Fusiform cells	6	1	2	0	11	8	5	6

(concluded)

[a]Numbers in parentheses indicate number of tissues examined.

TABLE 7. Neoplastic Lesions[a] in Mice Fed Hoe 33171 for 104 Weeks[b]

	Males/Dose Level (ppm)				Females/Dose Level (ppm)			
Organ/Neoplasm	0	2.5	10	40	0	2.5	10	40
Lymphoreticular								
Lymphosarcoma	9	6	7	11	12	9	16	14
Reticulum cell sarcoma	0	3	2	0	4	4	2	3
Leukemia	0	1	0	0	1	0	2	0
Lungs	(50)	(48)	(49)	(50)	(46)	(50)	(49)	(49)
Adenoma	4	7	4	2	1	3	1	0
Adenocarcinoma	4	1	1	2	1	3	1	4
Liver	(50)	(49)	(49)	(50)	(47)	(50)	(49)	(49)
Benign	0	2	1	3	1	0	0	1
Malignant	1	1	0	0	0	1	0	0
Testes	(50)	(48)	(49)	(49)				
Interstitial cell adenoma	2	1	1	0				
Uterus					(45)	(50)	(50)	(49)
Hemangioma					1	0	0	2
Leiomyoma					2	1	0	0
Adenocarcinoma					1	0	2	1
Fibrosarcoma					1	0	1	0
Ovaries					(45)	(50)	(48)	(49)
Granulosa cell tumor					14	8	13	8
Luteinized granulosa cell tumor					4	4	1	5
Tubular adenoma					6	4	6	6
Papillary cystadenoma					1	4	2	7
Anaplastic sarcoma					1	1	0	0

(continued)

[a] Incidence in animals killed or dying during study together with those killed at termination.

[b] If a tumor occurred only once in any group it was not included in this table

TABLE 7. Neoplastic Lesions[a] in Mice Fed Hoe 33171 for 104 Weeks[b] (Continued)

Organ/Neoplasm	Males/Dose Level (ppm)				Females/Dose Level (ppm)			
	0	2.5	10	40	0	2.5	10	40
Adrenals	(48)	(48)	(48)	(49)	(44)	(48)	(47)	(49)
Pheochromocytoma	1	1	0	0	0	0	0	0
Cortical adenoma	10	12	5	8	0	1	0	0
Pituitary	(37)	(37)	(26)	(41)	(30)	(32)	(37)	(26)
Adenoma	0	0	0	0	5	2	2	1
S/C Mass (Malignant)								
Subcutaneous hemangio-sarcoma	1	0	0	0	0	0	1	0
Mammary adenocarcinoma	0	0	0	0	3	4	1	1
Harderian Gland								
Adenoma	0	1	1	0	1	0	1	0

(concluded)

[a]Incidence in animals killed or dying during study together with those killed at termination.

[b]If a tumor occurred only once in any group it was not included in this table.

study authors' conclusion with regard to oncogenicity. The study authors state that the results indicate no carcinogenic property of the test materials. The reviewers concluded that a MTD was not used and therefore an opinion on oncogenicity is inappropriate. Other deficiencies of the study were variability of test compound in the dietary levels, lack of detailed clinical observations in the report, lack of summary tables for gross pathology findings, and data discussion in the report where the data were not present, i.e., 12-month findings on liver enzymes and kidney weights.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 11-17.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 136 through 142 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

034063

EPA: 68-02-4225
DYNAMAC No. 1-12H
January 27, 1986

DATA EVALUATION RECORD

HOE 033171

Chronic Toxicity Study in Dogs

STUDY IDENTIFICATION: Brunk, Leist, and Kramer. Toxicological testing of Hoe 033171-active ingredient technical by repeated oral administration to beagle dogs for 2 years. (Unpublished study No. 693 by and for Hoechst, A.G., Frankfurt/M, Federal Republic of Germany.) Accession Nos. 073972-073973.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-24-86

1. CHEMICAL: Hoe 033171. 004963

2. TEST MATERIAL: Hoe 033171, acclaim, active ingredient technical, code No. Hoe 033171 OH ZC94 0001, had a purity of 94 percent.

3. STUDY/ACTION TYPE: Two-year chronic toxicity study in dogs.

4. STUDY IDENTIFICATION: Brunk, Leist, and Kramer. Toxicological testing of Hoe 033171 - active ingredient technical by repeated oral administration to beagle dogs for 2 years. (Unpublished study No. 693 by and for Hoechst, A.G., Frankfurt/M, Federal Republic of Germany.) Accession Nos. 073972-073973.

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EPA Section Head

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Date: 2-7-86

7. CONCLUSIONS:

A. Hoe 33171 has been fed to dogs at doses of 0, 3, 15, and 75 ppm for 2 years. On the basis of this study the NOEL is 3 ppm. The LOEL is 15 ppm on the basis of reduced body weight at 78 weeks and at termination.

B. This study is Core Minimum based on lack of detailed data for analysis of dietary concentration, stability, or homogeneity and lack of data on food consumption.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Dietary premixes were prepared each 14 days by mixing the test substance with cornmeal. The premixes were incorporated in the dog diet manufactured by NAGUT Kraftfutterwerke Dr. Mueller K.G. Dietary concentrations were 0 (control), 3, 15, and 75 mg/kg diet (ppm). Homogeneity and stability tests were conducted every 3 months.

2. The dogs used in the study (six/sex/dose) were purebred English beagle dogs of the HOE: BEAK strain (Hoechst breed). They were 11 months of age and weighed 13.3 kg (range 11.0-14.9 kg) and 11.98 kg (range 10.8-13.7 kg) for male and female animals, respectively.

3. The dogs were housed individually in a kennel with access to an exercise area. The area was environmentally controlled for temperature.

4. Daily observations were made for mortality, behavior, general health, and food consumption. Body weights were measured weekly. Examination for neurologic, ophthalmologic, otologic, dental, and mucosal health were made before initiation, once very 3 months, and before termination of the study. Bromsulphthalein (BSP) hepatic function tests and phenolsulphonphthalein (PSP) renal function tests were also conducted according to this schedule. Methemoglobin was determined at termination only.

[1]Only items appropriate to the DER have been included.

5. Hematology (10 parameters), clinical chemistry (21 parameters), and urinalysis (11 parameters) were conducted initially, at approximately 6 weeks, at 3-month intervals, and before termination.

6. All animals were killed at termination, and a gross necropsy was performed. Approximately 40 tissues were taken, prepared, and examined histopathologically; of these, approximately 13 tissues were weighed.

7. The treatment groups were compared to controls when a sufficient number of animals was available. The level of significance determined was $p < 0.05$. Specific methods included parametric method by Dunnett or the distribution-free method by Nemenyi/Dunnett; statistical evaluations were conducted on male and female dose groups combined.

B. Protocol: A protocol was not presented in the report.

12. REPORTED RESULTS:

A. No data on dietary analysis for concentration, stability, or homogeneity were presented. Near the end of the first year (25th premix) the high- and mid-dose groups were switched and the dogs were fed the wrong doses for 5 days.

B. No deaths occurred during the study. All animals exhibited good health and showed no behavioral, neurological, ophthalmological, otologic, or dental abnormalities that could be associated with the feeding of the test material.

C. Selected body weight data are summarized in Table 1. The mean body weights of the high-dose (75 ppm) dogs of both sexes were significantly lower ($p < 0.05$) than the controls at termination of the study and body weight gains were also lower. The mean body weights of mid-dose males were also significantly decreased but mean weight gain did not differ significantly from control. The authors indicated that the effect on the mid-dose group was random and "can be traced back to corresponding differences at the start of the study." Food consumption results were not reported, but the study authors indicated that there were no effects on food intake that could be related to test substance ingestion.

D. Hematology results are summarized in Table 2. Although there were several hematology values that differed significantly from control values, particularly in high-dose animals, when data for males and females were analyzed together at the various intervals

TABLE 1. Summary of Mean Body Weights (kg) at Selected Intervals For Male and Female Dogs Fed Hoe 033171 for 2 Years

Dose Level	Initial	Study Week 13	26	52	78	Terminal	Body Weight Gain
				MALES			
0 ppm	13.58 0.52	14.80 0.46	15.28 0.62	15.53 0.73	17.00 0.93	17.10 1.02	3.52 1.10
3 ppm	13.58 1.30	14.73 1.22	15.10 1.28	15.15 1.31	16.23 1.60	16.50 1.68	2.92 0.87
15 ppm	12.53 0.95	13.52* 0.70	14.02 0.45	14.18 0.59	14.77* 0.67	15.18* 0.83	2.65 0.79
75 ppm	13.53 0.61	14.58 0.54	15.02 0.63	15.10 0.65	14.97* 0.75	15.45* 0.59	1.92* 0.59
				FEMALES			
0 ppm	12.12** 1.03	13.47 1.06	13.88 1.03	14.35 0.99	15.80 0.93	15.85 0.93	3.73 0.79
3 ppm	11.95 0.77	13.40 0.95	13.63 0.71	13.93 0.61	15.17 0.63	14.98 0.64	3.03 0.96
15 ppm	11.67 0.29	12.80 0.58	13.45 0.53	13.72 0.62	14.70 0.76	15.05 1.02	3.38 1.15
75 ppm	12.02 0.39	12.83 0.48	13.13 0.91	13.50 0.84	13.92* 1.25	13.85* 0.97	1.83* 1.15

* Significantly different from control ($p < 0.05$) using Dunnett's t-test. Also significantly different from the controls ($p < 0.05$) by analysis of covariance using the initial weight as the covariant.

** Heterogeneity of variances in all groups using Bartlett's test for homogeneity of variances ($p < 0.05$). (All calculations were made by the reviewers.)

TABLE 2. Summary of Selected Mean Hematology Data at Selected Intervals for Male and Female Dogs Fed Hoe 033171 for 2 Years

Dose Level	Pretest Interval RBC[a] (10^{12}/L)	Hb (g/L)	HCT (%)	PT (sec)	Plat (10^9/L)	1-Year Interval RBC (10^{12}/L)	Hb (g/L)	HCT (%)	PT (sec)	Plat (10^9/L)	Terminal Interval RBC (10^{12}/L)	Hb (g/L)	HCT (%)	PT (sec)	Plat (10^9/L)
MALES															
0 ppm	6.95	160.3	48.5	10.0	357.2	7.59	178.7**	54.2**	15.3**	345.7	7.74	182.8	55.2	7.9	325.5
	0.53	11.3	3.9	0.0	60.8	0.48	12.2	3.1	9.3	64.0	0.52	13.4	3.9	0.8	53.4
3 ppm	6.61	154.0	46.2	10.0	370.7	7.25	168.0	51.0	10.8	340.7	7.49	174.5	52.3	7.6	336.7
	0.37	5.6	2.0	0.0	62.5	0.25	4.8	1.3	1.6	38.4	0.35	6.2	1.3	0.8	51.4
15 ppm	7.00	160.3	48.2	10.2	375.0	7.51	172.3	52.3	11.3	380.2	7.50	174.3	52.3	7.9	382.3
	0.45	8.6	2.9	0.4	61.4	0.14	2.4	0.5	1.9	38.0	0.19	4.8	1.2	0.9	59.5
75 ppm	6.39	149.7	44.2	10.0	357.3	6.89*	157.8*	47.8*	11.3	368.8	6.80*	156.7	47.5*	9.7*	369.2
	0.30	6.2	2.1	0.0	46.7	0.44	8.2	3.1	1.8	50.2	0.39	8.2	2.9	1.0	53.6
FEMALES															
0 ppm	7.01	159.8	48.3	10.0	365.2	7.62	171.8	52.8	11.8**	384.3	7.29	172.0	51.7	7.9**	356.2
	0.24	5.2	1.9	0.0	28.3	0.41	9.0	2.6	1.7	56.1	0.49	13.4	4.1	0.7	71.1
3 ppm	6.71	154.5	46.7	10.0	353.5	7.12	165.0	49.8	10.3	405.8	7.21	167.3	50.2	7.6	407.3
	0.24	5.5	1.6	0.0	75.1	0.78	13.5	4.5	1.5	61.9	0.41	8.6	3.2	1.0	59.2
15 ppm	6.74	159.3	47.5	10.0	347.8	6.47*	155.0	46.5*	10.8	397.7	7.36	173.0	52.3	8.3	361.5
	0.38	6.9	2.2	0.0	72.8	0.29	5.6	2.3	0.8	66.0	0.53	12.6	4.4	1.3	41.6
75 ppm	6.99	164.7	49.0	11.5	358.0	7.17	163.8	49.2	23.0	409.3	6.74	157.7	47.3	9.9	442.7*
	0.33	5.1	1.8	3.7	27.1	0.55	11.7	3.8	29.4	38.7	0.57	10.9	3.5	4.1	33.7

[a] RBC: erythrocyte count; Hb: hemoglobin; HCT: hematocrit; PT: prothrombin time; Plat: platelet count.

* Statistically significant difference from control ($p < 0.05$) using Dunnett's t-test. However, they were not significant after application of the Kruskal-Wallis. All analyses were made by the reviewers.

** Heterogeneity of variances in all groups using Bartlett's test for homogeneity of variances ($p < 0.05$).

during the study, the authors concluded that "there were no significant deviations from control of toxicologic relevance as the values were either borderline changes or within the normal physiological range." Data at selected intervals for males and females analyzed separately are summarized in Table 2. Red blood cell (RBC) counts, hemoglobin (Hb), and hematocrit (HCT) tended to be decreased in high-dose males and females when compared to controls at most intervals and platelet counts increased in the high-dose females when compared to controls.

E. The results of the clinical chemistry determinations for initial, 1-year, and terminal intervals are summarized in Tables 3, 4, and 5, respectively. There were wide variations in the values between groups even at the initial interval; the differences were more pronounced in the males. Lactate dehydrogenase (LDH) values ranged from a mean of 32.5 to 1705.3 U/L in the males and 25.0 to 1319.8 U/L in the females. This same type of variation between groups occurred, but to a lesser extent, for serum triglycerides, glutamic-oxaloacetic-transaminase (SGOT), and alkaline phosphatase (ALP). These variations were less severe at the 1-year and terminal intervals. The authors concluded that those values that deviated from the control values were within the physiologic range of biological variation. The data from the renal and hepatic function tests were comparable between groups.

F. There were no alterations in the urinalysis results that could be detected. Urobilinogen values were only given for 21 months and at termination for technical reasons.

G. At necropsy, no grossly abnormal observations were found that could be related to the administration of the test material. The report authors evaluated the data using organ weights combined for males and females where possible. In their judgment, there were no alterations in organ weights that could be related to the administration of the test material. The ovaries at the high dose and the uterus at the mid and high doses were different from the control; however, this could be accounted for by the differences in the estrus cycle between the groups. The relative organ weights were different for lungs, liver, kidneys, brain, thyroid, ovaries, and uterus at the high dose ($p < 0.05$) from the control, but the authors considered this to be a consequence of the significantly reduced body weight rather than a organ weight change. Since the relative liver weights were significantly different in the authors' statistical analysis, we reanalyzed the individual liver absolute and relative values (Table 6) using Dunnett's t-test. Body weights were significantly ($p < 0.05$) lower in the male mid- and high-dose groups and in the female high-dose group using terminal values. Absolute liver weights did not differ from the controls in either sex at any dose. Relative liver weights were significantly ($p < 0.05$) higher in the male mid-dose and the female high-dose groups as a consequence of the difference in body weight.

TABLE 3. Summary of Selected Mean Clinical Chemistry Values for Male and Female Dogs Fed Hoe 033171 for 2 Years

Dose Level	Initial Interval											
	Na[a]	K	PO_4	Total Bili.	Glucose	Creat.	Chol.	Trig.	SGOT	SGPT	ALP	LDH
MALES												
0 ppm	148.7†	4.5	1.5†	7.3	5.2†	92.3†	4.1	0.80	28.7†	34.0	196.8	1705.3†
	1.2	0.2	0.1	0.8	0.6	11.3	0.6	0.18	17.7	9.8	25.2	237.8
3 ppm	146.7	4.7	1.8	8.1	5.6	93.3	3.5	0.59*	18.3	30.2	170.3	32.5*
	0.5	0.2	0.4	2.0	0.3	3.4	0.4	0.11	3.4	7.7	23.6	11.6
15 ppm	145.5	4.5	1.6	5.7	6.1*	81.2	3.6	0.54*	12.8*	29.0	131.7*	1574.2
	2.2	0.4	0.2	1.1	0.1	10.2	0.4	01.10	1.2	4.2	10.5	7[illegible].7
75 ppm	147.5	4.3	1.8	5.1*	5.8*	94.2	4.0	0.56*	13.8*	25.5	153.5*	1650.8
	2.7	0.3	0.1	0.6	0.2	4.5	0.7	0.12	2.6	6.7	15.7	287.2
FEMALES												
0 ppm	148.3	[illegible]	1.5	7.9	5.6	102.2†	3.7†	0.73	19.3	25.0	196.0	164.3†
	1.2	0.2	0.1	0.[illegible]	[illegible]	3.1	0.3	0.13	2.5	5.1	27.5	293.4
3 ppm	147.7	4.6	1.7*	6.8	[illegible].8	110.8	4.1*	0.88	19.3	21.5	194.5	25.0
	1.9	0.2	0.2	1.1	0.1	16.4	[illegible]	0.11	1.8		[illegible]6	[illegible]5
15 ppm	147.0	4.4	1.8*	5.8*	[illegible]	85.5	3.9	0.62	13.2*	24.5	148.0*	1319.8*
	3.1	0.2	0.1	0.8	0.3	22.8	0.2	0.13	1.6	5.3	27.2	514.4
75 ppm	149.7	4.2*	1.9*	6.6	5.8	97.7	4.4*	0.69	14.0*	21.3	160.5	47.5
	2.4	0.2	0.1	1.3	0.3	13.1	0.5	0.07	2.1	3.2	30.0	6.6

[a] Na: sodium (mmol/L); K: potassium (mmol/L); PO_4: inorganic phosphorus (mmol/L); Total Bili.: total bilirubin (µmol/L); Creat.: creatinine (µmol/L); Chol.: cholesterol (mmol); Trig.: triglycerides (mmol/L); SGOT: serum glutamic-oxaloacetic transaminase (U/L); SGPT: serum glutamic pyruvic transaminase (U/L); ALP: alkaline phosphatase (U/L); LDH: lactate dehydrogenase (U/L).

* Significantly different from control ($p < 0.05$) using Dunnett's t-test. However, they were not significant after application of the Kruskal-Wallis test. All analyses were made by the reviewers.

†Heterogeneity of variances in all groups using Bartlett's test for homogeneity of variances ($p < 0.05$).

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TABLE 4. Summary of Selected Mean Clinical Chemistry Values for Male and Female Dogs Fed Hoe 033171 for 2 Years

Dose Level	1-Year Interval											
	Na	K	PO_4	Total Bili.	Glucose	Creat.	Chol.	Trig.	SGOT	SGPT	ALP	LDH
MALES												
0 ppm	150.8	4.9	1.5	4.3	5.7	95.3	3.4	0.36	15.3	33.3	81.1	63.0
	3.5	0.3	0.1	0.6	0.5	14.7	0.5	0.06	2.2	5.3	28.4	19.6
3 ppm	146.5	4.4*	1.5	3.7	5.5	81.0	3.2	0.37	13.5	31.0	75.3	50.7
	3.9	0.1	0.1	0.4	0.2	4.9	0.5	0.07	2.4	5.8	11.1	13.9
15 ppm	147.7	4.5*	1.1*	3.6	5.7	92.8	3.5	0.39	13.8	28.3	75.0	77.3
	4.0	0.1	0.1	0.4	0.2	8.9	0.4	0.05	1.2	5.7	10.8	23.9
75 ppm	150.5	4.9	1.4	4.3	5.4	98.0	3.1	0.43	14.3	23.5*	83.2	57.3
	1.4	0.2	0.1	0.6	0.4	8.0	0.5	0.14	2.0	3.6	12.2	22.7
FEMALES												
0 ppm	145.8	4.5	1.5	4.5	5.5	77.0†	4.4†	0.62	13.3	26.8	96.8	67.5
	1.5	0.3	0.1	0.6	0.3	5.5	0.3	0.11	2.1	5.8	28.2	14.7
3 ppm	150.3	4.6	1.6	4.8	5.4	68.2	4.1	0.60	14.0	21.5	89.8	66.5
	4.2	0.2	0.1	1.0	0.2	8.2	0.8	0.18	4.0	2.9	12.5	7.3
15 ppm	417.7	4.8	1.4	4.2	5.6	89.8	4.0	0.64	12.2	19.2*	112.3	54.2
	151.0*	2.2	0.1	1.0	0.4	8.2	1.2	0.21	1.7	3.8	34.2	7.3
75 ppm	149.7	5.1*	1.5	4.5	5.5	78.2	4.5	0.62	13.2	20.0*	111.3	69.3
	3.7	0.4	0.1	0.6	0.4	21.1	0.6	0.17	1.9	5.3	14.9	19.9

[a] Na: sodium (mmol/L); K: potassium (mmol/L); PO_4: inorganic phosphorus (mmol/L); Total Bili.: total bilirubin (μmol/L); Creat.: creatinine (μmol/L); Chol.: cholesterol (mmol); Trig.: triglyceride (mmol/L); SGOT: serum glutamic-oxaloacetic transaminase (U/L); SGPT: serum glutamic pyruvic transaminase (U/L); ALP: alkaline phosphatase (U/L); LDH: lactate dehydrogenase (U/L).

* Significantly different from control ($p < 0.05$) using Dunnett's t-test. However, they were not significant after application of the Kruskal-Wallis test. All analyses were made by the reviewers.

†Heterogeneity of variances in all groups using Bartlett's test for homogeneity of variances ($p < 0.05$).

TABLE 5. Summary of Selected Mean Clinical Chemistry Values for Male and Female Dogs Fed Hoe 033171 for 2 Years

Dose Level	Terminal Interval											
	Na[a]	K	PO_4	Total Bili.	Glucose	Creat.	Chol.	Trig.	SGOT	SGPT	ALP	LDH
MALES												
0 ppm	148.7	4.4	1.3	3.9	5.3	79.0	3.9	0.38	13.2†	32.3	86.2	94.2
	0.8	0.2	0.1	1.2	0.2	9.8	0.5	0.03	1.2	13.0	32.3	23.1
3 ppm	148.0	4.5	1.3	3.2	5.3	80.7	3.6	0.22*	13.2	16.8*	79.2	90.2
	1.4	0.1	0.1	1.0	0.3	15.4	0.4	0.03	1.9	2.3	26.5	14.4
15 ppm	150.7*	4.5	1.3	3.0	5.3	75.7	3.5	0.47	18.3*	27.3	78.7	55.8*
	1.5	0.2	0.1	0.6	0.2	11.0	0.6	0.09	1.0	4.5	17.6	6.3
75 ppm	153.0*	4.6	1.3	2.4	5.0	78.3	3.7	0.42	19.2*	20.7**	80.0	99.7
	1.4	0.3	0.1	0.5	0.1	9.1	0.5	0.06	4.3	4.4	17.6	6.3
FEMALES												
0 ppm	149.2	4.6	1.5†	3.3†	5.5	72.7	4.8	0.46	11.0	16.3	109.7	81.3
	1.2	0.2	0.1	1.7	0.2	14.2	0.5	0.10	2.4	4.2	24.2	20.4
3 ppm	148.5	4.7	1.5	2.3	5.4	80.3	6.5*	0.62	12.5	16.5	112.7	108.2
	1.9	0.4	0.2	0.3	0.3	16.6	1.6	0.23	2.4	4.9	48.8	36.9
15 ppm	152.0*	4.7	1.4	2.5	5.3	77.2	4.6	0.57	15.0*	19.8	117.8	71.3
	1.9	0.4	0.4	0.4	0.2	18.1	0.7	0.15	2.3	2.7	36.4	20.5
75 ppm	154.3*	4.9	1.6	3.6	5.1*	69.7	5.5	0.76	16.3*	16.2	127.3	153.8*
	1.2	0.4	0.3	1.3	0.3	8.1	0.8	0.21	2.4	5.2	53.2	35.2

[a] Na: sodium (mmol/L); K: potassium (mmol/L); PO_4: inorganic phosphorus (mmol/L); Total Bili.: total bilirubin (µmol/L); Creat.: creatinine (µmol/L); Chol.: cholesterol (mmol); Trig.: triglycerides (mmol/L); SGOT: serum glutamic-oxaloacetic transaminase (U/L); SGPT: serum glutamic pyruvic transaminase (U/L); ALP: alkaline phosphatase (U/L); LDH: lactate dehydrogenase (U/L).

* Significantly different from control ($p < 0.05$) using Dunnett's t-test. However, they were not significant after application of the Kruskal-Wallis test. All analyses were made by the reviewers.

** Statistically significantly different from control ($p < 0.01$).

†Heterogeneity of variances in all groups using Bartlett's test for homogeneity of variances ($p < 0.05$).

TABLE 6. Mean Absolute and Relative Liver Weights and Body Weights at Termination of a 2-Year Dog Study on Hoe 033171

Dose (ppm)	Body Weight (kg)	Absolute Liver Weight (g)	Relative Liver Weight
		Males	
0	17.10	495.2	2.90
3	26.50	544.8	3.31
15	15.18*	527.7	3.49*
75	15.45*	503.5	3.26
		Females	
0	15.85	453.0	2.86
3	14.98	524.8	3.50
15	15.05	530.7	3.54
75	13.85*	529.8	3.82*

* Significantly different from control ($p < 0.05$). Analysis by ANOVA followed by Dunnett's t-test (calculations by the reviewers).

H. Organ findings that occurred equally in both control and dose animals included involution of the thymus and slight- to medium-grade lipomatosis of the parotid gland. These were considered to be spontaneous changes and not related to the administration of the test material. No histopathologic alterations were associated with the chronic oral administration of Hoe 033171 to dogs for a period of 2 years.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The feeding of 0, 3, 15, and 75 mg Hoe 033171/kg diet to dogs had no effect on survival. Feeding 3 and 15 mg/kg produced no compound-related effects on dogs over a 2-year period. The diet, containing 75 mg/kg of test material, caused significant ($p < 0.05$) reduction in body weight gains. "No pathological organ changes occurred in any of the groups." The NOEL for Hoe 033171 established in this study is 15 mg/kg diet or 15 ppm.

B. A quality assurance statement was signed and dated February 7, 1985. The study was inspected approximately 13 times during its conduct.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. All animals survived the study and appeared in good health. They showed no compound-related signs of toxicity or abnormal behavior.

B. Body weight was significantly suppressed ($p < 0.05$) in the high-dose animals of both sexes. The authors indicated, however, that the suppressed body weight in the mid-dose dogs was probably due to low initial weights. We analyzed the body weight data by analysis of covariance where the initial weight was the covariant. Male body weights were significantly lower than the controls ($p < 0.05$) for the mid- and high-dose groups at 78 weeks and at termination. The females did not differ from the controls at the mid dose at any interval. Although food consumption data were not provided, the authors indicated that all dogs ate well.

C. We agree with the authors that the dietary administration of Hoe 033171 for 2 years had no effect on hematology, clinical chemistry, or urinalysis values. There was a wide degree of variation on a group basis in clinical chemistry parameters as typified by LDH values. The LDH enzymes occur in a far larger quantity associated with the red cell than with the plasma; therefore, the very high values are possibly due to hemolysis. This may also be the reason for the variation in other values where results are sensitive to hemolysis.

There were no gross or microscopic alterations resulting from the administration of Hoe 033171 in the diet of dogs for 2 years. Absolute liver weights were not affected by the administration of the test material. The relative liver weight was higher than the control value but this was accountable on the basis of significantly reduced body weight. The NOEL is 3.0 ppm while the LOEL is 15 ppm due to an alteration in body weight.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 5-15.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 157 through 167 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004063

EPA: 68-02-4225
DYNAMAC No. 1-12-F5
January 27, 1986

DATA EVALUATION RECORD

HOE 033171

Metabolic Study in Rats

STUDY IDENTIFICATION: Kellner and Eckert. Hoe 033171-(chlorophenyl-U-14-C), study of kinetics and residue concentrations following repeated oral applications of 2 mg/kg/day in rats. (English translation of unpublished study No. A 30455 prepared by Hoechst Radiochemical Laboratory for Hoechst AG, Frankfurt am Main, W. Germany; dated December 4, 1984.) Accession No. 258971.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

1. CHEMICAL: Acclaim; Hoe 033171; ethyl-2-(4-[6-chloro-2-benzoxazolyl-oxy]-phenoxy)-propanoate.

2. TEST MATERIAL: Hoe 033171 was either unlabeled or uniformly labeled with [^{14}C] in the chlorophenyl ring. The purity of both compounds was 98 percent. The specific activity of [^{14}C]Hoe was 22.85 mCi/g.

3. STUDY/ACTION TYPE: Metabolic study in rats.

4. STUDY IDENTIFICATION: Kellner and Eckert. Hoe 033171-(chlorophenyl-U-14-C), study of kinetics and residue concentrations following repeated oral applications of 2 mg/kg/day in rats. (English translation of unpublished study No. A 30455 prepared by Hoechst Radiochemical Laboratory for Hoechst AG, Frankfurt am Main, W. Germany; dated December 4, 1984.) Accession No. 258971.

5. REVIEWED BY:

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W.T. Edwards
EPA Reviewer

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Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-7-86

7. CONCLUSIONS:

A. Male and female Wistar rats were administered 14 consecutive daily oral doses of 2 mg/kg unlabeled Hoe 033171 dissolved in sesame oil. On day 15, each rat was given an identical dose of [^{14}C]-Hoe 033171 (uniformly labeled in the chlorophenyl ring). Urine and feces were collected separately at fixed intervals for 7 days, after which time the animals were sacrificed and various tissues and organs were analyzed for Hoe 033171 residues. Total recoveries at the end of the 7-day test period were 94.6 percent of the administered dose in male rats and 100.4 percent in females. The females excreted about 25 percent more of the dosed radioactivity in the urine than the males (66 versus 50 percent). Fecal excretion was 31 and 40 percent of the administered dose for females and males, respectively. Elimination kinetics in the urine or feces of each sex were biphasic: Phase I half-lives were between 8.5 and 12.5 hours and phase II half-lives were between 27 and 73 hours.

Only about 3 to 4 percent of the administered radioactivity remained in the rat bodies at 168 hours after dosing. The tissues containing the highest concentrations of [^{14}C]Hoe 033171 equivalents were the kidneys, liver, blood, and fat (0.1-0.3 ppm). All other tissues contained less than 0.1 ppm.

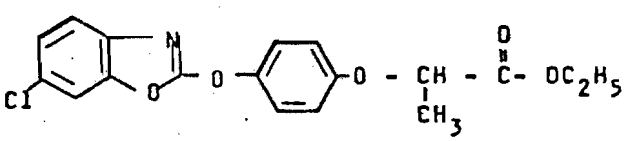
B. This study is acceptable.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The test materials used in this study were Hoe 033171, both unlabeled and uniformly labeled with [^{14}C] in the chlorophenyl ring. Both compounds were shown to be 98 percent pure and the radiolabeled compound cochromatographed with the unlabeled compound when analyzed by thin-layer chromatography (TLC) using three different, but closely related, solvent systems. The authors did not state whether [^{14}C]Hoe 033171 was diluted with unlabeled material prior to dosing; subsequently, it must be assumed that they used the undiluted labeled material. For the purposes of this DER the labeled compound will be referred to as [^{14}C]Hoe. The following is the structure of Hoe 033171:



[1]Only items appropriate to this DER have been included.

2. Five male and five female SPF Wistar rats (210-275 g) were each administered by gavage approximately 2 mg/kg (2.29-2.43 mg/kg for males and 2.02-2.22 mg/kg for females) of unlabeled Hoe 033171 dissolved in sesame oil. The animals were dosed daily for 14 consecutive days. On day 15, each animal was given an identical dose of [^{14}C]Hoe. Then, the animals were individually housed in metabolism cages, and urine and feces were collected separately at fixed intervals. The animals were sacrificed 168 hours (7 days) following the administration of [^{14}C]Hoe, and [^{14}C] residues in the spleen, kidneys, ovaries, liver, heart, lungs, muscle, fat, brain, bones, blood, and remaining carcass were quantified.

3. Urine was diluted with water:ethanol (1:1) and radioassayed by liquid scintillation counting (LSC). Feces were dried, pulverized, and then combusted before being radioassayed by LSC. Tissue samples were digested, then decolorized with H_2O_2 before radioassay. Care was taken to ensure that clear, homogeneous samples were counted. Proper blanks were run for each tissue to correct for quenching.

12. REPORTED RESULTS:

A. Table 1 shows the amount of [^{14}C] excreted in the urine and feces over the 7-day collection period. More radioactivity was eliminated in the urine than in the feces. Females excreted about 25 percent more [^{14}C]Hoe equivalents via the urine (66.2±4.6 percent of the administered dose) than did males (49.8±3.3 percent). Fecal excretion was 31.1±4.8 and 40.4±3.0 percent of the administered dose for males and females, respectively. Graphs showing the elimination of [^{14}C]Hoe equivalents in the urine and feces versus time are included as Appendix B (CBI Figures 1-4).

Elimination of [^{14}C] in the urine or feces of each sex was biphasic. Regardless of the sex of the animals, the biological half-lives (calculated from the graph by linear regression analysis) for the rapid phase I were similar for urine and feces, ranging from 8.5 to 12.5 hours. For the slower phase II, half-lives in urine were 41.3 hours for the females and 72.5 hours for the males. For feces, half-lives of 27.3 and 33.7 hours were calculated for males and females, respectively.

B. Table 2 shows the concentrations of [^{14}C]Hoe equivalents that were found in the tissues 168 hours after dosing with [^{14}C]Hoe. The blood level at sacrifice in both females and males was about 0.2 µg/mL. In the kidneys, 0.22±0.02 µg equivalents of [^{14}C]Hoe/g (ppm) were found in males and 0.03±0.03 ppm in females. Concentrations in the liver were 0.13±0.008 ppm and 0.09±0.01 ppm in males and females, respectively. In the males,

TABLE 1. Elimination of Radioactivity in Urine and Feces Following Repeated Oral Doses of Unlabeled Test Material at 2 mg/kg for 14 Successive Days and One Single Dose of [^{14}C]Hoe of 2 mg/kg on Day 15[a]

Time (hours) postadministration	Males		Females	
	Urine	Feces	Urine	Feces
0-8	3.89 ± 3.44	---	5.31 ± 1.66	0.56 ± 0.42[b]
8-24	27.70 ± 3.45	20.84 ± 3.30	36.58 ± 7.66	16.04 ± 4.70[b]
24-48	11.93 ± 1.89	12.30 ± 1.78	16.29 ± 3.96	14.54 ± 5.88
48-72	3.04 ± 0.63	2.78 ± 0.58	3.22 ± 1.47	2.00 ± 0.92
72-96	1.12 ± 0.16	0.65 ± 0.17	1.19 ± 0.37	0.59 ± 0.26
96-120	0.54 ± 0.09	0.36 ± 0.16	0.69 ± 0.24	0.20 ± 0.07
120-144	0.39 ± 0.07	0.32 ± 0.19	0.52 ± 0.19	0.22 ± 0.09
144-168	0.34 ± 0.04	0.11 ± 0.03	0.34 ± 0.10	0.30 ± 0.16
Sum (0-168)	48.95 ± 3.49 (49.8 ± 3.3)[c]	40.37 ± 3.03	64.15 ± 4.44 (66.2 ± 4.6)[c]	31.13 ± 4.82

[a]Values are mean ± SD percent of administered [^{14}C] of five rats per sex. The means and SD were calculated by our reviewers.

[b]Only four samples were used to calculate these means.

[c]These totals also include radioactivity washed from the walls of the metabolism cages.

TABLE 2. Concentrations of [^{14}C]Hoe Equivalents in the Organs and Tissues 7 Days after Repeated Oral Doses of 2 mg/kg of Unlabeled Test Material for 14 Successive Days and One Single Dose of 2 mg/kg of [^{14}C]Hoe on Day 15

Tissue	Concentration (ppm)	
	Male	Female
Spleen	0.04 ± 0.06	0.04 ± 0.01
Kidneys	0.22 ± 0.02	0.30 ± 0.03
Testes/Ovaries	0.02 ± 0.003	0.06 ± 0.01
Liver	0.13 ± 0.008	0.09 ± 0.01
Heart	0.06 ± 0.01	0.04 ± 0.005
Lung	0.08 ± 0.006	0.08 ± 0.01
Muscle	0.02 ± 0.005	0.02 ± 0.002
Subcutaneous Fat	0.13 ± 0.09	0.11 ± 0.02
Retroperitoneal Fat	0.19 ± 0.15	0.07 ± 0.03
Brain	0.007 ± 0.001	0.005 ± 0.001
Bone	0.02 ± 0.004	0.02 ± 0.004
Carcass	0.07 ± 0.009	0.04 ± 0.004
Blood	0.24 ± 0.03	0.21 ± 0.02

[a]Values represent mean ± SD of five rats per sex.

the retroperitoneal fat contained 0.19 ppm and the subcutaneous fat contained 0.13 ppm of [^{14}C]Hoe equivalents. The corresponding values for the females were 0.07±0.03 and 0.11±0.02 ppm. In all other organs and tissues examined, concentrations were below 0.1 ppm and some were even lower than 0.01 ppm. The total recovery of [^{14}C] 7 days postadministration was 94.56±1.34 and 100.36±0.67 percent for male and female rats, respectively.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Rats were administered daily oral doses of 2 mg/kg of unlabeled Hoe 033171 for 14 consecutive days. Twenty-four hours later, they were given a similar dose of [^{14}C]Hoe. Urine and feces were collected on each of the next 7 days, after which time the animals were sacrificed and residues of [^{14}C]Hoe equivalents were quantified. Elimination of radioactivity was higher in urine than in feces.

For females, 66 and 31 percent of the administered dose was excreted in the urine and feces, respectively. For male rats, 50 and 40 percent were excreted in the urine and feces, respectively. Elimination of [^{14}C] in urine and feces for each sex was biphasic: Phase I half-lives were between 8.5 and 12.5 hours and phase II half-lives were between 27 and 73 hours.

Residues in organs and tissue were determined 7 days postadministration. Concentrations were highest in the kidneys with about 0.30 ppm for the females and about 0.22 ppm for the males. Blood concentrations were approximately 0.22 ppm in each sex. Fat contained 0.13-0.19 ppm in the males and about 0.1 ppm in the females. Concentrations in the liver were also approximately 0.1 ppm. The concentrations in all the other tissues examined were lower than 0.1 ppm, some being lower than 0.01 ppm. Total recoveries of [^{14}C] were about 94.6 and 100.4 percent of the administered dose for males and females, respectively.

B. It was stated in the report that the study was conducted in compliance with the principles of Good Laboratory Practice and that no improprieties were observed that would affect the quality or integrity of the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS: In general, this study was well conducted. The animals and test materials used in this study were thoroughly characterized. Recovery of total labeled material was excellent, 94.6 percent for males and 100.4 percent for females. The elimination kinetics were clearly biphasic and similar for both urine and feces in each sex. One minor deficiency with this report is that the authors did not analyze the data on the elimination kinetics of [^{14}C]Hoe equivalents for statistical differences between sexes. In addition, the specific

activity of the [^{14}C]Hoe administered to the rats was not reported; consequently, it appears that the [^{14}C]Hoe was not diluted with unlabeled material.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 5-8, and Appendix B, CBI Figures 1-4.

Appendix A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 177 through 180 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

Appendix B

CBI Figures 1-4

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 182 through 185 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

EPA: 68-02-4225
DYNAMAC No. 1-12-F4
January 27, 1986

004963

DATA EVALUATION RECORD

HOE 033171

Metabolic Study in Rats

STUDY IDENTIFICATION: Kellner and Eckert. Hoe 033171-(chlorophenyl--U-14-C): Study of kinetics and residue concentrations following oral application of 10 mg/kg body weight in rats. (English translation of unpublished study No. A30453 prepared by Hoechst Radiochemical Laboratory, for Hoechst AG, Frankfurt am Main, W. Germany; dated November 30, 1984.) Accession No. 258971.

APPROVED BY:

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Department Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 1-27-86

1. CHEMICAL: Acclaim; Hoe 033171; ethyl-2-(4-[6-chloro-2-benzoxazolyl-oxy]-phenoxy)-propanoate.

004963

2. TEST MATERIAL: Hoe 033171 was uniformly labeled with [^{14}C] in the chlorophenyl ring. Its radiochemical purity was 98 percent and its specific activity was 22.85 mCi/g.

3. STUDY/ACTION TYPE: Metabolic study in rats

4. STUDY IDENTIFICATION: Kellner and Eckert. Hoe 033171-(chlorophenyl--U-14-C): Study of kinetics and residue concentrations following oral application of 10 mg/kg body weight in rats. (English translation of unpublished study No. A30453 prepared by Hoechst Radiochemical Laboratory, for Hoechst AG, Frankfurt am Main, W. Germany; dated November 30, 1984.) Accession No. 258971.

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Signature: W. Thomas Edwards
Date: 2-5-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-7-86

7. CONCLUSIONS:

A. Male and female Wistar rats were administered single oral doses (10 mg/kg) of [^{14}C]Hoe 033171 (uniformly labeled in the chlorophenyl ring). Male rats excreted 44 and 49 percent of the dose in urine and feces, respectively, whereas female rats excreted 60 and 35 percent, respectively. Excretion kinetics were biphasic for both urine and feces with phase I half-lives between 8 and 10 hours and phase II half-lives between 26 and 69 hours, regardless of sex. Examination of tissues and organs 7 days after dosing showed the highest concentrations of [^{14}C] to be in the fat, blood, and kidneys. Only 4 to 5 percent of the administered dose remained in the rat body 7 days postadministration. Total recoveries of administered radioactivity at the end of the 7-day test period were 98 percent for males and 100 percent for females.

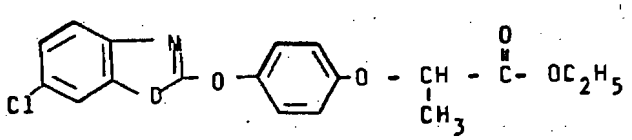
B. This study is acceptable.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The test material used in the study was Hoe 033171, uniformly labeled with [^{14}C] in the chlorophenyl ring. It had a radiochemical purity of 98 percent and cochromatographed with the unlabeled compound when analyzed by thin-layer chromatography (TLC) using three different, but closely related, solvent systems. The labeled material was diluted with unlabeled Hoe 033171 to a specific activity of 12.02 mCi/g. For the purposes of this DER the labeled test material will be referred to as [^{14}C]Hoe. The following is the structure of Hoe 033171:



[1]Only items appropriate to this DER have been included.

2. Five male and five female SPF Wistar rats (165-200 g) were each administered approximately 10 mg/kg of [^{14}C]Hoe dissolved in sesame oil as a single oral dose. After dosing, the animals were individually housed in metabolism cages, and their urine and feces were collected separately at fixed intervals. The animals were sacrificed at 168 hours (7 days) postadministration and the amount of radioactivity remaining in the spleen, kidneys, ovaries, liver, heart, lungs, muscle, fat, brain, bones, blood, and remaining carcass was quantified.

3. For quantification of [^{14}C], urine was diluted with water: ethanol (1:1) and radioassayed by liquid scintillation counting (LSC). Feces were dried, pulverized, and then combusted before they were radioassayed by LSC. Tissue samples were digested, then decolorized with H_2O_2 before radioassay. Care was taken to ensure that clear, homogeneous samples were counted. Proper blanks were run for each tissue to correct for quenching.

12. REPORTED RESULTS:

A. Following the administration of single oral doses of 10 mg/kg of [^{14}C]Hoe, male rats excreted 44 and 49 percent of the radioactivity in the urine and feces, respectively, by 168 hours after dosing (Table 1). Over the same time period, females excreted 60 and 35 percent of the administered [^{14}C] in the urine and feces, respectively. Excretion curves for [^{14}C]Hoe equivalents via urine and feces for both sexes (CBI Figures 1-4, see Appendix B) indicated that excretion kinetics were biphasic for urine and feces of both sexes. Estimated biological half-lives, calculated from the elimination constants, averaged between 8 and 10 hours for the rapid phase I for urine and feces regardless of sex. Phase II half-lives for the elimination via urine and feces were calculated to be 35.6 and 45 hours for males and 69.4 and 26.5 hours for the females, respectively.

B. The highest tissue concentrations of [^{14}C]Hoe equivalents 7 days after dosing were found in the fat (Table 2). Male rats had 1.26±0.55 and 1.97±0.81 ppm in subcutaneous and retroperitoneal fat, respectively, whereas female rats had 0.87±0.72 and 1.32±1.02 ppm in subcutaneous and retroperitoneal fat, respectively. The large standard deviations are the result of high interindividual differences in general and not because of a single outlier. The blood concentrations were 0.74±0.13 and 1.53±0.86 ppm for males and females, respectively. Relatively high concentrations of [^{14}C]Hoe equivalents were also measured in the kidneys, 1.28±0.12 ppm for females and 0.74±0.14 ppm for males. All other tissues and organs examined contained relatively low concentrations.

TABLE 1. The Excretion of [^{14}C] into the Urine and Feces of Rats Following Administration of a Single Oral Dose of [^{14}C]Hoe at 10 mg/kg[a]

Time (hours) postadministration	Males		Females	
	Urine	Feces	Urine	Feces
0-8	5.85±3.36	1.35±[b]	8.72±1.48	0.87±0.33
8-24	22.05±4.71[c]	30.80±3.04	33.43±3.36	18.58±6.22
24-48	10.20±0.60	13.02±2.46	11.55±1.87	11.12±1.62
48-72	2.48±0.21	2.18±0.50	3.01±1.21	2.73±1.32
72-96	1.14±0.21	0.95±0.48	0.97±0.29	0.82±1.00
96-120	0.63±0.13	0.33±0.08	0.49±0.13	0.44±0.64
120-144	0.38±0.12	0.21±0.06	0.38±0.08	0.57±1.04
144-168	0.28±0.07	0.16±0.02	0.30±0.08	0.13±0.01
Total (0-168)	43.02±3.57 (43.86)[d]	49.00±2.56 [c]	58.86±5.16 (60.35)[d]	35.27±5.10

[a] Values are mean ± SD percent of [^{14}C] administered to five rats per sex. The means and SD were calculated by our reviewers.

[b] No fecal samples were obtained for two of the five rats for this time interval.

[c] These values were not reported correctly by the study authors.

[d] These values include [^{14}C] that was washed from the cages.

TABLE 2. Concentrations of [^{14}C]Hoe Equivalents in Organs and Tissues 7 Days After Administration of a Single Oral Dose at 10 mg/kg

Tissue	Concentration (ppm)	
	Male	Female
Spleen	0.13±0.03[a]	0.17±0.04
Kidneys	0.74±0.14	1.28±0.11
Testes/Ovaries	0.08±0.02	0.46±0.18
Liver	0.34±0.04	0.40±0.04
Heart	0.22±0.09	0.31±0.11
Lung	0.26±0.04	0.31±0.03
Muscle	0.10±0.02	0.09±0.02
Subcutaneous Fat	1.26±0.55	0.87±0.72
Retroperitoneal Fat	1.97±0.81	1.32±1.02
Brain	0.02±0.01	0.02±0.004
Bone	0.07±0.02	0.08±0.02
Carcass	0.24±0.06	0.24±0.04
Blood	0.74±0.13	1.53±0.86

[a]Values represent the mean ± SD of five rats per sex.

From the concentrations measured in the different organs, tissues, and carcass, it can be estimated that the female rats at day 7 contained 4.25±0.80 percent of the administered dose (not including the gastrointestinal tract); male rats contained 5.09±1.17 percent. The total amount of radioactivity recovered after 7 days was 99.87±1.98 percent for the females and 97.96 percent for the males.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Following single oral doses of [^{14}C]Hoe at 10 mg/kg, radioactivity was eliminated in the urine and the feces. For the females, the amount excreted in the urine was about 60 percent of the administered dose (60.36±5.08 percent); this was approximately one-fourth higher than that for the males (43.86±3.77 percent). The elimination via the feces amounted to 49.60±2.57 percent for the males and 35.27±5.10 percent for the females. The half-lives for biphasic elimination via urine and feces ranged from 8 to 10 hours for phase I in both sexes. For phase II they ranged from 26.5 to 69.4 hours.

Residues in organs and tissues were determined 7 days postdosing. The highest concentrations were found in the fat from males and females and ranged between 0.87 and 1.97 ppm and in the kidneys of the females (1.28± 0.12 ppm). Blood levels were 0.74 ppm for the males and 1.53 ppm for the females. The concentrations in all the other tissues examined (spleen, ovaries, liver, heart, lung) were lower than 1 ppm; some were lower than 0.1 ppm (testes, bone, brain, muscle). Total recovery of [^{14}C] was 99.87 and 97.96 percent of the administered dose for females and males, respectively.

B. A statement in the report indicated that the study was conducted in compliance with the principles of Good Laboratory Practice and that no improprieties were observed that would affect the quality or integrity of the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS: Our reviewers agree with the authors' conclusions on the excretion and tissue distribution of Hoe 033171 in Wistar rats following the administration of a single oral dose at 10 mg/kg. However, some minor deficiencies were noted. Two values were found to be reported incorrectly (see DER Table 1), and the excretion curves (CBI Figures 1-4) were presented in such a way as to make recalculation of the phase I excretion half-lives difficult. Also, the authors presented no statistical analyses of the data on excretion kinetics.

Item 15--see footnote 1

16. CBI Appendix: Appendix A, Materials and Methods, CBI pp. 3-6, and Appendix B, CBI Figures 1-4.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 195 through 199 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

Appendix B

CBI Figures 1-4

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 201 through 204 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

EPA: 68-02-4225
DYNAMAC No. 1-12-F3
January 27, 1986

004963

DATA EVALUATION RECORD

ACCLAIM

Metabolic Study in Rats

STUDY IDENTIFICATION: Bürkle, W. L., Schmidt, E., Rutz, U., and Kellner, H. M. Hoe 033171-dioxyphenyl-1-^{14}C, metabolism in rats orally administered at two doses, 2 and 10 mg/kg body weight. (Unpublished study No. A30377 prepared and submitted by Hoechst Aktiengesellschaft Geschäfts-Bereich Landwirtschaft Pflanzenschutz-Forschung, West Germany; dated January 3, 1985.) Accession No. 258971.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

205

1. CHEMICAL: Acclaim; Hoe 33171; ethyl-2-(4-(6-chloro-2-benzoxazolyl-oxy)-phenoxy)-propanoate.

2. TEST MATERIAL: [1-^{14}C-dioxyphenyl]Hoe 33171 had a specific activity of 11.36 mCi/g and a radiochemical purity of 96 percent.

3. STUDY/ACTION TYPE: Metabolic study in rats.

4. STUDY IDENTIFICATION: Bürkle, W. L., Schmidt, E., Rutz, U., and Kellner, H. M. Hoe 033171-dioxyphenyl-1-^{14}C, metabolism in rats orally administered at two doses, 2 and 10 mg/kg body weight. (Unpublished study No. A30377 prepared and submitted by Hoechst Aktiengesellschaft Geschäfts-Bereich Landwirtschaft Pflanzenschutz-Forschung, West Germany; dated January 3, 1985.) Accession No. 258971.

5. REVIEWED BY:

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Date: 1/24/86

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6. APPROVED BY:

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Date: 2-5-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-7-86

7. CONCLUSIONS:

A. The metabolism of Hoe 33171 was investigated following oral administration of [1-^{14}C-dioxyphenyl]Hoe 33171 in a single dose to male Wistar rats at 10 mg/kg and female rats at 2 or 10 mg/kg.

A large proportion of the administered radioactivity was eliminated in the urine and feces during the initial 24 hours of posttreatment: high-dose males, 73 percent; high-dose females, 66 percent; and low-dose females, 80 percent. Sex- and dose-related differences in radiolabel excretion were apparent. In the 10-mg/kg dose groups, the females eliminated more radiolabel in the urine and less in the feces than did the males. In addition, the females receiving 2 mg/kg had a higher rate of urinary excretion of radioactivity than the females receiving 10 mg/kg, although fecal excretion rates between the two groups were similar.

Sex- and dose-related differences in the metabolic profiles were also apparent. In the 0- to 24-hour urine of male rats dosed at 10 mg/kg, a major metabolite, which accounted for 99 percent of the total urine radioactivity, was identified as 2-(4-hydroxyphenoxy)-propionic acid (HPP acid). Two major metabolites were identified in the 0- to 24-hour urine of female rats: HPP acid and 2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propionic acid (free acid of Hoe 33171). HPP acid and the free acid were excreted in the urine of the high- and low-dose females at ratios of 1:1 and 2:1, respectively. The two primary compounds identified in the 0- to 24-hour feces of each dose group were Hoe 33171 (17 to 38 percent of total fecal radioactivity) and the free acid (31 to 46 percent). The females receiving 2 mg/kg excreted more of the free acid and less of the parent compound into the feces than did the high-dose male and female rats.

B. This study provides acceptable data on the metabolism and elimination of Hoe 33171 in rats.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The test animals were 16- to 18-week-old male and female SPF Wistar rats. The animals were housed two per cage under

[1]Only items appropriate to this DER have been included.

controlled environmental conditions and allowed access to commercial diet and water ad libitum.

2. The test material, [1-^{14}C-dioxyphenyl]Hoe 33171, was dissolved in sesame oil and administered in a single oral dose to rats as follows: 1) 15 female rats each received a single 2-mg/kg dose and 2) 10 rats of each sex received a 10-mg/kg dose.

3. Urine and feces from individual animals of each group were collected and pooled 1, 2, 3, and 4 days following [^{14}C]Hoe 33171 administration. Composite urine and feces samples were then radioassayed using standard techniques.

4. For metabolite identification, the 0- to 24-hour urine and fecal samples were analyzed by high performance liquid chromatography (HPLC) and thin-layer chromatography (TLC). Details of sample preparation and analysis are presented in Appendix A. Identification of the radioactive HPLC peaks in the urine and feces was achieved by comparison with the retention times of authentic reference compounds.

B. Protocol: The protocol was not provided.

12. REPORTED RESULTS:

A. The recoveries of radioactivity from the urine and feces of rats following oral administration of [1-^{14}C-dioxyphenyl]Hoe 33171 at 2 or 10 mg/kg are presented in Table 1. A large proportion of the administered radioactivity was excreted in the urine and feces within 1 day after treatment in each group; high-dose (10 mg/kg) males, 73 percent; high-dose females, 66 percent; and low-dose (2 mg/kg) females, 80 percent. Radioactivity recovered in the day 2 urine and feces accounted for 17 to 25 percent of the administered dose. By days 3 and 4 posttreatment, only small amounts of radioactivity were recovered in the rat excreta. The total recovered radioactivities from the urine and feces of male and female rats receiving the high dose were 101 and 87, respectively, and 109 percent for the low-dose females.

In the rats given a single oral dose of [^{14}C]Hoe 33171 at 10 mg/kg, the females excreted more radioactivity in the urine than did the male rats, 55 and 48 percent of the administered dose, respectively, whereas fecal excretion of radioactivity was increased in the male (39 percent of the applied dose) over that of the female rats (25 percent). Female rats given the 2-mg/kg dose of [^{14}C]Hoe 33171 had an increased renal excretion rate of radioactivity over the 10-mg/kg female rats, 71 and 55 percent of the administered dose, respectively. However, fecal excretion rates of radioactivity were similar between the low- and high-dose females.

TABLE 1. Recovery of Radioactivity from Urine and Feces Following Oral Administration of [1-^{14}C-dioxyphenyl]Hoe 33171 to Rats

Dose Group (mg/kg)	Percent Recovery of Administered Radioactivity										% Total [^{14}C] Recovered
	Urine					Feces					
	Day 1	Day 2	Day 3	Day 4	Total	Day 1	Day 2	Day 3	Day 4	Total	
Males											
10	34.0	10.3	2.9	0.7	47.9	39.3	10.5	3.0	0.6	53.4	101.3
Females											
2	54.8	13.4	2.2	0.5	70.9	25.4	11.3	1.0	0.2	37.9	108.8
10	40.7	11.1	2.4	0.7	54.9	24.9	5.8	1.0	0.8	32.5	87.4

B. The metabolic profiles in the 0- to 24-hour urine samples of male and female rats dosed with 10 or 2 mg/kg of the radiolabeled test material are presented in Table 2 (CBI p. 21). The results obtained from the analyses of the urine samples were assumed to be representative of the urine samples collected at later time intervals. Based on this assumption, the percentage of the metabolites identified in the 0- to 24-hour urine samples are expressed as percentages of the administered dose. Ninety-nine to 100 percent of the total urinary radioactivity was identified by HPLC. The main metabolite identified in the urine of male rats dosed with [^{14}C]Hoe 33171 at 10 mg/kg was HPP acid, which accounted for 47.5 percent of the administered dose (99 percent of the urinary radioactivity). The primary metabolites in the urine of female rats were HPP acid and 2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propionic acid (free acid of Hoe 33171). The 10-mg/kg female rats excreted the HPP acid and free acid in equal amounts in the urine, whereas the 2-mg/kg females excreted the two metabolites at a ratio of 2:1.

The metabolic profiles in the 0- 24-hour feces of male and female rats dosed with [^{14}C]Hoe 33171 are presented in Table 3 (CBI p. 22). Sixty-four to 72 percent of the total fecal radioactivity was identified. In the male rats, 20 percent of the administered dose was excreted in the feces as unchanged Hoe 33171 and 17 percent was excreted as the free acid. The same compounds were identified in the feces of the female rats. Female rats receiving the high dose excreted equal amounts of free acid and Hoe 33171 into the feces, whereas the females receiving the low dose excreted the two compounds at a ratio of 3:1.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The purpose of this study was to determine the metabolites present in the excreta of rats as a function of dose and sex. In addition, the amounts of radiolabel excreted were obtained.

Female rats were orally dosed by stomach tube with [1-^{14}C-dioxyphenyl]Hoe 33171 at two dose levels: 2 and 10 mg/kg body weight. In addition, male rats were administered a single oral dose of the radiolabel at 10 mg/kg. The metabolite patterns in the 24-hour urine and feces were investigated for each dose group.

Female rats excreted more radioactivity in the urine than did the male rats. The low-dose (2 mg/kg) females excreted a larger percentage of the administered radioactivity into the urine than did the high-dose (10 mg/kg) females.

Table 2 : Direct HPLC analysis of the native 0 - 24 h urine samples

Peaks are calculated as percentage of the applied dose assuming unchanged metabolite pattern in the urine samples throughout the total excretion period (0 - 4 days p. appl.)
Increasing retention time indicates decreasing polarity

sex	dose level [mg a.i. / kg b.w.]	radioactivity content of the total urine as percentage of the applied dose	HPLC peaks given as percentages of the applied dose			sum of identified compounds
male	10	47.9	0.4	47.5	-	47.5
female	10	54.9	0.4	27.5	27.0	54.5
female	2	70.9	-	49.6	21.3	70.9
approximate retention times (min)			2.5	16.5	38.5	
characterization by comparison with reference compounds			-	HPP-acid	free acid	

*Copied from CBI p. 21, Table II.

Table 3 : HPLC analysis of the 0 - 24 h feces fractions from rats orally treated with Hoe 033171-dioxyphenyl-^{14}C

Peaks are calculated as percentage of the applied dose assuming unchanged composition of the fecally excreted radioactive compounds throughout the total excretion period (0 - 4 d p. appl.). Increasing retention time indicates decreasing polarity.

sex	dose level	total fecally excreted radioactivity as percentage of the applied dose	HPLC peaks given as percentages of the applied dose					sum of identified compounds
male	10	53.4	0.2	0.2	1.6	16.6	20.1	38.7
female	10	32.5	1.0	0.2	1.3	11.3	9.0	21.3
female	2	37.9	0.3	0.1	2.0	17.5	6.6	24.4
approximate retention times (min)			16.5	26	31	38.5	45.5	
characterization by comparison with reference compounds			HPP-acid	—	—	free acid	Hoe 033171	

*Copied from CBI p. 22, Table III.

Males excreted only one main metabolite in the urine, HPP acid. The high- and low-dose females excreted both HPP acid and 2-(4-(6-chloro-2-benzoxazolyl-oxy)-phenoxy)-propionic acid (free acid of Hoe 33171) at ratios of 1:1 and 2:1, respectively. Ninety-nine to 100 percent of the compounds excreted in the urine were identified.

The metabolic profile in the feces was more or less independent of sex at the high-dose level. Two main compounds were found in approximately the same ratio for the 10-mg/kg male and female rats; Hoe 33171 and the free acid accounted for 20 to 37 percent of the administered dose. In the 10-mg/kg and 2-mg/kg female rats, the dose level influenced the ratio between Hoe 33171 and the free acid in the feces, 1:1 and 1:3 in the high- and low-dose groups, respectively. Sixty-four to 70 percent of the compounds excreted in the feces were identified.

B. The study was conducted in compliance with the principles of good laboratory practice. The final report of this study was inspected by the Hoechst Aktiengesellschaft Quality Assurance (GLP) Unit.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS: The conclusions of the authors are supported by the data presented. The methodologies presented were adequate to identify the metabolites of [1-^{14}C-dioxyphenyl]Hoe 33171 in rats. However, presentation of the HPLC chromatograms for comparison of reference compounds to urine samples and fecal fractions would provide support for the results. Another deficiency with the study was that the study authors expressed the metabolite results, which were obtained by analysis of the 0- to 24-hour excreta, as percent of the administered dose assuming that the metabolic profiles seen for the 0- to 24-hour urine and feces were representative of the total excretion profiles over time. Although it is acceptable to analyze only the 0- to 24-hour urine and fecal samples for metabolites, the metabolic profiles determined for the 0- to 24-hour interval may change at a later time interval.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp 6-13, 19, 24, and 25.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 215 through 225 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
DYNAMAC No. 1-012-F2
January 27, 1986

DATA EVALUATION RECORD

ACCLAIM

Metabolic Study in Rats

STUDY IDENTIFICATION: Dorn, E., Schmidt, E., Rutz, U., Kellner, H. M., and Leist, K. H. Hoe 033171-[chlorophenyl-U-14-C], metabolism in male and female rats after single and repeated oral administration, respectively, of a low and a high dose, respectively. (Unpublished study No. A30490 prepared and submitted by Hoechst Aktiengesellschaft Geschaftsbereich Landwirtschaft Pflanzenschutz-Forschung, West Germany; dated February 11, 1985.) Accession No. 258971.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

1. CHEMICAL: Acclaim; Hoe 33171; Whip; fenoxaprop-ethyl; ethyl-2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propanoate.

2. TEST MATERIAL: 1) [U-chlorophenyl-^{14}C]Hoe 33171 (OH ZE98 0007) had a specific activity of 22.85 mCi/g and a radiochemical purity of 98 percent. 2) Unlabeled Hoe 33171 (OH ZB99 0001) had a purity of 97 percent.

3. STUDY/ACTION TYPE: Metabolic study in rats.

4. STUDY IDENTIFICATION: Dorn, E., Schmidt, E., Rutz, U., Kellner, H. M., and Leist, K. H. Hoe 033171-[chlorophenyl-U-14-C], metabolism in male and female rats after single and repeated oral administration, respectively, of a low and a high dose, respectively. (Unpublished study No. A30490 prepared and submitted by Hoechst Aktiengesellschaft Geschaftsbereich Landwirtschaft Pflanzenschutz-Forschung, West Germany; dated February 11, 1985.) Accession No. 258971.

5. REVIEWED BY:

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Date: 2-6-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-7-86

7. CONCLUSIONS:

A. Following oral administration of [U-chlorophenyl-^{14}C]Hoe 33171 to rats (single oral doses at 2 or 10 mg/kg or 14 daily doses of unlabeled Hoe 33171 at 2 mg/kg followed by a single oral dose of radiolabeled material of 2 mg/kg), 37 to 70 and 30 to 62 percent of the radioactivity was eliminated in the urine and feces, respectively. Females excreted more radiolabel in urine (54 to 70 percent) than males (37 to 58 percent). In addition, female rats metabolized the test material more quickly than males as shown by a higher proportion of radioactivity being excreted in urine between 0 and 24 hours postadministration (males, 22 to 31 percent, and females, 39 to 48 percent). Metabolites of Hoe 33171 were determined in the 0- to 24-hour excreta of male and female rats. The primary urinary metabolite, which was common to both sexes, was 6-chlorobenzoxazole-2-mercapturic acid, which accounted for 22 to 50 percent of the total radioactivity in urine. 2-(4-(6-Chloro-2-benzoxazolyloxy)-phenoxy)-propionic acid (free acid of Hoe 33171) was a major urinary metabolite of female rats given 10 mg/kg or repeated doses (2 mg/kg) accounting for 42 and 36 percent of the radioactivity in urine, respectively). The primary fecal metabolite, which was common to both sexes, was the free acid of Hoe 33171, accounting for 21 to 39 percent of the radioactivity in feces. Approximately 16 to 17 and 3 to 4 percent of the total radioactivity in feces was identified as unchanged Hoe 33171 in animals given single and repeated doses at 2 mg/kg, respectively. Male rats given 10 mg/kg excreted 24 percent of the radioactivity in the feces as unchanged Hoe 33171, while females excreted only 6 percent.

B. This study provides acceptable data on the metabolism and elimination of Hoe 33171 in rats.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. To prepare the 10-mg/kg dosing solution, unlabeled Hoe 33171 was mixed with [^{14}C]Hoe 33171 yielding a final specific activity of 12.02 mCi/g. For the 2-mg/kg dosing solution, undiluted radiolabeled Hoe 33171 was used.

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[1]Only items appropriate to this DER have been included.

2. Male and female Wistar (Hoe:WISKf-SPF 71) rats were dosed as follows: 15 rats of each sex received a single oral dose at 2 mg/kg; 15 rats of each sex received single oral doses of unlabeled test material (2 mg/kg) daily for 14 days, followed by one labeled dose at 2 mg/kg; and 10 rats of each sex received a single oral dose at 10 mg/kg.

3. Urine and feces were collected at 24, 48, and 96 hours post-administration. The samples collected at each interval were pooled according to sex and dose group. Aliquots of the pooled urine were radioassayed for total radioactivity directly, whereas feces were first combusted and then radioassayed by liquid-scintillation counting (LSC).

4. For metabolite identification, aliquots of the 0- to 24-hour composite urine samples were analyzed by thin-layer chromatography (TLC) using four different solvent systems. In addition, an aliquot of the composite urine sample was adjusted to pH 3 to 4, applied to a RP-18 cartridge, and eluted with ethyl acetate followed by methanol. The ethyl acetate and methanol eluates were analyzed by TLC and high performance liquid chromatography (HPLC).

   The 0- to 24-hour composite fecal sample was extracted with acetonitrile:water (8:2, v/v). The acetonitrile was evaporated off, and the remaining water phase was extracted with hexane. The aqueous phase was then adjusted to pH 3 to 4, applied to a RP-18 cartridge, and eluted with ethyl acetate followed by methanol. The hexane phase, ethyl acetate eluate, and methanol eluate were analyzed by HPLC.

   The metabolites present in the 0- to 24-hour urine and fecal samples were assumed to be representative of the metabolic profiles at all intervals and are expressed as percentages of the administered dose. The radioactivity that was most polar and not retained on the RP-18 cartridge was not analyzed for metabolites (designated fraction C).

B. Protocol: The protocol was not provided.

12. REPORTED RESULTS:

A. The amount of radioactivity excreted in the urine and feces of rats dosed orally with [^{14}C]Hoe 33171 is presented in Table 1. In each dose group, female rats excreted a higher proportion of radiolabel into the urine than did the males, approximately 1.14-fold (repeated dosing) to 1.9-fold (single high dose). Approximately 70.0 percent of the high dose was eliminated in the urine of females, but only 37.0 percent was eliminated in the urine of males. The excretion of radioactivity in the urine of

TABLE 1. Excretion of Radiolabel into Urine and Feces Following Oral Administration of [U-chlorophenyl-^{14}C]Hoe 33171

Dose Group (mg/kg)	Percent Recovered in Urine				Percent Recovered in Feces				% Total [^{14}C] Recovered in Urine and Feces
	24 hr	48 hr	96 hr	Total	24 hr	48 hr	96 hr	Total	
Males									
2 (single dose)	26.5	11.1	4.5	42.1	26.0	11.4	3.0	40.4	82.5
2 (repeated dosing)	31.1	17.8	9.4	58.3	20.2	11.6	7.64	39.4	97.7
10 (single dose)	22.3	10.9	3.8	37.0	42.3	14.5	5.0	61.8	98.8
Females									
2 (single dose)	38.5	11.5	3.9	53.9	23.0	8.74	2.03	33.8	87.7
2 (repeated dosing)	42.3	18.4	5.6	66.3	22.6	14.0	6.21	42.8	109.1
10 (single dose)	47.9	18.3	3.8	70.0	15.9	12.1	2.05	30.1	100.1

male and female rats (58 and 66 percent of the administered dose, respectively) given repeated doses excreted higher levels than those of males and females receiving a single 2-mg/kg dose (42 and 54 percent, respectively).

B. The distribution of metabolites identified in the 0- to 24-hour urine samples from male and female rats are shown in Table 2 (CBI p. 40). HPLC separation of fraction B (medium polar compounds) resulted in the detection of two to five different metabolites accounting for 0.33 to 3.8 percent of the administered radioactivity. None of the metabolites from fraction B were identified. The major urinary radioactivity was present in the nonpolar fraction (A). HPLC separation of fraction A resulted in the detection of nine metabolites (Table 2; see Appendix B for the structures of the metabolites), six of which were identified by comparison with authentic reference compounds. In all rats a major metabolite was 6-chlorobenzoxazole-2-mercapturic acid (BO-merc. acid), which accounted for 15 to 26 percent of the administered dose. However, the free acid of Hoe 33171 accounted for 23 and 28 percent of the administered radioactivity in the female rats receiving 10 mg/kg and 2 mg/kg (repeated dose), respectively (Table 2).

The distribution of metabolites in the 0- to 24-hour fecal samples from the rats is presented in Table 3 (CBI p. 41). In all rats, approximately 8 to 13 percent of the administered dose was not extractable from the feces. Of the 21 to 49 percent of the dose that was extractable, most of the radioactivity consisted of nonpolar compounds (fraction A). Polar (fraction C) and medium polar (fraction B) compounds accounted for less than 5 percent of the administered dose. HPLC separation of fraction A revealed the same metabolites as identified in the urine. The primary metabolite present in the feces of all rats was the free acid of Hoe 33171, accounting for 8 to 22 percent of the administered dose. Unchanged Hoe 33171 accounted for 1 to 15 percent of the administered dose in the feces.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Groups of male and female rats received single doses of 2 or 10 mg/kg of Hoe 33171 or daily doses of 2 mg/kg for 15 consecutive days to investigate the effect of sex, dose level, and repeated dosing on metabolism.

Female rats excreted more radiolabel in the urine than did the males. No apparent differences in radiolabel excretion were noted among the groups.

Table 2 : Percentage of the separated metabolites in the urine given in % of the total radioactivity applied

	Retention-time (min)	(%)					
Trial							
Sex		♂	♀	♂	♀	♂	♀
Dose (mg/kg)		10	10	2	2	2	2
Number of applications		1	1	1	1	14 + 1	14 + 1
Group C (polar)		0.56	1.2	0.67	4.0	2.2	1.7
Group B (medium polar)							
B1	10.3	1.1	-	1.3	0.65	3.8	3.8
B2	14.1	0.33	0.56	0.50	0.81	-	0.6
B3	15.4	-	-	-	-	1.0	-
B4	17.3	1.7	1.3	1.7	1.2	0.93	-
B5	19.2	-	-	-	-	1.9	-
B7	22.0	-	-	-	-	0.70	-
Group A (non-polar)							
A1[1] 5-OH-BO	19.4	4.0	7.0	4.5	5.5	3.6	3.4
A2	21.3	-	0.45	0.50	0.49	2.6	2.4
A3[1] 4-OH-BO	22.9	1.4	2.9	1.9	1.9	2.6	2.9
A4 BO	25.0	1.7	4.6	1.7	5.0	1.5	3.0
A5 BO-Merc.ac.	26.7	15.5	14.6	19.1	19.6	26.0	18.5
A6 BO-SH	28.7	2.1	2.8	2.7	5.2	3.7	4.2
A7	30.2	1.5	1.1	2.5	-	2.7	1.3
A8	31.3	-	1.7	-	-	-	-
A9 free acid	37.5	1.0	27.7	1.1	4.7	1.3	23.2
Sum of unidentified metabolites in C, B, A		5.2	6.3	7.2	7.15	15.8	9.8
Sum of identified metabolites in C. B. A		25.7	59.3	31.0	41.9	36.7	55.2

The designation of the metabolites is derived from the peak-number in the HPLC-chromatograms. Increasing peak-numbers refer to decreasing polarity.

1) Two additional peaks were observed in group B with the numbers B6 (19.4 min) and B6 (22.9 min). These had the same retention times as the Peaks A1 and A3 of group A. The reason was obviously the partial separation in the separation step by means of RP-18 cartridges. The percentages of A1 und A3 therefore contain the percentages of these compounds in group B.

*Copied from CBI p. 40, Table 5.

Table 3: Percentage of the separated metabolites in the feces given as % of the total radioactivity applied

	Retent. time (min) in HPLC	%					
Trial							
Sex		♂	♀	♂	♀	♂	♀
Dose (mg/kg b.w.)		10	10	2	2	2	2
Number of applic.		1	1	1	1	14 + 1	14 + 1
Total	—	61.8	30.1	38.4	33.8	39.4	42.8
Non-extractable radioactive compounds	—	13.0	9.6	8.0	8.8	11.5	11.2
Extractable radioactive comp. (Fraction A, B and C)	—	48.8	20.5	30.4	25.0	27.9	31.6
Most polar fraction C	—	3.8	1.7	0.84	0.58	0.43	0.31
Medium polar fraction B	—	0.6	0.45	1.45	0.88	1.6	1.0
Non-polar fraction A (total)	—	42.2	15.8	24.8	22.8	15.7	26.0
5-OH-BO	19.4	—	—		—	0.47	0.69
	21.3	—	—		—	0.26	-
4-OH-BO	22.9	—	—		—	0.47	-
BO	25.0	1.9	0.75	3.1	1.6	1.7	2.2
BO-Herc. ac.	26.7	0.25	0.27	0.67	—	0.51	1.7
BO-SH	28.7	0.45	0.33	0.50	0.47	0.39	-
	30.2	1.8	1.3	1.8	1.7	1.3	2.4
	31.3	1.1	0.66	0.65	0.78	0.71	1.2
free acid	37.5	21.7	10.6	12.6	12.5	8.4	16.7
Hoe 033171	45.1	15.0	1.7	6.3	5.7	1.4	1.1

Remark: Non-polar compounds, predominantly unchanged Hoe 033171, were separated before application of the RP-18 cartridge to the respective fraction. But the measured percentages of these non-polar compounds were added to the respective percentages of the identical compounds in fraction A

*Copied from CBI p. 41, Table 6.

The mercapturic acid derivative of chlorobenzoxazole was the major metabolite in the pathway beyond the free acid in each dose group and was excreted almost exclusively into the urine (15 to 26 percent of the administered dose). Additional metabolites were identified as 4- and 5-hydroxy-6-chloro-2,3-dihydrobenzoxazol-2-one, its nonhydroxylated fragment, and its 2-thione analogue as a fragment of the mercapturic acid, each accounting for 1.5 to 7 percent of the administered dose. No relevant qualitative differences in the metabolic profile as a function of sex, dose level, or number of dose administrations were observed. At the single low dose (2 mg/kg) the quantitative results were similar for male and female rats. However, the results of repeated dosing (at 2 mg/kg) or an increased single dose (10 mg/kg) indicated that the female rats did not have the capacity to metabolize all of the absorbed Hoe 33171 beyond the free acid. The amount of the free acid in the urine of female rats increased to 23 percent (repeated dosing) and 28 percent (high dose). By comparison, the male rats absorbed the high dose (10 mg/kg) to a lesser extent and were able to metabolize Hoe 33171 to products beyond the free acid.

Therefore, at low-dose levels, which are more relevent for the assessment of practical conditions like uptake of residues by consumers or contamination of the applicator, no relevant differences between male and female rats were noted. However, at dose levels exceeding 2 mg/kg body weight the metabolic capacity of female rats was exceeded.

B. The study was periodically inspected by the Hoechst Aktiengesellschaft Pharma Quality Assurance (GLP) Unit.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The conclusions of the authors are supported by the data provided, and the methods used were adequate to identify the metabolites of [U-chlorophenyl-^{14}C]Hoe 33171 in rats. However, the mass spectrometry data for the identification of urinary metabolites and HPLC chromatograms for comparison of reference compounds with metabolites found in urine and fecal fractions were not provided. Another deficiency noted was that the study authors expressed the metabolite results, which were obtained from analyzing 0- to 24-hour excreta samples, as percent of administered dose. This was based on their assumption that the metabolic profiles seen for the 0- to 24-hour urine and feces samples were representative of the total excretion profiles over time. Although it is acceptable to analyze only the 0- to 24-hour urine and feces samples for metabolites, the metabolic profiles may change at a later time interval. In addition, a marked difference was noted in the metabolism and elimination of [^{14}C] between males and females receiving the high dose. Male rats excreted about 62 percent of the dose in the feces whereas the females excreted only 30 percent in the feces and the rest in the urine. Of the [^{14}C] excreted, about 24 percent was the unchanged

parent compound in males, but only 6 percent in females. These data do not necessarily indicate differences among sexes, since increased [^{14}C] elimination in feces of male animals may be due to diarrhea associated with dosing that was not reported by the authors.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 8-14 and 29-35, and Appendix B, Metabolite Structures, CBI pp. 17 and 18.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 237 through 251 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

APPENDIX B

Metabolite Structures

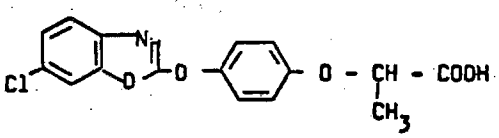
Hoechst

A30450

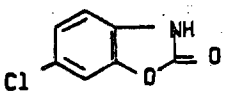
Abteilung: Analytisches Laboratorium
Dr. E. Dorn, E. Schmidt, U. Rutz
Dr. H.-M. Kellner, RCL
Dr. K.H. Leist, Ph.-Fo.-Toxikologie

Datum: 11.02.85
Bericht-Nr.: Fo.336/84
Seite: 17 (42)

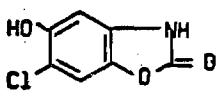
	Abbreviation
- Hoe 033171 (active ingredient)	a.i.
- Hoe 053022 (free acid)	fr. ac.



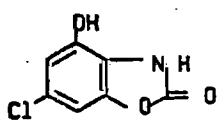
- Hoe 054014 (6-chloro-2,3-dihydro-benzoxazol-2-one) BO



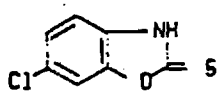
- Hoe 064124 (6-chloro-5-hydroxy-2,3-dihydro-benzoxazol-2-one) BO-5-OH



- Hoe 067978 (6-chloro-4-hydroxy-2,3-dihydro-benzoxazol-2-one) BO-4-OH



- 6-chloro-2,3-dihydro-benzoxazol-2-thione BO-SH

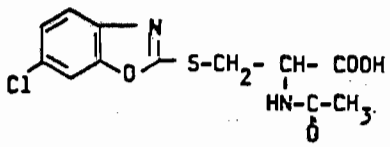


Hoechst

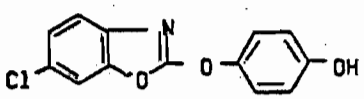
A30490

Abteilung Analytisches Laboratorium
Dr. E. Dorn, E. Schmidt, U. Rutz
Dr. H.-M. Kellner, RCL
Dr. K.H. Leist, Ph.-Fo.-Toxikologie

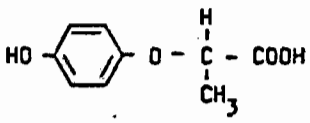
- 6-chloro-benzoxazol-2-mercapturic acid (Hoe 069225) — BO-Merc. ac.



- 4-(6-chloro-2-benzoxazolyloxy)-phenol (Hoe 040356) — BO-phenol



- 2-(4-hydroxy-phenoxy)propanoic acid Hoe 020686) — HPP-acid



The latter compound (HPP-acid) could not be detected in the radiochromatograms as a free metabolite since the radiolabeling was located in the chlorophenyl ring of the parent compound. The chemically very labile BO-merc. acid was subjected to the optimized processing scheme after addition to urine of untreated rats and remained stable.

EPA: 68-02-4225
DYNAMAC No. 1-12C
January 27, 1986

DATA EVALUATION RECORD

ACCLAIM

Determination of Residues in Rat Tissues

STUDY IDENTIFICATION: Schütz, Donaubauer, Leist, and Kramer. Determination of residues in organs and tissues of rats. (Unpublished study No. A30804 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated February 26, 1985.) Accession No. 258955.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

1. CHEMICAL: Acclaim; Hoe 33171; Whip; fenoxaprop-ethyl; ethyl-2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propanoate.

2. TEST MATERIAL: Hoe 33171, active technical ingredient, batch Nos. 11123 (Op. 6+7/81) and 11283 (Op. 6+7+6/81), codes Hoe 33171 OH AT 206 and Hoe 33171 OH AS 201, were 95.8 and 94 percent pure, respectively.

3. STUDY/ACTION TYPE: Determination of residues in the organs and tissues of rats.

4. STUDY IDENTIFICATION: Schütz, Donaubauer, Leist, and Kramer. Determination of residues in organs and tissues of rats. (Unpublished study No. A30804 prepared and submitted by Hoechst Aktiengesellschaft Pharma Forschung Toxikologie, West Germany; dated February 26, 1985.) Accession No. 258955.

5. REVIEWED BY:

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Signature: W. Thomas Edwards
Date: 2-6-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-11-86

7. CONCLUSIONS:

A. Hoe 33171 was fed to male and female rats at 0, 5, 30, and 180 ppm in the diet for up to 24 months. Two male and two female rats were sacrificed after 6, 12, 18, and 24 months of feeding, and tissues were analyzed for Hoe 33171 residues. The results showed a dose-related increase in the residue levels found in the tissues of both male and female rats. No definite sex-related differences were observed in the residue levels between male and female rats. Also, there was no accumulation of residues with time in the tissues of rats fed Hoe 33171 for 24 months, suggesting steady state metabolism.

B. Under the conditions in which this study was conducted, the study is acceptable.

Item 8--see footnote 1.

9. BACKGROUND:

The test animals used for this study were a satellite group in a 2-year chronic study in rats entitled Hoe 33171-Active Ingredient Technical (code: Hoe 33171 OH AS 201) Chronic Feeding Study (24 months) in Rats. This study was designed to determine the levels of Hoe residues that would occur in the rat body after long-term exposure.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Groups of 10 male and 10 female Wistar rats, Hoe:WISKf (SPF71) strain, were fed the test substance Hoe 33171 in the diet at concentrations of 0, 5, 30, or 180 ppm for up to 104 weeks (24 months).

2. Two males and two females were sacrificed at 6, 12, and 18 months after study initiation, and the remaining animals were sacrificed at study termination (24 months). At sacrifice, the following tissues were examined: blood, intestine, fat, brain, heart, liver, spleen, muscle, kidneys, and carcass. Tissues were combined according to sex and dose group to produce a composite sample for analysis.

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[1] Only items appropriate to this DER have been included.

3. The composite tissue sample was refluxed for 8 hours with hydrochloric acid in acetonitrile. This treatment splits Hoe 33171 to form 6-chloro-2,3-dihydrobenzoxazole-2-one. The mixture was diluted with water and then filtered to remove undissolved material. Aliquots of the filtrate were added to an Extrelut column. The column was washed with hexane and the 6-chloro-2,3-dihydrobenzoxazole-2-one was eluted with 20 percent diethylether in hexane. The eluate was evaporated, acetylated with acetic anhydride, then purified on a SEP-PAK C-18 cartridge followed by silica gel column chromatography. The 3-acetyl-6-chloro-2,3-dehydro-benzoxazole-2-one was quantified by electron capture gas chromatography.

B. Protocol: A protocol was not provided.

12. REPORTED RESULTS:

A. In order to assess the extraction efficiency of the analytical method, a preliminary study was performed in which control tissue samples were spiked with known quantities of Hoe 33171. The results from this recovery study are presented in Table 1. Control tissue samples were spiked with 0.01, 0.05, or 0.10 mg/kg Hoe 33171, and the mean percent recoveries ranged from 63 percent (heart) to 96 percent (carcass).

B. The results from the determination of residues in the tissues of rats fed Hoe 33171 at 0, 5, 30, and 180 ppm for up to 24 months are shown in Table 2. The results of the analytical determination of tissue residues were not corrected for extraction efficiency. Tissues from control animals showed no Hoe 33171 residues. The concentration of residues found in the tissues of male and female rats fed Hoe 33171 at 5, 30, or 180 ppm increased with increasing dose; however, there was no time-related accumulation of residues. Within each dose group, there were no significant differences in the residue levels between male and female rats.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that the feeding of Hoe 33171 at 5, 30, or 180 ppm resulted in dose-related increases in residue levels found in the organs and tissues of rats. However, there was no accumulation of residues over time nor were there any differences in residue levels observed between male and female rats.

B. The study was inspected on February 28, 1985, by S. J. Harston of Hoechst Aktiengesellschaft Pharma Research Quality Assurance (GLP) Unit.

TABLE 1. Percent Recovery of Hoe 33171 in Tissues of the Rat

Tissue	Mean Percent Recovery[a]
Blood	84.2± 9.6
Liver	66.9± 9.8
Kidneys	76.4±22.1
Heart	63.3± 4.3
Brain	66.3±12.0
Spleen[b]	85.7± 8.6 (106.1±13.1)
Intestine	79.5±17.6
Fat	72.2±15.2
Muscle	73.2± 9.4
Carcass	95.8±23.7

[a] Mean value ± standard deviation of three or four determinations.

[b] Value in parentheses is that calculated by our reviewers; it differs from the study authors' value by a factor of 1.2

TABLE 2. Tissue Residues (ppm) in Rats Fed Hoe 33171 for 104 Weeks

Dose Group (ppm)	Blood Month 6	12	18	24	Liver Month 6	12	18	24	Kidneys Month 6	12	18	24
Males												
Control	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.03	:0.01	<0.01	<0.01	<0.05	<0.01
5	0.2	0.3	0.3	0.4	0.2	0.2	0.1	0.3	0.6	0.6	0.4	0.9
30	2.1	2.7	2.1	1.2	1.3	1.4	1.3	1.4	3.9	3.6	2.9	5.8
180	22	8.3	17	4.4	7.3	7.2	5.4	5.9	27	23	23	27
Females												
Control	<0.04	<0.01	<0.01	<0.03	<0.03	<0.01	<0.02	<0.02	<0.02	<0 01	<0.05	<0.01
5	0.2	0.3	0.3	0.3	0.1	0.4	0.1	0.09	0.6	1.2	1.0	1.2
30	1.0	0.5	1.4	1.9	1.4	0.6	1.5	1.6	3.7	4.7	5.2	5.2
180	9.9	13	11	7.6	10	8.4	8.8	8.7	19	25	21	2i

	Heart Month 6	12	18	24	Brain Month 6	12	18	24	Spleen Month 6	12	18	24
Males												
Control	<0.02	<0.02	<0.04	<0.02	<0.01	<0.01	<0.01	<0.01	<0.04	<0.04	<0.02	<0.03
5	ND[a]	0.1	ND	0.2	0.01	0.01	ND	0.02	ND	0.1	ND	0.07
30	0.5	0.6	0.6	0.E	0.07	0.08	0.06	0.07	0.3	0.3	0.2	0.6
180	3.7	4.4	3.8	5.4	0.7	0.4	0.8	0.6	3.2	2.2	3.0	3,1
Females												
Control	<0.2	<0.01	<0.03	<0.1	<0.02	<0.01	<0.01	<0.01	<0.04	<0.01	<0.04	<0.02
5	0.1	0.1	0.1	0.1	ND	ND	ND	ND	ND	0.1	ND	0.06
30	1.1	1.1	0.5	0.6	0.06	0.05	0.04	0.06	0.4	0.6	0.3	0.4
180	2.2	2.2	3.7	3.9	0.2	0.6	0.4	0.6	2.3	2.4	1.8	1.8

(continued)

[a]ND: not detected.

TABLE 2. Tissue Residues (ppm) in Rats Fed Hoe 33171 for 104 Weeks (Continued)

Dose Group (ppm)	Intestine Month 6	12	18	24	Fat Month 6	12	18	24	Muscle Month 6	12	18
Males											
Control	<0.03	<0.01	<0.01	<0.01	<0.01	<0.01	<0.02	<0.04	<0.01	<0.01	<0.01
5	0.1	0.04	0.05	0.09	0.07	0.1	0.05	0.08	ND[a]	ND	ND
30	0.7	0.3	0.5	0.9	1.3	0.5	0.6	0.8	0.2	0.2	0.3
180	4.2	2.8	2.6	3.4	8.6	4.2	4.3	3.7	1.9	1.8	1.8
Females											
Control	<0.04	<0.01	<0.01	<0.02	<0.01	<0.01	<0.03	<0.01	<0.01	<0.1	<0.01
5	0.07	0.1	0.08	0.08	0.2	0.3	0.1	0.1	ND	ND	ND
30	0.7	1.0	0.7	0.7	1.5	2.0	0.7	0.4	0.4	0.2	0.3
180	4.4	3.6	3.1	4.9	9.0	5.9	4.8	2.7	1.4	1.3	0.7

	Carcass Month 6	12	18	24
Males				
Control	<0.01	<0.01	<0.01	<0.01
5	0.04	0.05	0.04	0.06
30	0.3	0.3	0.3	0.4
180	1.8	2.1	2.2	2.6
Females				
Control	<0.01	<0.01	<0.02	<0.02
5	0.05	0.07	0.06	0.08
30	0.4	0.5	0.4	0.4
180	2.2	2.5	2.5	2.4

(concluded)

[a]ND: Not detected.

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14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The results presented support the study authors' conclusions; however, we note one deviation. The results suggested a possible sex-related difference in the residue levels found in the liver of the 180-ppm males and females; the liver of the female rats contained higher residue levels than did the males. Whether this difference was significant could not be determined. Larger test groups and individual animal analyses (as opposed to composite tissue samples) may have provided more complete results. Residue levels of Hoe 33171 found in the tissues are most likely underestimated, since they are not corrected for the extraction efficiencies. The extraction efficiencies were determined at residue levels of 0.1 ppm or less, whereas tissue residue levels were usually found to be greater than 0.1 ppm. To determine accurate extraction efficiencies, the tissue samples would have to be spiked with a concentration of Hoe 33171 similar to the concentration of residues actually found in the tissues.

In addition, although the analytical method is able to detect any residues of Hoe 33171 that contain the 6-chloro-2,3-dihydrobenzoxazole-2-one portion of the compound, the method cannot detect 2-(4-hydroxyphenoxy)propanoic acid residues that result from cleavage of Hoe 33171 at the ether linkage to the benzoxazole.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI p. 3 from report No. 85.0205 and pp. 1, 2, and 48-56 from report No. Fo.331/84.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 264 through 275 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

EPA: 68-02-4225
DYNAMAC No.1-24-05
November 26, 1985

004963

DATA EVALUATION RECORD

WHIP

Metabolic Study in the Monkey, Rabbit, and Rat

STUDY IDENTIFICATION: Dorn, E., Schmidt, E., Kellner, H. M., Eckert, H G., and Leist, K. H. Hoe 33171-14-C, comparative investigation of th metabolism and radioactivity levels of tissues in the pregnant cynomolgu monkey, rabbit, and rat after oral administration of the active ingredien via stomach tube. (Unpublished study No. A29711 prepared and submitted b Hoechst Aktiengesellschaft, Bereich Landwirtschaft, Pflanzenschutz Forschung, Frankfurt, West Germany; dated October 1, 1984.) Accession No 256667.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-26-85

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1. CHEMICAL: Whip; Hoe 33171; ethyl-2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propanoate.

004963

2. TEST MATERIAL: 1) Unlabeled Hoe 33171, code Nos. Hoe 033 171 OH ZE9E 0002 and Hoe 033 171 OH ZE96 0001 had reported purities of 96.2 and 96.5 percent, respectively. 2) [^{14}C-U-chlorophenyl]Hoe 33171, code No. Hoe 033 171 OH ZE98, had a specific activity of 25.43 mCi/g and a radiochemical purity of 98 percent; code No. Hoe 033 171 OH ZE96 0002 had a specific activity of 25.4 mCi/g and a radiochemical purity of 97 percent.

3. STUDY/ACTION TYPE: Metabolic study in the monkey, rabbit, and rat.

4. STUDY IDENTIFICATION: Dorn, E., Schmidt, E., Kellner, H. M., Eckert, H. G., and Leist, K. H. Hoe 33171-14-C, comparative investigation of the metabolism and radioactivity levels of tissues in the pregnant cynomolgus monkey, rabbit, and rat after oral administration of the active ingredient via stomach tube. (Unpublished study No. A29711 prepared and submitted by Hoechst Aktiengesellschaft, Bereich Landwirtschaft, Pflanzenschutz-Forschung, Frankfurt, West Germany; dated October 1, 1984.) Accession No. 256667.

5. REVIEWED BY:

Lynne L. W. Binari, M.S.
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6. APPROVED BY:

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Metabolism
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W. T. Edwards
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Signature: W. Thomas Edwards
Date: 1-21-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 1-23-86

7. CONCLUSIONS: 004963

A. The comparative metabolism of Hoe 33171 in pregnant Wistar rats, Himalayan rabbits, and a cynomolgus monkey was investigated. The purpose of this study was to estimate the residue levels and metabolites that would reach a human fetus following maternal exposure to the herbicide during organogenesis.

The levels of radioactivity found in the tissues of the rats were higher than those found in the rabbits. In both species, the levels of radiolabel found in the blood 6 hours after dosing were greater than those found in the fetuses (11- and 23-fold in the rats and rabbits, respectively). Radioactivity measured in the blood of the monkey could not be compared with that of the rats and rabbits because of the differences in the administered doses and collection intervals of the blood. No other tissues from the monkey were examined.

Differences in the patterns of radiolabel excretion into the urine and feces were apparent between the three species. Although renal excretion was the predominant pathway for radiolabel elimination in each species, the ratio of urinary to fecal excretion that occurred by 48 hours postadministration differed between the rats (2:1), rabbits (24:1), and monkeys (5:1). The major metabolites found in the 24-hour urine samples of the rats and rabbits were the free acid of Hoe 33171 and 6-chlorobenzoxazol-2-mercapturic acid (BO-merc. acid); however, the amount of each metabolite expressed as percent of total urinary radioactivity differed between the rats and rabbits. The rats produced 3 times as much of the free acid as did the rabbits, 43 and 14 percent, respectively. The major metabolite identified in the urine of the monkey was the free acid, accounting for approximately 19 percent of the urinary radioactivity. Unchanged Hoe 33171 was not detected in the urine of the monkey, rabbit, or rat. The feces were not further analyzed for the presence of metabolites.

B. This study provides some supplementary information on the metabolism of Hoe 33171 by pregnant rats, rabbits, and a cynomolgus monkey; in general, the results are inconclusive.

Items 8 through 10--see footnote 1.

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[1] Only items appropriate to this DER have been included.

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11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The test animals used were a single female cynomolgus monkey approximately 4 years of age, eight female Himalayan rabbits approximately 6 months of age, and 15 female Wistar rats (Hoe: WISKf-SPF71) approximately 65-75 days old.

2. The test materials were unlabeled Hoe 33171 and [^{14}C-U-chlorophenyl]Hoe 33171. The [^{14}C]Hoe 33171 was mixed with unlabeled Hoe 33171 at final specific activities of 1.02, 1.365, and 2.77 mCi/g and used to dose the monkey, rabbits, and rats, respectively. The test material was dissolved in sesame oil for dose administration.

3. The female monkey received daily oral doses of test material (the first and last doses were with the labeled material) at 10 mg/kg from days 20 through 50 post coitum (p.c.). The first day of positive sperm detection in the vagina was designated as day 0. Urine and feces were collected 24 hours following the first dose. Following the second radiolabeled dose (day 50), urine samples were collected at 24, 28.5, and 48 hours and fecal samples were collected at 24 and 48 hours postadministration. Blood was collected 8 hours following [^{14}C]Hoe 33171 administration (days 20 and 50).

4. Five female rabbits were given daily oral doses of test material at 50 mg/kg from days 7 through 19 p.c. The final dose of test material (day 19) was radiolabeled; all other doses were unlabeled Hoe 33171. Three additional female rabbits were utilized as controls. Animals were individually housed following dose administration. Urine and feces were collected from three of the rabbits 6 hours following [^{14}C]Hoe 33171 administration; these animals and the three control rabbits were sacrificed at this time. From the other two rabbits dosed with [^{14}C]Hoe 33171, urine and feces were collected at 24 and 48 hours, and the animals were then sacrificed. Urine and fecal samples were individually pooled at each of the collection intervals. At sacrifice, the following tissues were collected from all rabbits: blood, liver, kidneys, uterus, placenta, and fetuses.

5. Ten female rats received daily oral doses of unlabeled Hoe 33171 at 50 mg/kg from days 7 through 15 p.c. On day 16 p.c. the animals were given a single oral dose of [^{14}C]Hoe 33171 at 50 mg/kg and housed individually. Five additional female rats were used as controls. The control rats and five treated rats were sacrificed at 6 hours following [^{14}C]Hoe 33171 dosing at which time urine and feces were collected. Urine and feces were collected from the five remaining female rats at 24 and 48 hours (time of sacrifice) following

[^{14}C]Hoe 33171 dosing. Urine and feces were separately pooled at each of the collection intervals. At sacrifice, the following tissues were collected from all rats: blood, liver, kidneys, uterus, placenta, and fetuses.

6. Urine, feces, and tissues were radioassayed using standard techniques. Urine and liver samples were analyzed for metabolites by high performance liquid chromatography (HPLC) and/or thin-layer chromatography (TLC). Details of sample preparation and HPLC and TLC conditions are outlined in Appendix A (CBI pp. 34-38).

B. Protocol: A protocol was not presented.

12. REPORTED RESULTS:

A. The concentrations of radiolabel found in the tissues of pregnant rabbits and rats 6 and 48 hours after dosing with [^{14}C]Hoe 33171 at 50 mg/kg are presented in Table 1. A comparison of the radiolabel residue levels found in the tissues of the rabbits and rats at 6 hours postadministration indicated that there were increased residue levels, especially in the blood, of the rats. No direct comparison with the monkey's blood level of [^{14}C] was possible since its dose level (10 mg/kg) was 5 times lower than that given to the rabbits and rats. However, at 8 hours postadministration the radiolabel level in the blood of the monkey was 4.2 ppm.

There was a rapid decrease in the levels of radioactivity found in the tissues of the rats and rabbits from 6 to 48 hours after dosing (approximately 16- and 28-fold, respectively). However, the radiolabel levels found in the rats still exceeded those found in the rabbits which were 3- to 6-fold higher except in the kidneys. Tissue residue levels of the monkey were not available.

B. The recoveries of radiolabel in the urine and feces of the pregnant monkey, rabbits, and rats dosed with [^{14}C]Hoe 33171 at 10, 50, and 50 mg/kg, respectively, are presented in Table 2. By 48 hours postadministration of [^{14}C]Hoe 33171, 42, 73, and 55 percent of the dose was recovered in the urine of the monkey, rabbits, and rats, respectively, whereas 9, 3, and 27 percent was recovered in the feces, respectively. The total recovered radioactivities from the urine and feces of the dosed pregnant monkey, rabbits, and rats were 51, 76, and 82 percent of the [^{14}C]Hoe 33171 dose by 48 hours posttreatment. Renal excretion of radiolabel occurred earlier in the rats than in the rabbits. The rats excreted a significant percentage (5.3 percent) of the dose during the initial 6 hours postadministration, whereas the rabbits showed a faster rate of renal excretion of radiolabel. In rabbits, 59 percent of the dose was recovered in the urine by 24 hours postadministration compared to 41 percent in the rats. The rats excreted a higher percentage (27 percent of the dose) of the administered radiolabel into the feces than did the pregnant rabbits (3 percent).

TABLE 1. Radioactive Residue Levels of Hoe 33171 Equivalents (ppm) in Tissues Following Oral Administration of [^{14}C]Hoe 33171[a]

	Rats		Rabbits	
Tissue	6 hrs[b]	48 hrs	6 hrs	48 hrs[c]
Liver	160 ± 21	8.8 ± 1.4	42 ± 6.2	4.4
Kidneys	156 ± 13	16.0 ± 2.0	136 ± 36	14.7
Blood[d]	109 ± 3.7	9.9 ± 2.4	34 ± 12	3.9
Uterus	55 ± 6.6	4.1 ± 0.63	17 ± 2.1	2.4
Placenta	41 ± 4.7	2.9 ± 1.0	9.5 ± 1.9	1.4
Fetus	10 ± 0.88	0.69 ± 0.23	1.5 ± 0.46	0.5

[a] Mean values ± standard deviation.

[b] Hours following dose administration.

[c] Standard deviations were not provided.

[d] The corresponding blood value for the cynomolgus monkey at 8 hours after administration of the radioactive dose (10 mg/kg) was 4.2 ppm.

TABLE 2. Percent Recovery of Radioactivity from Urine and Feces Following Oral Administration of [^{14}C]Hoe 33171

Species/[^{14}C]-Hoe 33171 application	Percent Recovery of Administered Dose					% Total Recovered [^{14}C]
	Urine			Feces		
	0-6 hrs	0-24 hrs	24-48 hrs	0-24 hrs	24-48 hrs	0-48 hrs
Cynomolgus monkey 21 days p.c.	—	30.1	—	0.3	—	—[a]
Cynomolgus monkey 50 days p.c.	—	32.2	9.7	6.5	2.2	50.6
Himalayan rabbits 19 days p.c.	0.001	59.2	13.8	2.3	0.6	75.9
Wistar rats 16 days p.c.	5.3	40.5[b]	14.4	14.2	12.7	81.8

[a] Urine and feces only collected during initial 24 hours after dose administration.

[b] Includes 0 to 6 hour recovery data.

C. Radioactive metabolites present in the 24-hour urine samples were separated into three groups of differing polarity. The amounts of radioactivity found in each group, expressed as percent of the total urinary radioactivity, are presented in Table 3 (CBI p. 53). The 24-hour urine samples of the monkey, rabbits, and rats contained similar amounts of the most polar compounds: 1.5, 4.5, and 4.3 percent of the urinary radioactivity, respectively. The majority of the urinary radioactivity consisted of nonpolar compounds, and the ratios of nonpolar:medium polar compounds increased from the monkey (1.7:1) to the rabbit (3.4:1) to the rat (6.7:1). HPLC separation of the medium and nonpolar compounds of the urine samples is presented in Table 4 (CBI p. 54). A major metabolite identified in the 24-hour urine of the monkey, rabbits, and rats was the free acid of Hoe 33171 (See Appendix B for metabolite structures), accounting for 19, 14, and 43 percent of the urinary radioactivity, respectively. In the rabbits and rats, 23 and 19 percent of the urinary radioactivity, respectively, was identified as 6-chlorobenzoxazol-2-mercapturic acid (BO-merc. acid). Seven percent of the urinary radioactivity of the monkey was identified as 6-chloro-2,3-dihydrobenzoxazol-2-thione (BO-SH); however, this was thought to be BO-merc. acid converted to BO-SH because the monkey's "urine samples had to be concentrated much more intensively to obtain a radioactivity concentration which exceeded the limit of detection of the HPLC-analysis." TLC of the corresponding fractions indicated the presence of BO-merc. acid. Two to 10 percent of the urinary radioactivity of the monkey, rabbits, and rats was identified as 6-chloro-2,3-dihydrobenzoxazol-2-one (BO) and 6-chloro-5-hydroxy-2,3-dihydrobenzoxa-zol-2-one (BO-5-OH). Residue levels (µg equivalents Hoe 33171/g) of the free acid of Hoe 33171 in the livers of the pregnant rats and rabbits are presented in Table 5 (CBI p. 56). The concentrations of free acid in the liver tissue of the rats were 6-fold higher than in the liver tissue of the rabbits.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Hoe 33171 was administered to pregnant rats (50 mg/kg), rabbits (50 mg/kg), and a cynomolgus monkey (10 mg/kg) during embryo organogenesis. The comparative discussion of the metabolism of Hoe 33171 in the monkey, rats, and rabbits is primarily based on the HPLC analysis of 24-hour urine samples following the final dose (monkey, 50 days p.c.; rat, 16 days p.c.; rabbit, 19 days p.c.).

The study authors assessed that the qualitative similarity in the metabolic profiles found in the urines between the rat, rabbit, and monkey indicates that the metabolic pattern in man is similar. However, obvious quantitative differences were observed with respect to biotransformation of the test material and residue accumulation in the tissues between the three species. A comparison of the radiolabel residue levels found in the tissues of the rabbits and rats at 6 hours postadministration indicated

Table 3 : Separation of the metabolites in the 0 - 24 hrs urine (last dosage) into groups of different polarity

Group	Species		
	Cynomolgus monkey (%)	Rabbit (%)	Rat (%)
(C) Most polar (not retained in the reversed phase cartridge when applied in aqueous solution)	1.5	4.5	4.3
(B) Medium polar (elution of medium polar compounds from RP-18)	33.5	23.1	13.3
(A) Non-polar (elution of non-polar compounds from RP-18)	56.5	78.7	88.8

*Copied from CBI p. 53, Table 2.

Table 4*: Percentage of the separated metabolites in the 0 - 24 hrs urine after the last application, given in % of the total radioactivity in the urine sample.
The designation of the metabolites (e. g. C 1, K 6) are derived from the peak-number in the HPLC chromatogram of the respective fraction from the resp. species.

C = metab. in Cynom. K = metab. in rabbit R = metab. in rat	Group C, (most polar)	Group B (medium polar)						Group A (non-polar)																		
		MR 1	MR 2 = MK 1	MK 2 = MC 1	MK 3 = MC 2	MK 4	MR 3	C 1	C 2	C 3	K 6	K 9	R 1 = K 10 = C 4	R 2 = K 11 = C 5 = BO-5-OH	R 3 = C 6	R 4 = K 12 = C 8	R 5 = K 13 = C 9 = BO	R 7 = K 14 = BO-Merc.ac.	R 9 = K 15 = C 10 = BO-SH	R 11 = K 16	R 12 = K 17 = C 11	R 13 = K 18 = C 12	R 14 = K 19 = C 13	K 20 = C 14	R 15 = K 21 = C 15 = free acid
Cynomolgus (C)	1,5	-	-	9	12	-	-	0,3	0,8	0,3	-	-	0,5	1,6	2,3	5,1	5,8	-[2]	7,3	-	4,2	3,8	3,2	1,9	18,8
Rabbit (K)	4,5	-	4	10	5	3	-	-	-	-	3,3	1,3	1,9	6,8	-	3,5	9,4	23,1	1,3	0,9	0,8	4,0	5,6	0,9	14,3
Rat (R)	4,3	5	3	-	-	-	2	-	-	-	-	-	0,6	4,4	3,2	1,7	4,6	19,4	1,5	1,0	1,0	0,9	2,7	-	43,2

Abbreviations: - = not detectable (LOD ranged 0.5 - 1 %); 1) Prefix "M" refers to the medium polar compounds in group B and helps to distinguish them from the group A metabolites 2) see text chapter "Results", page 43)

*Copied from CBI p. 54, Table 3.

Table 5: Distribution of radioactive compounds throughout the different fractions of the working-up procedure of liver samples 6 hrs. after application.

	µg equivalents of active ingredient / g							
				Acetonitrile-phase		Hexane-phase		Total
Species	Total radio-act.-contents	Bound radioact.	Extract. radioact.	total	free acid	total	free acid	free acid
Rabbit	40,8	6,0	35	25	20	10	2,3	22
Rat	159	12	147	129	125	18	12	137

During the different working steps some radioactivity was lost due to high content of precipitates causing adsorption of dissolved radioactive metabolites. The composition of the lost radioactivity was assumed to be identical to the retained. Consequently, the measured values are corrected to 100 % recovary in each processing step resulting in the values given in this Table 5.

*Copied from CBI p. 56, Table 5.

faster absorption of the dose by the rats. The rat showed the highest levels of radiolabel in the tissues as a result of fast absorption and slow detoxification rates. In addition, the accumulation of residues in all tissues sampled decreased from the rat to the rabbit, and the corresponding residue level in the blood of the monkey (the only tissue level that was measured and corrected to a dose of 50 mg/kg) was the lowest among the three species. From these experimental findings it was concluded that a decrease in toxicological effect occurs in the sequence rat-rabbit-monkey-man.

B. The final report of this study was inspected by the Hoechst Aktiengesellschaft Pharma Research Quality Assurance (GLP) Unit. "This report was prepared in compliance with the principles of good laboratory practice; during the experimental phase of this study no inspection by the quality assurance unit was carried out."

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

This study provides some useful information on the metabolism of Hoe 33171 in pregnant rats, rabbits, and a cynomolgus monkey. The results indicated that metabolism of Hoe 33171 by the rat, rabbit, and monkey results in similar metabolic profiles in the urine. However, there were quantitative differences in the various metabolites, and there were unique minor metabolites detected in each species. After dosing pregnant rats and rabbits with [^{14}C]Hoe 33171, the postadministration radiolabel levels in the tissues of the rats were greater than those in rabbits at 6 and 48 hours. In the pregnant rabbits there was less transfer of radiolabeled material to the fetuses than in the rats.

There were a number of deficiencies in the study that make the data difficult to interpret. The sample collection intervals were insufficient for determining the rates of absorption and elimination of [^{14}C]Hoe 33171 by the rats and rabbits or for making comparative evaluations between the two species. In addition, direct comparisons concerning the metabolism of Hoe 33171 cannot be made between the monkey and the other two species because of the different doses administered. Furthermore, tissue residues of the monkey were not determined. Only 51 percent of the applied dose was recovered in the excreta of the monkey 48 hours postadministration suggesting that these animals had a slower metabolic rate. However, the study authors stated, "this result corresponds to the experience with other monkey studies using other test substances without having a causal explanation for that finding except of slow and drop by drop excretion of urine when the animal was taken out of the cage for the purpose of blood sampling."

The study authors concluded that the qualitative similarities in the metabolic profiles found in the urine between the rat, rabbit, and

monkey suggested that a similar metabolic pattern occurred in man. However, the results showed some qualitative and quantitative differences between the three species; hence, the data do not support this conclusion. Moreover, the authors have not presented any data or references on human metabolism to substantiate this claim. In addition, some minor deficiencies were noted: individual data for [^{14}C] tissue residues in control and dosed rats and rabbits and the HPLC chromatograms of the authentic reference compounds and urine samples were not reported. Also, the feces samples from the rats, rabbits, and monkey were not analyzed for metabolites.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 12-16, 23-26, 30-38, 57-63; Appendix B, Hoe 33171 Metabolite Structures, CBI pp. 41-43.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 290 through 314 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

APPENDIX B

Hoe 33171 Metabolite Structures

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 316 through 318 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
DYNAMAC No. 1-012E
January 27, 1986

DATA EVALUATION RECORD

ACCLAIM

Two-Generation Reproduction Study in Rats

STUDY IDENTIFICATION: Tesh, J. M., Willoughby, C. R., and Whitney, J. C. Hoe 33171 technical grade (code: Hoe 33171 OH AS 201): Effects upon reproductive performance of rats treated continuously throughout two successive generations. (Unpublished study Nos. A30806 and A31073 prepared by Life Science Research, Suffolk, England, for Hoechst Aktiengesellschaft, Abteilung für Toxicologie, Franfurt, West Germany; dated May 13, 1985.) Accession Nos. 258965-258970.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

004963

1. CHEMICAL: Acclaim; Whip; Hoe 33171; fenoxaprop ethyl; ethyl 2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propanoate.

2. TEST MATERIAL: Hoe 33171 technical grade (code: Hoe 33171 OH AS 201) was described as a white powder with a stated purity of 94.0%.

3. STUDY/ACTION TYPE: Two-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Tesh, J. M., Willoughby, C. R., and Whitney, J. C. Hoe 33171 technical grade (code: Hoe 33171 OH AS 201): Effects upon reproductive performance of rats treated continuously throughout two successive generations. (Unpublished study Nos. A30806 and A31073 prepared by Life Science Research, Suffolk, England, for Hoechst Aktiengesellschaft, Abteilung für Toxicologie, Franfurt, West Germany; dated May 13, 1985.) Accession Nos. 258965-258970.

5. REVIEWED BY:

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6. APPROVED BY:

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Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-8-86

7. CONCLUSIONS:

A. We conclude that the LOEL and NOEL for parental effects on rats are 180 and 30 ppm of Hoe 33171, respectively, based on increased liver and kidney weights and increased incidences of nephrocalcinosis at 180 ppm.

The LOEL for progeny is 5 ppm, the lowest dietary level tested, based on decreases in survival of offspring and terminal body weights and significant changes in kidney and liver weights for F_{2a} and F_{2b} litters at all dietary levels. The NOEL for progeny could not be established.

B. This study is classified Core Minimum.

Item 8--see footnote 1.

9. BACKGROUND:

A range-finding study was conducted in rats exposed to dietary levels of 0, 40, 160, or 320 ppm Hoe 33171 beginning 9 days prior to mating and throughout the mating, gestation, and lactation periods.

Significant increases in absolute liver weights were noted for parental males in the 320-ppm group and weanlings in all dose groups. There were significant increases in relative kidney weights for male and female weanlings in the 320-ppm group and for male weanlings at 40 ppm. Significant decreases in relative thymus weights occurred in male weanlings in all test groups and in female weanlings in the 160- and 320-ppm groups.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A.)

1. Test Material: The test material, Hoe 33171 technical grade, described as a white powder (code: Hoe 33171 OH AS 201), was received on 6/21/82 and stored at -21°C. Before incorporation into the diet, the test material was sifted in an ultracentrifugal mill equipped with a 1-mm screen. The milled test material was then incorporated into the ground feed in a series of graded dilutions using a horizontal screw-type mixer

[1] Only items appropriate to this DER have been included.

to give a final concentration of 180 ppm. The remaining dose levels were prepared using serial dilutions to give concentrations of 30 and 5 ppm. Control animals were given untreated feed.

Samples of 100 g from each batch were collected weekly for analysis and stored at 4°C; 100-g samples were also stored at room temperature for up to 3 months.

The test diet was analyzed for homogeneity of the mix prior to study initiation. Samples from the 5- and 180-ppm diets were collected from six different locations in the mixer. Analysis of concentration at each dietary level was conducted at the start of dosing for each generation, prior to mating, and at parturition.

2. Animals and Test System: Sprague-Dawley [Crl: CD (SD) BR] weanling rats were received from Charles River U.K. Ltd., Margate, Kent, England, and group-housed by litter and sex and acclimated for 16 days. Prior to study initiation, the animals were randomly assigned to four groups. At study initiation, body weights ranged from 152 to 211 g and from 126 to 172 g for males and females, respectively; the rats were approximately 5 to 6 weeks of age. Animals were housed five/cage/sex until mating. After 11 weeks on study, males and females were paired on a one-to-one basis. Siblings were not mated. During the mating period, vaginal smears were prepared daily and examined for evidence of sperm. Gestational day (GD) 0 was designated as the day on which evidence of mating was observed. Females not mated after 21 days were paired with another proven male for up to 14 days.

After weaning the first litters (F_{1a}), parents were given a rest period of 10 days and mated a second time to produce the F_{1b} generation.

Following weaning of the F_{1b} litters, 30 males and 30 females were selected as F_1 parental animals. One male and one female were randomly selected from each litter in each group (abnormal animals were excluded). After 14 weeks on the test diets, animals were paired to produce F_{2a} litters. Mating procedures were the same as previously described for the first and second matings. Different pairings were used for the second mating of each generation; mating of siblings was avoided if possible. Females not producing a viable litter 26 days preceding the second mating or after the last day of the second mating were sacrificed and subjected to a complete necropsy. The uteri of females without visible implantations were stained (method not specified) to confirm pregnancy status.

All surviving F_0 and F_1 parental animals were sacrificed by carbon dioxide asphyxiation after weaning of the second litters and subjected to complete necropsies.

Complete necropsies were also conducted on one male and one female randomly selected from each litter after weaning. Remaining offspring (those not selected for complete necropsies or for F_1 parental animals) were sacrificed, grossly examined for external and visceral abnormalities, and discarded. Abnormal tissues were fixed in 4% formaldehyde or Davidson's fluid and later examined histologically. Animals found dead or sacrificed moribund during the study were given complete necropsies, and abnormal tissues were saved.

3. Parameters Measured: Animals were observed daily for signs of toxicity, general health, and mortality. Body weights of males and unmated females were measured weekly. Mated females were weighed and body weights were recorded on GD 1, 7, 14, and 21 and on lactational days 1, 7, 14, 21, and 25. Food consumption was measured once weekly until the animals were paired, and after mating on GD 1, 7, 14, and 21 and lactational days 1, 7, and 14. Water consumption was measured daily until animals were paired and then daily throughout gestation and lactation.

   Vaginal smears were examined for 10 days prior to the first mating for each generation to determine the presence of normal estrus cycles.

   From GD 21, mated females were examined three times daily for evidence of parturition. All litters were examined approximately 24 hours after parturition (lactational day 1). The number of live and dead pups, litter weight, and the sex and appearance of each pup were recorded. Litter weights and sex determinations were recorded on lactational days 1, 14, and 25. The rate of physical development was assessed on a total litter basis. Completion of each of the following parameters was recorded: pinna unfolding, hair growth, tooth eruption, and eye opening. Responses to auditory and visual stimuli were recorded at weaning.

   For complete necropsies, selected organs were weighed and then tissues were fixed in 4% formaldehyde. Tissues from the control and 180-ppm dietary groups of F_0 and F_1 parental animals and from selected F_{1b} and F_{2b} weanlings were examined histologically. Reproductive organs from parental animals and F_{1b} weanlings in the 5- and 30-ppm dietary groups were also examined histologically. Tissues from F_{1a} and F_{2a} weanlings were saved but not examined.

B. Protocol: A protocol was not provided.

12. REPORTED RESULTS:

A. Test Material: Analyses of Hoe 33171 in feed revealed that dietary concentrations ranged from 72 to 124% of target concentrations. Mean values of 4.6, 27.1, and 165.9 ppm were obtained for nominal concentrations of 5, 30, and 180 ppm, respectively. The authors reported that the stability of the test material was analyzed (the results were presented in the Addendum); however, the analysis was reported in German.

B. Parental Effects:

1. Mortality and Health: No pharmacological signs attributable to test material administration were reported in either the F_0 or F_1 generations. During weeks 26-27 of the F_0 generation, the males developed swellings in the throat and dry eyes and had weight losses that the authors considered to be characteristics of RCV/SDA viral infection (sialodacryodenitis). Similar findings were reportedly observed in a few F_0 females (during their second lactation period). The clinical signs generally disappeared within 7 days; isolated findings of corneal opacity and dryness were noted at necropsy. Approximately 3% of the animals selected for the F_1 generation exhibited corneal opacity; these numbers increased as the study progressed until approximately 25% of the animals were affected. The authors stated that these findings occurred in control and test groups and were attributed to an RCV/SDA-like viral infection contracted before weaning. Corneal opacity persisted until termination and was evident at necropsy.

One mortality occurred during the F_0 generation. A female from the 30-ppm group died of undetermined causes at the end of her second pregnancy. Five animals died or were sacrificed during the F_1 generation. One male with an abnormally shaped skull in the 30-ppm group failed to gain weight and was sacrificed at 6 weeks of age; necropsy findings included serous fluid in the cranial cavity, soft and misshapen brain, and a pale spleen. Two females from the control and one female from the 180-ppm group were sacrificed or died during their second lactation period (F_{2b}), and fluid accumulation was found in the thorax of both at necropsy. One female in the 30-ppm group, sacrificed on GD 22 of her second pregnancy (F_{2b}), was found to have stomach ulcers and a possible brain hemorrhage at necropsy. The authors did not attribute any of these findings to test material administration.

2. Body Weights: There were no adverse effects on body weights noted for any of the test groups when compared to controls during the F_0 generation. The authors reported a statistically significant increase ($p < 0.05$) in body weight gain from weeks 0 to 28 for males in the 180-ppm group. However, this change was not considered biologically significant. As stated

earlier, there were slight transient decreases in the body weights of males during weeks 26 and 27 that were attributed to a viral infection.

Body weights for F_1 males in the 180-ppm group were significantly lower ($p < 0.01$) than controls at selection (3 weeks of age). Body weight gains for males were comparable among groups, however, and no adverse effects on body weights were noted for females during the F_1 generation. Table 1 summarizes the effects of Hoe 33171 on body weights during the premating period for the F_0 and F_1 generations.

3. Food and Water Consumption and Test Material Intake: No differences in food consumption were noted between control and test groups during either generation (Tables 2 and 3). The water intake for F_0 females in all dose groups was slightly decreased during the 3 weeks prior to the first mating. The authors did not consider these changes to be compound related. No other differences were observed in water consumption during either generation.

The authors reported that the test material intake of the three test groups was in an approximate ratio of 5:30:180. The calculated group mean values for test material consumption during premating periods for both generations are presented in Table 4. In the 180-ppm group, initial chemical intakes were approximately 22-29 mg/kg/day; as the study progressed, values decreased until the first mating when intakes were approximately 9-12 mg/kg/day. These values reportedly increased during the second lactational phase for both generations.

4. Macroscopic and Microscopic Observations and Organ Weights: There were no biologically significant changes noted grossly or histologically in F_0 or F_1 parental animals. Symptoms such as dark Harderian glands, eye lesions, corneal opacities, congested salivary glands, and enlarged and congested lymph nodes were noted at necropsy but were attributed to a suspected RCV/SDA viral infection and not test material administration.

There were significant increases in absolute and relative liver weights for F_0 males and F_1 females in the 180-ppm groups and in relative kidney weights for F_0 females in the 30- and 180-ppm groups. Significant decreases were also noted in absolute and relative spleen weights for F_0 females in the 30- and 180-ppm groups and for F_1 females in the 30-ppm group. No differences in organ weights were noted between controls and F_0 males or females in the 5-ppm group or F_1 females in the 5-ppm group and F_1 males in any test group.

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TABLE 1. Effects of Hoe 33171 on Parental Mean Body Weights of Rats During the Premating Periods of a Two-Generation Reproduction Study

Generation	Dietary Level (ppm)	Body Weight (g) at Premating Week 0	6	11	14
F_0 Males	0	181	452	553	--
	5	183	460	561	--
	30	183	466	572	--
	180	185	463	572	--
F_0 Females	0	145	266	314	--
	5	144	261	306	--
	30	144	263	304	--
	180	143	259	304	--
F_1 Males	0	84	389	498	546
	5	83	389	496	540
	30	85	390	495	539
	180	74**	372	486	534
F_1 Females	0	71	227	269	292
	5	74	227	270	292
	30	74	234	282	302
	180	71	224	273	293

**Significantly different from control value ($p < 0.01$).

TABLE 2. The Effect of Hoe 33171 on Parental Mean Feed Consumption in Rats During the Premating Periods of a Two-Generation Reproduction Study

Generation	Dietary Level (ppm)	Feed Consumption (g/rat/week) at Week 1	6	11
F_0 Males	0	179	201	193
	5	178	201	192
	30	181	207	201
	180	181	205	198
F_0 Females	0	142	153	146
	5	138	144	139
	30	139	149	136
	180	142	144	139
F_1 Males	0	157	195	193
	5	157	186	189
	30	158	196	193
	180	143	186	185
F_1 Females	0	124	137	145
	5	127	140	138
	30	130	151	149
	180	123	146	144

TABLE 3. Effects of Hoe 33171 on Mean Maternal Body Weight (g) During Gestation and Lactation

Generation	Dietary Level (ppm)	Body Weight (g)			
		Gestation Day		Lactation Day	
		1	21	1	25
F_{1a}	0	316	439	348	345
	5	302	429	345	347
	30	305	434	342	350
	180	304	428	342	356
F_{1b}	0	352	475	374	370
	5	348	471	377	381
	30	350	477	383	386
	180	344	471	377	384
F_{2a}	0	301	425	344	336
	5	291	415	332	332
	30	303	430	346	341
	180	298	424	344	348
F_{2b}	0	339	460	375	363
	5	336	462	376	376
	30	348	477	383	383
	180	340	470	382	386

TABLE 4. Calculated Group Mean Values for Parental Consumption of Hoe 33171 in Rats During Premating Periods of a Two-Generation Reproduction Study

Generation	Dietary Level (ppm)	Hoe 33171 Consumption (mg/kg/day) at Premating Week				
		1	3	6	11	14
F_0 Males	0	0	0	0	0	--
	5	0.60	0.44	0.32	0.25	--
	30	3.63	2.65	1.93	1.53	--
	180	21.6	15.6	12.7	9.05	--
F_0 Females	0	0	0	0	0	--
	5	0.62	0.51	0.40	0.33	--
	30	3.77	3.07	2.48	1.94	--
	180	23.4	18.4	14.6	11.9	--
F_1 Males	0	0	0	0	0	0
	5	0.80	0.58	0.37	0.27	0.25
	30	4.90	3.52	2.37	1.69	1.53
	180	29.8	21.2	14.4	9.96	8.87
F_1 Females	0	0	0	0	0	0
	5	0.81	0.61	0.45	0.37	0.32
	30	4.98	3.85	2.98	2.29	2.00
	180	29.3	22.4	18.2	13.7	12.2

Examination of bone marrow smears from F_0 males in the 180-ppm group revealed that although there were no abnormalities in the types of cells noted, the composition was abnormal in that an excessive number of cells were present. These findings were not observed in F_0 females or F_1 males or females and, therefore, were not considered compound-related.

C. Reproductive Effects:

1. Mating Performance and Fertility: No differences in the length of the estrus cycle were noted between control and test groups. A summary of the effects of Hoe 33171 on reproductive parameters is presented in Table 5. There were no adverse effects noted in mating performance or fertility of the F_0 animals during either pairing. In fact, the fertility indices were slightly higher for test groups when compared to controls after the first mating (F_{1a}). Several animals proved infertile after two matings: two males from the control group and one male from the 30-ppm group and two females from the control group, one female from the 30-ppm group, and one female from the 180-ppm group. However, the authors reported that there were no indications showing that the findings in these dose groups were compound related.

   During the F_1 generation, an increased number of animals failed to mate at the first estrus during both the first and second pairings in the control, 30-ppm, and 180-ppm groups. However, the majority of animals mated successfully at the subsequent estrus; therefore, the study authors did not attribute the changes in the dosage groups to test material administration. Gestation length and gestation indices were comparable between control and treated groups for both generations.

2. Progeny: No compound-related pharmacological signs were noted in offspring from either generation. Prior to weaning, the F_{1b} offspring contracted the viral infection mentioned earlier and developed exudate around the eyes and corneal opacities. The authors reported that all groups were similarly affected.

   Viability indices at birth, litter sizes, and male to female sex ratios were comparable among the control and dose groups for both generations (Table 5). No differences were noted in survival of litters between control and dose groups during lactation for the first generation (F_1). Survival of offspring in the dose groups of the second generation (F_2) was decreased at days 4 and 25 (Table 6). These decreases were significant on day 4 for the 5- and 180-ppm groups of the F_{2a} generation and the 180-ppm group of the F_{2b} generation and on day 25 for the 5-ppm group of the F_{2a}

TABLE 5. Summary of the Effect of Hoe 33171 on Reproductive Parameters for Two Generations of Rats

Generation	Dietary Level (ppm)	No. Males Mated	No. of Proven Males	Fertility Index (%)	No. Females Mated	No. Females Pregnant	Fertility Index (%)	No. Litters Born	Gestation Index	Mean No. Live Pups/ Litter	Born Viable (%)
F_{1a}	0	30	21	77	30	23	77	23	100	13.1	99
	5	30	28	90	30	29	97	29	100	12.7	100
	30	29	21	90	30	27	90	27	100	13.8	99
	180	30	20	93	30	29	97	29	100	13.1	100
F_{1b}	0	30	26	87	30	26	87	26	100	13.9	100
	5	30	29	97	30	29	97	29	100	13.3	100
	30	29[a]	24[a]	83	29[a]	26[a]	90	24	92	13.5	100
	180	30	26	87	30	27	90	27	100	13.9	100
F_{2a}	0	30	21	70	30	24	80	23	96	12.2	95
	5	30	28	93	30	28	93	27	96	12.6	99
	30	29	21	72	30	24	80	24	100	13.1	99
	180	30	20	67	30	26	87	26	100	12.1	100
F_{2b}	0	30	24	80	30	25	83	25	100	11.8	99
	5	30	26	87	30	26	87	26	100	12.9	99
	30	29	20	69	30	23	77	21	91	13.5	99
	180	30	25	83	30	26	87	25	96	13.4	100

[a]Excludes mating of female 1066 with male 1189—pregnancy was not conclusively established.

TABLE 6. Summary of Effects of Hoe 33171 on Mean Group Pup Survival and Body Weight Values During the Lactation Period in Two Generations of Rats

Generation	Dietary Level (ppm)	Pup Survival (%) from Days 1-4	4-25	1-25	Pup Body Weight (g) Day 1	Day 4	Day 25	Body Wt. Change (g) Days 1-25
F_{1a}	0	95	95	90	6.2	8.7	64.8	58.6
	5	84**	95	80**	6.0	8.2	63.2	57.2
	30	88**	92	84*	5.9	8.0	61.4	55.5
	180	92	94	86	6.0	8.1	58.9	52.9**b
F_{1b}	0	95	96	91	6.0	8.4	57.7	51.7
	5	94	95	89	6.0	8.6	57.7	51.7
	30	98*	98	95*	6.2	8.8	59.5	53.3
	180	96	96	92	6.0	8.2	54.4	48.4
F_{2a}	0	94	97	91	6.2	8.0	59.8	53.6
	5	72**/*a	90**	65**/*a	5.8	7.1	57.3	51.5
	30	82**	93*	76**	6.1	7.7	59.2	53.1
	180	70**/*a	96	68**	5.9	7.6	56.0	50.1
F_{2b}	0	95	87	91	6.3	8.7	63.2	56.9
	5	86**	89	77**	6.0	7.8	61.2	55.2
	30	87**	93*	80**	6.1	8.1	62.8	56.7
	180	81**/*a	88	72**/**b	5.9	7.8	55.4	49.5**b

*Significantly different from control value ($p < 0.05$) according to reviewers' analysis.

**Significantly different from control value ($p < 0.01$) according to reviewers' analysis.

*aSignificantly different from control value ($p < 0.05$) according to authors' analysis.

**bSignificantly different from control value ($p < 0.01$) according to authors' analysis.

Note: The authors analyzed survival data using the Chi-square test, Fisher's exact probability test, or the Mann Whitney U-test. We used Fisher's exact probability test for analysis.

generation and the 180-ppm group of the F_{2b} generation. The authors stated that the reductions in viability indices for the F_{2a} generation were largely due to the total loss of a small number of litters, and survival of the remaining litters was not affected. In the F_{2b} generation, there were fewer total litter losses but an increased loss of offspring from greater numbers of litters in the 180-ppm group. Lactation indices (No. pups in each litter weaned/No. pups alive at day 4) were comparable among control and test groups for both generations.

Initial body weights for offspring were similar between control and test groups for both generations. However, body weight gains for the lactation interval of days 1 to 25 were decreased in the 180-ppm group during both generations; significant decreases ($p < 0.01$) occurred in F_{1a} and F_{2b} litters. Physical development and response to auditory and visual stimuli were comparable between control and test groups for both generations. The authors reported that an abnormally low percentage of F_{1b} litters responded to the pupil closure test, stating this was partly due to pupils being occluded by discharge or corneal opacity. In addition, the incidence of litters with the failure of one or both pupils to dilate in the dark was increased for all groups but occurred in an apparently dose-related pattern. However, because similar findings were not noted in F_{1a}, F_{2a}, or F_{2b} offspring, the authors attributed these eye problems to the viral infection contracted by the F_{1b} offspring prior to weaning and not to the administration of Hoe 33171.

No compound-related findings were noted at necropsy for offspring from either generation. Necropsy and histopathologic findings indicative of the suspected RCV/SDA-like viral infection were noted in F_{1b} offspring. There was a significant increase in the incidence of nephrocalcinosis in F_{1b} and F_{2b} female offspring in the 180-ppm group and slight, nonsignificant increases in F_{2b} males compared to controls. Males from F_{1b} litters were reportedly not affected.

There were significant increases in relative liver weights in offspring in the 180-ppm group from both generations when compared to controls. Relative kidney weights were significantly increased for F_{1a} and F_{1b} males and females and F_{2a} males and F_{2b} females in the 180-ppm group when compared to controls. Significant decreases in absolute thymus weights were noted in F_{1a} males and females, F_{2a} males, and F_{2b} males and females in the 180-ppm group when compared to controls.

Absolute testes weights were significantly reduced in the 180-ppm group of the second generation when compared to controls, but relative weights were comparable between controls and the 180-ppm group. Other significant differences in absolute and relative organ weights were noted but the authors stated that these were of no biological significance to test material administration. Examination of bone marrow smears from selected weanlings from control and 180-ppm groups from both generations revealed no compound-related changes.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The dietary administration of Hoe 33171 to rats over two generations had no effect on the general health, food or water consumption, and body weights during maturation, gestation, or lactation. The following reproductive parameters were comparable between the control and test groups: gestation length, initial litter size, initial body weights of offspring, sex ratios, and development of offspring. Differences in mating performance and fertility were not considered to be compound related.

Survival of offspring after birth was reduced for all test groups from the second generation when compared to controls. The authors stated that the biological significance was "unclear" because these reductions did not occur in a dose-related manner. Furthermore, the viral infection may have adversely affected reproductive performance and offspring survival of the second generation. The examination into familial links of animals that demonstrated poor reproductive performance revealed an association (relating back to the initial litter source) among females with litter death or failed pregnancies.

The authors concluded that a dietary level of 180-ppm of Hoe 33171 had adverse effects on the growth of offspring prior to weaning and produced enlarged kidneys and livers based on significantly reduced body weight gains of F_{1a} and F_{2b} weanlings and increased relative liver weights in offspring from the 180-ppm group of both generations and increased relative kidney weights for F_{1a} and F_{1b} males and females and F_{2a} males and F_{2b} females in the 180-ppm groups.

Dietary levels of 30-ppm Hoe 33171 or less had no adverse effects on rats over two generations.

B. A quality assurance statement was signed and dated May 15, 1985.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. 1. Test Material Analysis: Mean recovery values of Hoe 33171 in the test diet ranged from 72 to 124% of target concentrations. Results of these analyses indicated that either a

homogenous mixture was not achieved or extraction methods were not adequate for complete recovery of the test material.

2. Parental Effects: Test material intake was in an approximate ratio of 5:30:180 throughout the study. Body weights, food and water consumption, general health, and mortalities were comparable between the control and dose groups. During study weeks 26 and 27, the males exhibited symptoms of an SDA-like viral infection, which included weight loss, swelling in the throat, and dry eyes. All groups were similarly affected. No compound-related findings were noted at necropsy. Histopathologic examination revealed a slight increase in the incidence of nephrocalcinosis in females in the 180-ppm group compared to controls for both generations; no other compound-related changes occurred.

   There were significant increases in absolute and relative liver weights in F_0 males and F_1 females in the 180-ppm group. Significant increases in relative kidney weights were noted for F_0 females in the 30- and 180-ppm groups. Other significant changes in organ weights were not biologically significant.

3. Reproductive Effects: There were no differences noted in mating performance, gestation lengths, initial body weight, and number of offspring or gestation indices between control and dose groups from either generation. Male fertility indices were decreased during the F_1 generation, but all groups were similarly affected; therefore, the decreases could not be attributed to test material administration. Decreases in survival of offspring during lactation were reportedly noted during the second generation (F_{2a} and F_{2b} litters) for all dose groups when compared to controls (Table 6). After analysis of survival data using Fisher's exact probability test, we found significant decreases in the 5- and 30-ppm groups from the F_{1a} generation as well as significant decreases in the 30- and 180-ppm groups from the F_{2a} generation and the 5- and 30-ppm groups from the F_{2b} generation (Table 6). Therefore, we assess that the decreased survival of offspring was compound related at all doses. Most litters from the dose groups had some pups die and, in addition, there were total losses of a number of litters in the dose groups of the F_{2a} and F_{2b} generations, which contributed to the decreases noted; there were total losses of zero, five, three, and five litters in the control, 5-, 30-, and 180-ppm groups, respectively, for the F_{2a} generation and one, three, two, and three litters in the control, 5-, 30-, and 180-ppm groups, respectively, for the F_{2b} generation (Table 7).

TABLE 7. Effects of Hoe 33171 on Pup Mortality During the Second Generation of a Two-Generation Study in Rats

Generation	Dietary Level (ppm)	No. Females Mated	Total No. Litters	No. Litters with Mortalities	% Incidence	No. Total Litters Lost	% Incidence
F_{2a}	0	30	23	9	39	0	0
	5	30	27	13	38	5	19
	30	30	24	11	46	3	13
	180	30	26	11	42	5	19
F_{2b}	0	30	25	7	28	1	4
	5	30	26	12	46	3	12
	30	30	21	9	43	2	10
	180	30	25	16	64	3	12

In each case, death of the entire litter occurred prior to lactational day 7; determination of survival values for the lactational interval of days 4-25 revealed smaller differences between control and dose groups (Table 6). Necropsy findings for the majority of pups found dead were lack of milk in the stomach, indicating that pups were not receiving nutrition. The authors did not report any examination of the dams to determine whether milk was being produced by mammary glands or whether mothers were taking care of their pups. Therefore, a possible compound-related decrease in milk production or maternal care cannot be ruled out.

There were no differences in the rate of physical development or response to auditory and visual stimuli that could be attributed to test material administration. Significant decreases in body weight gain (lactation days 1-25) occurred in offspring from the 180-ppm group during the F_{1a} and F_{2b} generations. Mean terminal body weights for weanlings in the 180-ppm group selected for necropsy (approximate age was 28 days) were lower than those of controls in both generations; significant decreases occurred in F_{2a} males in the 180-ppm group and F_{2b} females in all dose groups when compared to controls (Table 8).

Necropsy findings were comparable between control and dose groups for both generations. Histopathological examination of selected F_{1b} and F_{2b} weanlings revealed increased incidences of nephrocalcinosis in males and females in the 180-ppm group when compared to controls. We consider these increases to be compound related.

B. We disagree with the study authors on the following points:

1. Levels of Hoe 33171 in test diets were not within an acceptable range. Analysis revealed that actual concentrations ranged from 72 to 124% of target values; a 10% deviation is generally considered acceptable.

2. There were compound-related decreases in survival of offspring at all doses.

3. The increased incidence of nephrocalcinosis in parental females as well as female offspring was considered to be a compound-related effect.

C. The following discrepancies and deficiencies were noted in the study report:

1. Levels of Hoe 33171 in test diets were not within an acceptable range.

TABLE 8. Mean Terminal Body Weights for Selected Rat Weanlings Fed Hoe 33171 for Two Generations (Age = 28±2 Days)

Generation	Dietary Level (ppm)	Terminal Body Weight (g) Male	Female
F_{1a}	0	75	71
	5	75	67
	30	71	65
	180	68	64
F_{1b}	0	66	62
	5	68	62
	30	70	63
	180	64	59
F_{2a}	0	69	63
	5	67	63
	30	71	64
	180	62*	56
F_{2b}	0	73	71
	5	72	65*
	30	72	65*
	180	66	55**

*Significantly different from control value ($p < 0.05$).

**Significantly different from control value ($p < 0.01$).

2. NOEL for offspring toxicity could not be established due to adverse effects noted even at the lowest level tested.

3. Litters were not culled on lactational day 4.

4. Histopathological examination of kidneys for all dose levels should have been conducted to further assess possible compound-related effects.

5. Slight discrepancies were noted between individual animal data, summary tables, and text.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Methods, CBI pp. 7-22.

APPENDIX A

Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 341 through 356 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 66-02-4225
TASK: 024-21
November 5, 1985

DATA EVALUATION RECORD

HOE 33171

Teratogenicity Study in Rabbits

STUDY IDENTIFICATION: Baeder, Weigand, and Kramer. An oral embryotoxicity study of Hoe 33171 active ingredient (technical grade) (code: Hoe 33171 OH AT204) in Himalayan rabbits. [Unpublished study No. A24756 prepared and submitted by Pharma Research Toxicology, Hoechst AG, Frankfurt/Main, Federal Republic of Germany; dated October 21, 1982.] Accession No. 256667.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-5-85

1. CHEMICAL: Hoe 33171 OH AT204, active ingredient of Whip 1 EC herbicide.

2. TEST MATERIAL: Technical grade Hoe 33171 OH AT204, batch No. 10 750, consisted of 93 percent active ingredient.

3. STUDY/ACTION TYPE: Teratogenicity study in rabbits.

4. STUDY IDENTIFICATION: Baeder, Weigand, and Kramer. An oral embryotoxicity study of Hoe 33171 active ingredient (technical grade) (code: Hoe 33171 OH AT204) in Himalayan rabbits. [Unpublished study No. A24756 prepared and submitted by Pharma Research Toxicology, Hoechst AG, Frankfurt/Main, Federal Republic of Germany; dated October 21, 1982.] Accession No. 256667.

5. REVIEWED BY:

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Date: November 5, 1985

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Teratogenicity and Reproductive Effects
Technical Quality Control
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Date: 11-5-85

Thomas Edwards
EPA Reviewer

Signature: Thomas Edwards
Date: 2-6-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-11-86

7. CONCLUSIONS:

A. Based on the data presented, the NOEL for maternal toxicity from Hoe 33171 is 12.5 mg/kg/day and the LOEL is 50 mg/kg/day in rabbits. These values are based on decreases in food consumption and in maternal body weight gain. The NOEL for embryo/fetal lethality could not be established due to the presence of conceptuses that were aborted, delivered early, and resorbed in all dosed groups. The group mean number of live fetuses for all surviving dams was lower in all of the dosage groups compared with controls, and the decrease in the 200 mg/kg/day group was statistically significant. In addition, the percentage of surviving fetuses after a 24-hour period was significantly reduced for the 200 mg/kg/day group. Therefore, 12.5 mg/kg/day (the lowest dosage used) is the LOEL for embryo/fetal lethality. The NOEL and LOEL for fetotoxicity are 50 and 200 mg/kg/day, respectively, based on statistically significant reductions in fetal body weights and on increases in the incidence of rib anomalies in fetuses from the 200 mg/kg/day group. The NOEL and LOEL for teratogenicity are 50 and 200 mg/kg/day, respectively, based on the presence of diaphragmatic hernias in the 200 mg/kg/day group.

C. The study as presented has serious deficiencies; no results or methodology on analysis of the concentration of active ingredient in the test article were presented. Although the authors stated that stability analysis was conducted, no results were presented. Therefore, this study is classified Core supplementary, and may be upgraded if the above information is submitted.

8. RECOMMENDATIONS:

We recommend that the results of analytical tests performed to determine the concentration and stability of dosage formulations be submitted. These results will allow the reviewers to determine if animals were properly dosed (a good laboratory practice requirement).

9. BACKGROUND:

A preliminary range-finding experiment was conducted using pregnant rabbits that were gavaged daily with doses of 3, 10, 32, 100, 200, or 400 mg/kg from gestation days 7-19. The study authors concluded that there were no observable effects at 100 mg/kg/day, whereas 200 mg/kg/day resulted in weight reduction in both mothers and fetuses.

Item 10--see footnote 1.

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[1] Only items appropriate to this DER have been included.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. The test material consisted of technical grade Hoe 33171 dissolved in sesame oil. Dosages were administered by gavage at 0, 12.5, 50.0, or 200.0 mg/kg/day.

2. The test animals were mated Himalayan rabbits dosed on gestation days 7-19, killed on day 29, and subjected to teratological examination.

3. The parameters measured included:

a. Maternal

(1) Clinical health assessed daily
(2) Food consumption checked continually
(3) Body weight change measured weekly
(4) Corpora lutea
(5) Organ weights
(6) Limited gross pathology

b. Embryonic/Fetal

(1) Mortality
(2) Body weight
(3) Crown-rump length
(4) Placental weight
(5) Sex
(6) 24-hour survival
(7) Gross, visceral (by methods described by Wilson) and skeletal malformations, variations, and developmental delays.

B. Materials and Methods are submitted in lieu of protocol; see Appendix A.

12. REPORTED RESULTS:

A. Test Material Analysis: No test results on numerical concentration, homogeneity, or stability were given for the test material, although it was stated that stability analyses were conducted and that the test material was stable for at least 3 days.

B. Food Consumption and Body Weights: These results are given in Table 1. During treatment, maternal body weight was decreased in comparison with the controls at the high dose only. Maternal weights in this group increased after dosing ceased, but remained below the control mean. A reduction in defecation was also noted for the intermediate- (50 mg/kg/day) and high-dose (200 mg/kg/day) dams. The liver and spleen were also enlarged at 200 mg/kg/day.

TABLE 1. Summary of Maternal Food Consumption, Weight Change, and Organ Weights Following Hoe 33171 Treatment in Rabbits

	Dosage (mg/kg/day)							
	0 (Vehicle)		12.5		50		200	
Food Consumption[1]								
Days of Pregnancy	N	X±SD	N	X±SD	N	X±SD	N	X±SD
0- 7	12	2.80±0.64	11	2.78±0.80	12	2.83±0.54	8	3.05±0.54
7-14	12	2.30±0.92	10	2.87±0.92	10	1.45±0.64	6	0.57±0.71
14-20	13	2.15±1.05	9	2.11±0.75	9	1.64±1.30	6	0.14±0.16
20-29	10	2.63±0.58	9	2.59±0.45	6	2.59±0.81	4	3.62±0.34
Net Body Weight Change (g)								
Days of Pregnancy	N	X	N	X	N	X	N	X
0- 7	15	36	12	5	13	16	8	2
7-14	15	6	12	12	13	-37	8	-196
14-20	15	20	12	47	13	25	8	-101
20-29	15	160	12	139	13	125	8	359
total (0-29)	15	222	12	203	13	129	8	64*
Mean Organ Weight (in grams)								
Organ	X±SD		X±SD		X±SD		X±SD	
Liver	53.51±7.95		55.69±4.97		56.66±6.91		63.54±8.28*	
Spleen	0.61±0.16		0.72±0.15		0.72±0.17		1.09±0.32*	
Kidney	15.01±1.82		15.13±1.13		16.13±1.43		15.73±2.27	
Heart	5.53±0.66		5.21±0.60		5.38±0.76		5.46±0.72	

[1]In g/100 g body weight.

*Significantly different from control ($p \leq 0.05$).

C. Clinical and Necropsy Observations and Mortalities: No signs of ill health were seen in the control rabbits. One low-dose (12.5 mg/kg/day) dam died after 10 doses with Hoe 33171 (gestation day 16) and another littered prematurely (day 29). No untoward effects were seen at the intermediate dose. At the high dose, one dam died following the eleventh dose and another after 12 doses (gestation days 17 and 18, respectively, Table 2). Additionally, three high-dose dams aborted their litters (between gestation days 19 and 23) and another littered prematurely on day 24 (Table 2). A decrease in defecation was reported for 4/15, 3/15, 8/15, and 15/15 females from the 0, 12.5, 50, and 200 mg/kg/day groups, respectively. Alopecia was noted in two high-dose dams. Enlarged livers and spleens were observed during necropsy in some high-dose dams; one of them had a discolored liver.

D. Reproductive Parameters: The relevant data are shown in Table 2. There were 1, 2, and 1 dams with totally resorbed litters in the low-, intermediate-, and high-dose groups, respectively. There were also two prematurely delivered litters (one at the high dose) and three aborted litters (all at the high dose), as described under clinical signs. All other litters were delivered live at term. Other reproductive parameters, including corpora lutea and implantations, were reportedly within normal ranges for the laboratory and strain.

E. Fetal Evaluation: Offspring-related data are given in Table 2. No effect was seen on fetal or placental weight or fetal length except at the high dose, where fetuses were said to be "slightly underdeveloped," or with a "slight reduction in body weight and length" and "slightly lighter placentas." No treatment-related effects were reported on prenatal deaths, and sex ratios were unchanged, but the 24-hour survival rate of the high-dose fetuses was considerably decreased. The incidence of diaphragmatic hernia was increased in the fetuses from the high dose group, as was the proportion of fetuses with rudimentary 13th ribs, and these increases were said to be dose related. No compound-related increases in visceral defects were reported.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Study Authors' Conclusions:

1. No effects were seen on either offspring or dams at the low dose.

2. At 50 mg/kg/day, the only significant effect was a decrease in maternal food intake during treatment.

TABLE 2. Summary of Reproductive Parameters and Fetal Data Following Hoe 33171 Treatment in Rabbits

	Dosage (mg/kg/day)			
	0 (Vehicle)	12.5	50	200
Number of:				
Dams mated/pregnant	16/15	15/15	16/15	15/15
Days dying	0	1	0	2
Litters aborted	0	0	0	3
Litters totally resorbed	0	1	2	1
Litters delivered early	0	1	0	1
Viable litters on day 29	15	12	13	8
Corpora lutea [1]	7.9	7.6	7.8	8.8
Implantation [1]	6.8	6.5	7.2	7.1
Resorptions [2]	0.33	0.67	1.08	0.63
Dead fetuses [2]	0.40	0.42	0.85	0.75
Live fetuses [2]	6.1	5.4	5.2	5.8
Fetuses from all surviving dams that had conceived [3] (litters included)	6.1 (15)	4.6 (14)	4.5 (15)	3.8 (12)*
Fetal Data:				
Sex ratio (% M/F) [1]	56/44	54/46	38/62	43/57
Placental weight (g±SD) [2]	5.6±0.41	5.8±0.55	5.79±0.44	5.08±0.66*
Body weight (g±SD) [2]	43.5±3.9	44.6±3.7	43.6 ±3.0	35.3 ±3.0*
Crown-rump length (cm±SD) [2]	9.8±0.4	9.7±0.3	9.8 ±0.2	9.2 ±0.2*
Twenty-four hour survival (%) [2]	92.5	95.3	92.2	61.2*
Diaphragmatic hernia (%) [1]	0	0	0	7.9 [4]

*Significantly different from vehicle control ($p \leq 0.05$).

[1] Based on data from all pregnant dams.

[2] Based only on dams with viable litters at day 29.

[3] Remaining in utero until day 29, delivered early, or aborted.

[4] Five fetuses from a total of four litters. One of these also had an umbilical hernia, whereas one otherwise normal fetus at this dose had an apparent spina bifida.

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3. At the high dose, there were decreases in maternal food consumption and body weight and increases in maternal mortality, abortions, and premature deliveries. Fetal body weights and crown-rump lengths were slightly decreased, and reductions were seen in placental weight and 24-hour survival rate. There were also increases in the incidences of diaphragmatic hernia and extra ribs.

4. According to the study authors, the NOEL for maternal toxicity of Hoe 33171 in rabbits is at least 12.5 mg/kg/day. Among the doses tested, the NOEL for developmental toxicity has been determined to be 50 mg/kg/day, with a LOEL of 200 mg/kg/day. Specific rationales for these conclusions were not provided.

B. Quality Assurance Measures: A quality assurance statement was signed and dated October 21, 1982.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Maternal Toxicity: No significant evidence of dose-related toxicity to the dams was observed at the low dose of Hoe 33171. At both the intermediate and high doses, the dams' food consumption appeared to be decreased considerably, with values that were stated by the study authors to be "outside the normal range" for rabbits at their laboratory. They did not indicate that the values were significantly different from concurrent control values, but they nevertheless stated that food consumption was reduced, along with a "reduction in defecation." Because individual food consumption data were not provided, we could not statistically analyze the data. Body weight of the high-dose females was decreased during treatment; the study authors stated that there was a decrease, but nowhere did they indicate statistical significance in comparison with the concurrent controls. Our statistical analysis by use of ANOVA followed by Duncan's multiple range test found the high-dose rabbits' weight gain to be significantly less than that of the concurrent controls (Table 1, $p \leq 0.05$). The study authors also did not indicate any inhibition of maternal weight gain during treatment at the intermediate dose, but overall weight gain in this group was only slightly more than half as great as that of the controls (128 g vs. 222 g). Considering the reduced food consumption at this dose, a real decrease in weight gain seems a likely consequence, although the difference was not statistically significant. Statistically significant differences are difficult to detect in such cases, however, due to the within-group variability in weight gain typically seen with rabbits. At the high dose, a further sign of toxicity was the enlargement of both liver and spleen. These results support the study authors' conclusion of a NOEL of at least 12.5 mg/kg/day for maternal toxicity, with a LOEL of 50 mg/kg/day.

B. Developmental Toxicity: The reproductive health of the parents appeared to be good, with most mated rabbits conceiving and having adequate rates of implantations compared with the number of corpora lutea. Although the reported resorption rates and numbers of living or dead fetuses did not appear to be affected by treatment with Hoe 33171, true offspring survival rates were obscured because the litters that were totally resorbed or aborted were not included in calculating the means presented. If this data is included, significant treatment effects can be shown. This can be seen from the data provided in Table 2, which shows a decline in live fetuses per litter from the control value of 6.1 to the high-dose level of 3.8. Such results suggest that even the 12.5 mg/kg dose may have decreased the number of living fetuses still in utero by gestation day 29. Nevertheless, the difference from the control value was statistically significant only for the high dose, according to our reanalysis by ANOVA followed by Duncan's test for multiple comparisons ($p \leq 0.05$).

There was a significant inhibitory effect on the weights of both fetuses and placentas as well as on crown-rump length and fetal survival, all at the high dose (as shown in Table 2). Such effects indicate toxicity to the fetus and may have been in part a result of the significant maternal toxicity as seen by decreased maternal food consumption. Further evidence of fetal toxicity could be seen in the increase in extra rib rudiments at the high dose.

The only obviously treatment-related specific malformation was diaphragmatic hernia. This defect was seen in 7.9 percent of the high-dose fetuses, with five fetuses from four different litters involved, but had been extremely rare in historical controls (one fetus seen in controls from 32 experiments). One of the affected fetuses also had an umbilical hernia. Another high-dose fetus apparently had spina bifida.

According to the reported results, the NOEL for developmental toxicity and teratogenicity associated with Hoe 33171 in the rabbit would apparently be 50 mg/kg/day.

C. Inadequacies in the Study Report: The study report, as presented, had a number of deficiencies as outlined below:

a. No actual data were presented regarding the concentration or stability of the active ingredient in the test article, nor were any methods presented for such an analysis. The study author stated that the test article was found by analysis (type not specified) to be stable for 3 days.

b. Although maternal clinical signs, food consumption, and organ weights were described or summarized, individual data were not shown.

c. Although maternal body weight gain, food consumption, and live offspring per dam were decreased by treatment, the study authors' statistical results failed to show this in comparison with the concurrent controls (see table on p. 18 of original report).

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 9-11.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 368 through 370 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

004963

EPA: 68-01-6561
TASK: 114
October 1, 1985

DATA EVALUATION RECORD

WHIP

Teratogenicity Study in Rabbits

STUDY IDENTIFICATION: Baeder, Weigand, and Kramer. Testing for embryotoxicity in Himalayan rabbits following oral administration. (Unpublished study No. G2K0400 prepared and submitted by Hoechst Aktiengesellschaft, Pharma Forschung Toxikologie, Frankfurt, Federal Republic of Germany; dated September 29, 1983.) Accession No. 256667.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 9-30-85

1. CHEMICAL: Whip, HOE 033171, fenoxoprop-ethyl, ethyl 2[4(6-chloro-2-benzoxazolyloxy-)-phenoxy-]-propanoate.

2. TEST MATERIAL: Whip, HOE 033171 OH ZC96 0002, technical grade, serial No. 11977, consisted of 96.2 percent active ingredient.

3. STUDY/ACTION TYPE: Teratogenicity study in rabbits.

4. STUDY IDENTIFICATION: Baeder, Weigand, and Kramer. Testing for embryotoxicity in Himalayan rabbits following oral administration. (Unpublished study No. G2K0400 prepared and submitted by Hoechst Aktiengesellschaft, Pharma Forschung Toxikologie, Frankfurt, Federal Republic of Germany; dated September 29, 1983.) Accession No. 256667.

5. REVIEWED BY:

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W. T. Edwards
EPA Reviewer

Signature: W Thomas Edwards
Date: 10-7-85

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 10-31-85

7. CONCLUSIONS:

A. The NOEL for maternal toxicity in this study was assessed at 50 mg/kg, the highest dose level tested; therefore, the maternal LOEL could not be determined. Based on a slight increase in embryolethality at the 50 mg/kg dose level, the embryonic/fetal NOEL and LOEL were 10 and 50 mg/kg, respectively. The teratogenic potential of HOE 033171 could not be determined due to deficiencies in study design (see item 14C).

B. Due to the deficiencies noted in this study report, this study was considered as supplementary data.

8. RECOMMENDATIONS:

We recommend that the teratogenic potential of the test material be tested utilizing a dose level capable of eliciting maternal toxicity. In addition, we suggest that individual data for maternal and fetal parameters be submitted in future reports to allow adequate assessment of study data by the reviewers.

9. BACKGROUND:

Preliminary tests were conducted to characterize the maternal response to HOE 033171. Food consumption was reported to be decreased at a 50 mg/kg dose level. However, information on species, strain, sex, age, and dose levels was not reported.

Item 10--see footnote 1.

11. MATERIALS AND METHODS:

A. Materials and Methods:

1. The test material, HOE 033171 OH ZC96 0002, serial No. 11977, containing 96.2 percent active ingredient, was prepared fresh every 4 days at concentrations of 4, 20, and 100 g/L. An equal volume of 0.5 mL/kg was administered at dose levels of 2, 10, and 50 mg/kg by oral gavage once daily from days 7 to 19 post-coitus. The vehicle and vehicle control was sesame oil. Doses were adjusted to changes in animal weight.

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[1]Only items appropriate to this DER have been included.

2. Virgin Himalayan rabbits from Hoechst breeding colony, HOE:HIMK(SPFWiga) strain, 9 to 10 months of age and with a mean body weight of 2646 g, were mated with fertile males. Vaginal smear were performed to detect the presence of sperm. If sperms were detected, females were mated again to ensure insemination. The day of mating was designated as day 0 of gestation. Fifteen females were assigned to each study group. Daily observations of general health and behavior were conducted and results were recorded. Food intake was observed continuously. Body weights were obtained once weekly for 3 weeks, then after a 9-day interval. Animals were given food pellets ad libitum; in addition, they were given 40-50 g of autoclaved hay daily.

   Any females aborting were sacrificed and examined for uterine status. On day 29 of gestation all females were sacrificed by intravenous injection and uterine contents were delivered by Caesarean section. (The substance used to sacrifice the animals was not reported.) Females were subjected to a gross necropsy. Maternal heart, liver, kidneys, and spleen were weighed.

3. Corpora lutea were counted and uterine contents were examined for the number of live and dead fetuses, resorptions, and placentae. Fetal body weights, placental weights, and diameter of resorption sites were measured. Fetuses were examined for external abnormalities and reared for 24 hours in an incubator kept at 32°C and 60 percent relative humidity. Fetal deaths were noted. Fetuses were then sacrificed using chloroform. The sex of fetuses was determined, and crown to rump lengths were measured.

   Approximately half of each litter (and all aborted fetuses and those found dead in utero) were fixed in alcohol, dissected, eviscerated, and macerated in aqueous KOH. The skeletons were then stained with Alizarin Red S and examined under magnification for abnormalities. The remaining fetuses were fixed in Bouin's solution, cross-sectioned, and examined under magnification according to methods described by Wilson.

B. Protocol: Materials and Methods were presented in lieu of a protocol. See Appendix A for complete Materials and Methods.

12. REPORTED RESULTS:

A. Test Material: No report of analysis of concentration or homogeneity of dosing solutions was presented. The study authors reported that solutions remained stable for 3 days based on earlier analytical trials.

B. Maternal Effects: No compound-related mortalities occurred during the study. One control female died on gestation day 5 due to a dosing (gavage) error and was replaced. One female in the high-dose group (50 mg/kg) was sacrificed because of vaginal bleeding on gestation day 22. At necropsy, it was determined that she was aborting; her uterus contained eight implantation sites, seven of which were resorptions.

No other toxic or behavioral signs of biological significance were seen, although the study authors reported a decrease in the amount of excrement throughout all the groups (controls included) during dose administration. No differences in body weights among groups were seen during the study. The study authors reported slight decreases in food consumption in the high-dose group during the first week of treatment. Food consumption values for animals receiving 2 and 10 mg/kg of HOE 033171 were similar to those of control animals.

The maternal body weight and food consumption data are summarized in Tables 1 and 2, respectively.

Table 1. Effect of HOE 033171 on Mean Maternal Body Weights (kg) in Rabbits

Dose (mg/kg)	Gestation Day				
	0	7	14	20	29
0	2.67	2.71	2.72	2.78	2.93
2	2.62	2.64	2.63	2.69	2.81
10	2.65	2.68	2.68	2.75	2.90
50	2.67	2.69	2.69	2.74	2.67

Table 2. Effect of HOE 033171 on Mean Maternal Daily Food Consumption (g)[a] in Rabbits

Dose (mg/kg)	Gestation Day			
	0-7	7-14	14-20	20-29
0	75.1	66.4	67.6	74.5
2	75.5	60.2	57.3	70.0
10	76.9	66.3	64.2	73.6
50	78.1	47.0	69.2	72.3

[a] These values were calculated from reported food consumption values (g/100 g body weight.) by using mean weights for groups given for gestation days 0, 7, 14, and 20.

Pregnancy was confirmed at sacrifice by the presence of implantation sites. The pregnancy rate was 100 percent for all dose levels. One female each in the low- (2 mg/kg) and mid-dose (10 mg/kg) groups were found to have aborted during the study. The study authors stated that the abortions probably occurred at night and went undetected.

There were no differences in mean number of corpora lutea or implantation sites among groups. No unusual findings were reported at necropsy.

C. Embryonic and Fetal Effects: The test material had no effect on fetal viability, 24-hour survival, sex ratio, or fetal body weights and lengths. Diameter of resorption sites was not reported. A slight increase in embryolethality was noted at the high-dose level due to a slight increase in the incidence of resorptions. This was not significantly different from the control ($p > .05$). Table 3 summarizes the data on fetal viability.

Table 3. Effect of HOE 033171 on Resorptions and Fetal Viability in Rabbits

Parameter	Dose Level (ppm) 0	2	10	50
Fetal survival after 24 hours (%)	98	89	97	92
Resorptions	1.13(16)[a]	0.79(13)	0.36 (5)	1.64(23)
Live fetuses	5.7 (83)[a]	5.1 (82)	6.6 (92)	5.1 (73)
Dead fetuses	0.13 (2)[a]	0.29 (5)	0.21 (3)	0.21 (3)

[a] Mean per litter (% of implantations).

No major malformations attributable to HOE 033171 were found that would indicate a teratogenic effect.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that HOE 033171 administered to Himalayan rabbits at 50 mg/kg exhibited maternal toxicity in the form of slightly reduced food consumption values during the first week of administration (days 7-14 of gestation). No effects were seen in dams dosed at 2 and 10 mg/kg with HOE 033171.

The only embryonic or fetal dose-related effects due to HOE 033171 were slight increases in resorptions for the 50 mg/kg dosed animals. All other incidences of abnormalities were comparable to those of controls and were not considered biologically significant. Based on these results, the study authors concluded that the NOEL for HOE 033171 in the rabbit is 10 mg/kg for both maternal and embryonic/fetal toxicities.

B. A quality assurance statement was signed and dated October 11, 1983.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Our assessment of the study results was that there was no maternal toxicity present at any dose level of HOE 033171 tested. Slight decreases in food consumption were seen in the high-dose group 1 week after initiation of dose administration but there were no corresponding decreases in body weight nor was the decrease in food consumption large enough to consider it a sign of toxicity. Decreases in excrement occurred in all groups and were not considered dose related. Other clinical observations and necropsy findings in dams from all groups were comparable.

There were no dose-related effects seen in any of the embryonic/fetal parameters except for a slight increase in resorption rate at the high-dose level, which was not significantly different from controls ($p > 0.05$). This suggests an increase in embryolethality at this dosage level. No compound-related teratogenic effects were noted.

B. There are differences between the study authors' and our conclusions. The study authors concluded that decreases in food consumption at the high-dose level (50 mg/kg) during the first week of dosing were biologically significant; therefore, they concluded that maternal toxicity was noted at this dose level. We could not conclude that the slight decrease in food consumption was indicative of a toxic effect. As the study authors stated, "food consumption in rabbits is difficult to measure because of spillage occurring when the rabbit digs feed out of its feeder." There was no corresponding decrease in body weight for that group during that time period to indicate a decrease in food consumption. Also, all animals were reported to be healthy throughout the gestational period. The study authors reported that in addition to pelleted feed, each rabbit was given hay (40-50 g). No indication was given as to whether the hay was included in the food consumption calculation. Based on these factors, we could not conclude that the slight decrease in food consumption seen at the high-dose level was dose related. The study authors concluded that the maternal NOEL was 10 mg/kg based on decreased food

consumption. We concluded that no maternal toxicity was seen; the maternal NOEL should be 50 mg/kg, the highest dose level tested.

C. The following problems with the study report may adversely affect the validity of the results or of the study authors' interpretation:

1. Dose levels tested were not sufficient to elicit maternal toxicity; therefore, the teratogenic potential of HOE 033171 could not be assessed.

2. We could not independently verify maternal and fetal parameters given in summary tables; no individual data were presented with the exception of number of corpora lutea, resorptions, implantations, and male and female fetuses per litter.

3. We could not verify the purity of the test material or its concentration or stability in dosing solutions; no data from chemical analyses were presented.

4. The study authors gave no indication that uterine weights were taken at necropsy. We question the omission of this parameter when other maternal organs were weighed and presented.

5. We questioned the thoroughness of cranial examinations because expected brain tissue variants, such as discoloration associated with hematomas or ventricular brain dilations, were not reported.

6. The study authors gave no indication of the strain, number, age, or breeding history of the males used for breeding; therefore, we could not determine if males used in this study were acceptable.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 6-8.

APPENDIX A

Materials and Methods

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 380 through 382 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
DYNAMAC No. 1-24-C4
January 27, 1986

DATA EVALUATION RECORD

WHIP

Dermal Teratogenicity Study in Rats

STUDY IDENTIFICATION: Becker, H., and Sachsse, K. Embryotoxicity study in the rat (dermal application). (Unpublished report No. 028765 by Research and Consulting Company A.G., Itingen, Switzerland, for Hoechst Aktiengesellschaft, Pharma Forschung Toxikologie, Frankfurt, West Germany; dated October 17, 1984.) Accession No. 256667

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-27-86

393

1. CHEMICAL: Whip; HOE 033171; ethyl-2[4(6-chloro-2-benzoxazolyloxy-)-phenoxy-]-propanoate.

2. TEST MATERIAL: HOE 033171--Substance Technical Grade, code: HOE 033171 OH 2096 0001, was received from the sponsor and stored at -21°C. A certificate of analysis, supplied by the sponsor, indicated a purity of 96.5 percent, and stability for at least 6 months when stored at -21°C.

3. STUDY/ACTION TYPE: Dermal teratogenicity study in rats.

4. STUDY IDENTIFICATION: Becker, H., and Sachsse, K. Embryotoxicity study in the rat (dermal application). (Unpublished report No. 028765 by Research and Consulting Company A.G., Itingen, Switzerland, for Hoechst Aktiengesellschaft, Pharma Forschung Toxikologie, Frankfurt, West Germany; dated October 17, 1984.) Accession No. 25666.

5. REVIEWED BY:

Robin B. Phipps, B.S.
Principal Reviewer
Dynamac Corporation

Signature: Robin B Phipps
Date: September 30, 1985

Guillermo Millicovsky, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: G Millicovsky
Date: 9-30-85

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Teratogenicity and Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: I Cecil Felkner
Date: 1-27-86

W. T. Edwards
EPA Reviewer

Signature: W T Edwards
Date: 2-13-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-17-86

7. CONCLUSIONS:

A. Because no biologically significant maternal and/or fetal effects were noted at any dose level used in this study, 1000 mg/kg/day, the highest dose level tested, is assessed as the tentative NOEL for dermal application of HOE 033171 in rats. The LOELs for maternal, embryo/fetal, and teratogenic effects could not be determined.

B. Core Classification: The study report did not provide sufficient information for our assessment of the teratogenic potential of HOE 033171 when administered dermally to pregnant rats. Therefore, this study is classified Core Supplemental.

8. RECOMMENDATIONS:

In the event that additional work is conducted with HOE 033171, the following steps are recommended:

1. The highest dose level selected for a teratogenicity study should elicit some systemic maternal toxicity.

2. If the test material is applied dermally, the study authors should submit data demonstrating that HOE 033171 is incorporated into the maternal system (e.g., presence of the test material in maternal serum) and/or that the test material produces systemic toxicity (e.g., changes in maternal liver weight).

3. The testing laboratory should analyze the dosing mixtures for stability and concentration of the test material.

4. The incidences of maternal clinical signs and dermal and gross pathology findings should be tabulated and presented in the study report.

9. BACKGROUND:

The Research and Consulting Company conducted a preliminary study (Project No. 928912, reported on July 31, 1984) in which a dose level of 1000 mg/kg/day elicited no adverse effects on the parameters investigated. No other details or results from the preliminary study were included in the teratogenicity study report.

Item 10--see footnote 1.

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[1] Only items applicable to this DER have been included.

11. MATERIALS AND METHODS (PROTOCOL):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Technical grade HOE 033171 (Code: HOE 033171 OH 2096 0001) was stored at -21°C. The sponsor's certificate of analysis indicated a purity of 96.5 percent and stability for at least 6 months when stored at -21°C. Sesame oil served as the vehicle and control material. The test material/sesame oil mixtures were reported to be stable under conditions of use. Test material/vehicle mixtures were prepared and applied daily on days 6-15 of gestation at levels of 0 (vehicle only), 100, 300, or 1000 mg/kg/day. A dose volume of 1.25 ml/kg of body weight was evenly applied to an area of shaved skin on the back of each rat and covered with an occlusive dressing. After a 6-hour exposure, the dressing was removed and the skin was flushed with lukewarm tapwater.

2. Test Animals: Wistar rats (KFM-Han, outbred, specific pathogen free) were received at the test facility and acclimated to laboratory conditions for at least 7 days prior to mating. These animals were 11-12 weeks of age when mated, and body weights ranged from 183-224 g after mating. Twenty-five mated females were assigned to each of the four treatment groups using a computer-generated random algorithm.

3. Parameters Evaluated: Dermal irritation scores for erythema and edema (Draize Scale) were recorded prior to and following each daily application period, and for 2 days following the last dose. Maternal clinical observations and body weights were recorded daily during gestation. Food consumption was measured on gestation days 6, 11, 16, and 21. On day 21 of gestation, the dams were sacrificed and fetuses were removed by cesarean section. Maternal gross observations and gravid uterine weights were recorded. Corpora lutea were counted and the uteri were examined for number and placement of implantations, resorptions, and live or dead fetuses. Uteri without grossly visible implants were immersed in ammonium sulfide to confirm pregnancy status. Fetuses were examined externally, sexed, and individually weighed. One-third of the fetuses were examined viscerally by Wilson's free-hand sectioning technique, and the remaining two-thirds were examined for skeletal abnormalities after alizarin staining by Dawson's technique.

Maternal data were analyzed by one-way analysis of variance or Fisher's exact test. Reproduction data (total number of implantations, number of fetuses, number of resorptions) were analyzed by nonparametric methods.

B. Protocol:

A study protocol was not presented in the final report.

12. REPORTED RESULTS:

No analytical data on the stability, homogeneity, or concentration of the test material/vehicle mixtures were presented in the study report.

The authors reported no compound-related effects on maternal clinical signs, dermal irritation, body weight gain (Table 1), food consumption (Table 2), or reproductive parameters (Table 3). Vaginal bleeding was observed on gestation day 13 in two Group 4 (1000 mg/kg) females and on day 14 in two Group 2 (100 mg/kg) females; the authors attributed the discharge to the method of occlusive dressing. Erythema was noted for 4, 4, 2, and 2 females dosed at 0, 100, 300, or 1000 mg/kg, respectively. The authors considered these findings a normal result of dermal application of the test material, and not compound related. The study authors reported significantly reduced food consumption on gestation days 6-16 for Groups 3 and 4 compared to control. However, because the reduction was greater in Group 3 (300 mg/kg) than in Group 4 (1000 mg/kg), the authors did not consider the differences compound related. Maternal gross necropsy findings were not reported or discussed.

No compound-related differences were reported for reproductive or fetal parameters, including results of the external, visceral, and skeletal examinations.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that dermal application of HOE 033171-Technical to Wistar rats on days 6-15 of gestation "did not reveal any embryotoxic or teratogenic potential up to the highest dose level of 1000 mg/kg body weight/day." The authors determined the maternal and fetal NOELs to be greater than 1000 mg/kg/day.

B. A signed statement from the test facility's Quality Assurance Unit was presented in the study report, and dated October 30, 1984.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Maternal Effects: No maternal deaths occurred during the study. Bloody vaginal discharge was observed in two Group 4 (1000 mg/kg) females on day 13 of gestation, and in two Group 2 (100 mg/kg) females on day 14 of gestation. These four females carried litters until sacrifice, with no evidence of abortion. Dermal

TABLE 1 [illegible] HOE 033171 on Mean Maternal Body Weight Gain in Rats

Group	Body Weight Gain (g ± S.D.) During Gestation Days			
	0-6[a]	6-15[a]	15-21[a]	0-21[a]
1 (0 mg/kg/day)	21.[illegible]	33.6±6.69	62.1± 8.64	117.2±14.83
2 (100 mg/kg/day)	20.[illegible]	26.9±7.52*	58.3±12.56	106.5±21.06
3 (300 mg/kg/day)	21.[illegible]	25.6±7.56*	60.3±11.64	105.9±18.83
4 (1000 mg/kg/day)	21.[illegible]	24.2±8.46*	64.2±11.25	109.3±17.10

[a] Analyzed by reviewers, using ANOVA followed by Duncan's test for multiple comparisions.

* Significantly different from control value ($p < 0.05$).

TABLE 2. Effect of HOE 033171 on Mean Maternal Food Consumption in Rats

Group	Food Consumption (g/day ± S.D.) During Gestation Days		
	0-6	6-16[a]	16-21
1 (0 mg/kg/day)	22.1±2.1	46.8±3.30	26.3±1.8
2 (100 mg/kg/day)	21.9±1.8	44.7±4.31	25.4±1.6
3 (300 mg/kg/day)	24.8±1.7	42.9±2.75*	26.4±2.4
4 (1000 mg/kg/day)	26.3±1.8	44.0±4.17*	27.1±1.7

[a] Analyzed by reviewers, using ANOVA followed by Duncan's test for multiple comparisions.

* Significantly different from control value ($p < 0.05$).

TABLE 3. Summary of Reproduction and Fetal Data for Rats Dosed with HOE 033171

Parameter	Dosage Level (mg/kg/day) 0	100	300	1000
No. of mated females	25	25	25	25
No. of pregnant females	25	23	20	20
Pregnancy rate (%)	100	92	80	80
Mean (per dam):				
No. of corpora lutea	13.9± 1.9	12.5± 2.5	13.4± 1.7	13.4± 1.2
No. of implantation	13.3± 1.8	11.6± 3.0	12.4± 2.6	12.2± 2.6
Preimplantation loss (%)[a]	4.1± 6.7	8.7±15.8	8.2±13.8	9.1±18.4
No. of resorptions	1.0± 1.3	0.8± 0.9	0.8± 0.8	0.8± 0.8
Postimplantation loss (%)[b]	7.6±10.4	7.0± 7.7	6.0± 6.6	7.5± 8.8
No. of live fetuses	12.3± 2.2	10.8± 3.0	11.7± 2.6	11.4± 2.7
Fetal weight	4.6± 0.4	4.6± 0.5	4.4± 0.5	4.6± 0.4

[a] $\frac{\text{No. corpora lutea} - \text{no. of implantations}}{\text{no. of corpora lutea}} \times 100$

[b] $\frac{\text{no. of implants} - \text{no. of live fetuses}}{\text{no of implants}} \times 100$

erythema was noted for 4 controls, 4 low-dose, 2 mid-dose, and 2 high-dose females. We consider the dermal irritation incidental and not indicative of compound effect. Analysis of body weight data by our reviewers showed significantly decreased body weight gains ($p<0.05$) for all dosage groups during the dosing period (days 6-15). Total body weight gains for days 0-21 of gestation were also reduced for all dosage groups, although differences form control were not statistically or biologically significant. Slight but statistically significant reductions in food consumption during the dosing period were reported for mid- and high-dose females. The reductions in body weight gain and food consumption during the period of compound administration may have been compound-related effects; however, the differences between control and dosage groups were small and did not follow a dose-related pattern. In the absence of other adverse maternal effects, the reductions in body weight gain and food consumption were not considered sufficient evidence of overt maternal toxicity. Reproductive parameters, including mean number of corpora lutea, were comparable for all groups.

B. Embryonic/Fetal Effects: The number of implantations and incidence of post-implantation loss appeared to be within normal limits and were generally comparable between the control and dosage groups. Although the incidence of preimplantation loss appeared to be compound related, differences from control were not statistically significant at any dose level due to large variations within the groups. Mean litter size and fetal weight were comparable between the control and compound-treated groups. The only anatomical variations noted during external and visceral fetal examinations were: "agenesia of the tail" in a Group 2 fetus, abnormally shaped tail in a Group 3 fetus, and dilated renal pelves in a Group 3 fetus. "Absent sternebrae," primarily No. 5 and No. 6, were observed in all groups, including control, with no apparent relation to compound administration. Wavy ribs were seen in one control fetus. No other skeletal "malformations and/or anomalies" were reported. No group differences were apparent for degree of ossification in the extremities, calcaneum, sternebrae, or vertebrae.

C. The following are differences between the study authors' and reviewers' conclusions:

1. The study authors attributed the vaginal bleeding noted in 2 low-dose and 2 high-dose females to the method of occlusive dressing. Although we cannot establish a compound-related effect based on these data, we do not consider the discharge to be a result of the occlusive dressing since vaginal bleeding was not observed in control animals, which were similarly wrapped.

2. The study authors stated that no adverse compound-related differences in maternal body weight gains or food consumption were established. Furthermore, they did not consider the significantly reduced food consumption for the mid- and high-dose females to be compound related. In contrast, we determined that the reductions in body weight gains during the period of compound administration were statistically significant for all dosage groups compared to controls. We assess that the reduced body weight gains and reduced food consumption may have been compound related, although the differences from control were not great enough to be considered biologically significant.

3. The authors determined the maternal and fetal NOELs for dermal application of HOE 033171 to be greater than 1000 mg/kg/day. We agree with their assessment of the NOEL for maternal toxicity. However, because overt maternal toxicity was not demonstrated at the highest dose level tested, we could not assess the fetotoxic or teratogenic potential of the test material.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 9-16.

APPENDIX A

Materials and Methods
(CBI pp. 9-16)

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 393 through 400 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.

004963

EPA: 68-02-4225
TASK: 024-DN
November 5, 1985

DATA EVALUATION RECORD

WHIP (HOE 033171)

Teratogenicity Study in Monkeys

STUDY IDENTIFICATION: Osterburg, I. Oral embryotoxicity study in the Cynomolgus monkey. (Unpublished study No. 245-169/6 by Hazleton Laboratories, West Germany, for Hoechst Aktiengesellschaft, Frankfurt, West Germany; dated November 12, 1984.) Accession No. 256667.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-5-85

004963

1. CHEMICAL: Whip; HOE 033171.

2. TEST MATERIAL: Technical grade HOE 033171 consisted of 96.2 percent active ingredient.

3. STUDY/ACTION TYPE: Teratogenicity study in monkeys.

4. STUDY IDENTIFICATION: Osterburg, I. Oral embryotoxicity study in the Cynomolgus monkey. (Unpublished study No. 245-169/6 by Hazleton Laboratories, West Germany, for Hoechst Aktiengesellschaft, Frankfurt, West Germany; dated November 12, 1984.) Accession No. 256667.

5. REVIEWED BY:

Guillermo Millicovsky, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: G Millicovsky
Date: 11-5-85

Robin B. Phipps, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Robin B. Phipps
Date: November 5, 1985

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Teratogenicity and Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 11-5-85

W. T. Edwards
EPA Reviewer

Signature: W. Thomas Edwards
Date: 2-6-86

Clint Skinner, Ph.D.
EPA Section Head

Signature: Clint Skinner
Date: 2-11-86

7. CONCLUSIONS:

A. The maternal and embryo/fetal NOELs could not be determined due to the presence of maternal mortalities at 50 mg/kg/day, clinical signs at both 10 and 50 mg/kg/day, and excessive incidence of aborted pregnancies at both of the above levels. Therefore, the LOELs for maternal toxicity and embryo/fetotoxicity were assessed at 10 mg/kg/day, the lowest dose tested.

The teratogenic potential of the test material could not be assessed due to the major deficiencies in study methodology (see section 14C). These deficiencies included:

1. No concurrent controls were used.

2. The deficiencies in the historical control data presented limited their usefulness for our review.

3. Maternal toxicity was elicited even at the lowest dosage used (10 mg/kg/day).

4. As indicated above, the highest dosage used (50 mg/kg/day) produced an excessive incidence of maternal mortality and abortion.

5. Only one dosage group (10 mg/kg/day) had a sufficient number of fetuses.

6. The description of the methods used for visceral and skeletal examinations of fetuses were not sufficient for us to evaluate their acceptability.

B. Due to the study deficiencies discussed in this review, this study was considered supplementary data.

8. RECOMMENDATIONS:

We suggest that if additional studies are conducted to assess the teratogenic potential of HOE 033171 in monkeys, three properly selected dosage levels be used and that a vehicle control group of pregnant animals be dosed concurrently.

We also recommend that analytical results of tests performed to determine the concentration and stability of dosage formulations be submitted in future studies. These results will allow the reviewers to confirm if animals were properly dosed.

Items 9 and 10 - see footnote 1.

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[1] Only items appropriate to this DER have been included.

II. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: The test material was described as technical grade HOE 033171 (code: HOE 033171 OH ZC96 0002) consisting of 96.2 percent active ingredient. Dosage suspensions were prepared every 3 to 5 days using sesame oil as the vehicle. The dosage levels used in this study were 10 and 50 mg/kg/day. Neither a third dosage level nor a control group were used in this study.

Dosage suspensions were administered once daily by intragastric intubation from gestation days (GD) 20 through 50. Dosages were adjusted for maternal body weights recorded on GD 20, 27, 34, 41, and 48; dosage volumes were adjusted to 2 mL/kg or body weight.

2. Test Animal and Test System: Cynomolgus monkeys (Macaca fascicularis) were imported from Hazleton Research Primates, Reston, VA. Sexually mature females weighing between 2.4 and 4.7 kg, having previously delivered one healthy fetus through Caesarean section, were quarantined for 2 weeks. These animals were determined to be TB-negative, acclimatized to laboratory conditions for at least 3 weeks, and mated on a 1:1 basis with untreated, fertile males. Copulation was confirmed by the presence of sperm in vaginal smears, and the day of copulation was designated GD 0. Pregnancy was confirmed by injecting serum obtained from mated female monkeys on GD 18 and 19 into the subcutaneous compartment of the dorsal skin of mice. Increases in size and vascularization of murine uteri were interpreted as indicators of pregnancy in the monkeys. A total of 23 and 11 females were assigned to the 10 and 50 mg/kg/day groups, respectively. Animals assessed as pregnant were subjected to rectal uterine palpation on GD 30, 44, 58, 72, and 86. On GD 99 to 101 pregnant females were anesthetized, and fetuses were delivered by Caesarean section.

3. Observations and Measurements: Animals were observed at least once daily to determine their health status and possible toxicological effects. Food consumption was observed (but not measured) daily, and body weights were recorded on GD 20, 27, 34, 41, 48, 55, 62, 69, 76, 83, 90, 97, and prior to Caesarean section. Blood samples were obtained periodically during gestation to assess effects of the test article on selected maternal clinical chemistry parameters. Pregnant animals were anesthetized on approximately GD 100, sacrificed, and examined for gross pathological changes. Fetuses were delivered by Caesarean section, weighed, measured, sexed, examined grossly for external abnormalities, and photographed. Full necropsies were performed on all fetuses; livers, spleens

kidneys, adrenals, lungs, hearts, thymuses, eyes, brains, testes, ovaries, and uteri were removed, weighed, fixed in formalin, and retained. Diaphragms, stomachs, and small and large intestines were also fixed and retained. Fetal carcasses were stained and examined for skeletal abnormalities.

12. REPORTED RESULTS:

Test Material: The study report does not contain information (methods or results) regarding determinations of concentrations or stability of the test material in the sesame oil vehicle. However, the study author stated that the sponsor guaranteed the homogeneity and stability of the test material.

Maternal Effects: Five mortalities were reported during the course of this study; all of them occurred among animals dosed with 50 mg/kg/day. A total of five and three animals aborted in the 10 and 50 mg/kg/day groups, respectively. Reductions in food intake and/or diarrhea were reported for all animals in this study, mainly during the treatment period. In addition, the study author reported reductions in the mean serum levels of cholesterol, triglycerides, and total lipids between GD 20 and 83 for animals with live fetuses in the 10 mg/kg/day group.

Fetal Effects: The number of live fetuses obtained during scheduled laparotomies were 16 and 3 for the 10 and 50 mg/kg/day groups, respectively. The study author reported slight reductions in the mean body weights of fetuses from the 10 mg/kg/day group when compared with historical controls; however, the report stated that the decrease was associated with one extremely small fetus and three others that were moderately small.

Results from fetal examinations consisted mostly of reported cases of "uneven rib thickness" and "bent tail." These findings were considered as incidental variations which had been previously noted in historical control fetuses.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author concluded that a dosage of 50 mg/kg/day was associated with extreme maternal toxicity including lethality; 10 mg/kg/day was less toxic to pregnant animals but may have induced the abortions noted in the study. It was further concluded that the results of this study gave no indication of embryotoxicity or teratogenic potential for the test material.

B. A quality assurance statement was signed and dated November 12, 1984.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Concurrent control animals were not used in this study. Instead, the study author presented data from control animals from previous studies; however, the deficiencies in these historical control data (see section 14C of this review) limited their usefulness for the purpose of our review. The absence of acceptable control data and the unavailability of other critical data in this study precluded our definitive assessment of the teratogenic potential of the test material in monkeys. Therefore, our evaluation of test material-related effects is limited to the following comments:

1. Maternal Effects: The test material was associated with a 45 percent incidence of maternal mortality among the 11 animals in the 50 mg/kg/day group; however, no mortalities were noted in the 10 mg/kg/day group. The absence of concurrent or historical control data precluded our evaluation of reported data for maternal clinical signs and clinical chemistry. The incidence of abortions was 24 and 27 percent for the 10 and 50 mg/kg/day groups, respectively. The percentage of mated animals with living fetuses was 76 and 27 percent for the 10 and 50 mg/kg/ day groups, respectively. Since each pregnant animal had a maximum of one live fetus, a total of 16 and 3 live fetuses were recovered for the 50 and 10 mg/kg/day groups, respectively.

2. Embryonic/Fetal Effects: We assess that both dosage levels were associated with embryo/fetal lethalities as demonstrated by the excessive incidence of aborted pregnancies. Fetal body weights for the 10 mg/kg/day group were reportedly slightly reduced when compared with historical controls. Since fetal body weights were not reduced for the 50 mg/ kg/day group, we concluded that no compound-related effects on fetal body weights were elicited at 10 mg/kg/day. Further, the absence of concurrent controls precluded our definitive evaluation of these data. No clear pattern of teratogenesis was evident from the limited data presented in the study report.

B. The following are differences between the study author's interpretations of the study results and the reviewers' interpretations.

1. The study author reported that the dosage of 10 mg/kg/ day may induce abortions (5/21 animals; 24 percent). We support that conclusion; however, we assess that the 50 mg/ kg/day dosage was also associated with the three abortions among the 11 mated animals (27 percent) in that group. We further assess that an even higher incidence of abortions may have resulted if more pregnant animals in the high-dose group had survived.

2. The study author concluded that the results of this study gave no indication of embryotoxicity associated with the test material. Based on the occurrences of abortions we do not rule out the possibility that both dosages were not only embryo/fetotoxic, but also embryo/fetolethal.

3. A definitive assessment of the teratogenic potential of the test material was precluded due to the severe deficiencies of this study (see section 14C).

C. The following deficiencies in the design and conduct of this study have negatively impacted the scientific validity of the reported results.

1. Since this study had no concurrent controls, historical control data were included in an appendix of the study report. However, several deficiencies were noted in these data, including:

   a. The absence of maternal clinical signs during gestation
   b. The absence of maternal body weights during gestation
   c. The absence of individual identification numbers for male breeders, mated females, and fetuses.

   We also noted inconsistencies in the historical data for fetal examinations. For example, the incidence of fetuses with rib variations was reportedly 1/9 (11 percent), 2/10 (20 percent), 3/7 (43 percent), and 8/10 (80 percent) for the four control groups presented. The progressive increase in the incidence of this finding may have resulted from the ability of the technical staff to diagnose this finding in the latter studies, rather than representing actual biological increase in the phenotypic expression of this costal variation. However, in the absence of parental identification we could not determine the genetic relationships (if any) of fetuses in the four historical control studies. These deficiencies precluded our assessment of potential test material-related effects on pregnant animals and fetuses, except for the very limited assessment presented in section 14A.

2. Three dosage levels should have been implemented in this teratogenicity study, instead of only two.

3. The dosage level of 50 mg/kg/day used in this study was unacceptably high since it was associated with 45 percent maternal mortality, 27 percent aborted pregnancies, and a resulting total of only 3 live fetuses recovered for examination. In addition, the absence of a dosage level eliciting no maternal toxicity is a major deficiency of this study.

3. No definitive assessment of the teratogenic potential of the test material was possible at the dosage of 50 mg/kg/day since data from only three fetuses were available and since a concurrent group of vehicle controls was absent.

4. The limited description of the methods used for visceral and skeletal examinations of fetuses in this study did not allow us to determine the acceptability of these methods, thus precluding our evaluation of the accuracy of the resulting findings. Therefore, we could not make a definitive assessment of the data on fetal findings presented for the 16 fetuses in the 10 mg/kg/day group.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. 4-9.

APPENDIX A

Materials and Methods
CBI pp. 4-9

Fenoxaprop-ethyl Toxicology Reviews

Page _____ is not included. The page contains detailed test methods/results submitted by the pesticide registrant.

Pages 410 through 415 are not included. The pages contain detailed methods/results submitted by the pesticide registrant.