



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

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MAR 25 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fenoxycarb - Reevaluation of Toxicology Data Endpoints
as a Result of the RfD/Peer Review Meeting held on
2/24/94

Tox. Chem. No.: 652C
PC No.: 125301
DP No.: NA
Submission No.: NA

FROM: Marion P. Copley, D.V.M., Section Head
Review Section IV, Toxicology Branch I
Health Evaluation Division (7509C)

Marion Copley
3/24/94

TO: Marion Johnson/Richard Mountford, PM #10
Herbicide-Fungicide Branch
Registration Division (7505C)
and

George Ghali
Science Analysis Branch
Health Evaluation Division (7509C)

THRU: Karl Baetcke, Ph.D., Chief
Toxicology Branch I
Health Evaluation Division (H7509C)

Karl Baetcke
3/25/94

I. CONCLUSIONS:

The HED RfD/Peer Review Committee met on 2/24/94 to set a division RfD and to evaluate the adequacy of the CORT studies. At the recommendation of the committee the NOEL/LELs of several studies are being modified as noted in the discussion section. This memorandum will serve as the supplemental DERS for all NOEL/LEL changes except where noted.

The Committee also recommended that Fenoxycarb be presented to the HED Cancer Peer Review Committee for evaluation of the adequacy of dose selection in the cancer study in female mice as well as the possible cancer issue in male mice.

Doses in the oral subchronic rat and mouse studies are in terms of dose to the animal (mg/kg/day).



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II. REQUESTED ACTION:

The RfD Committee recommended several modifications in the CORT studies for Fenoxycarb.

III. DISCUSSION/SUPPLEMENTAL DERs/EXECUTIVE SUMMARIES:

82-1 Oral subchronic mouse and rat studies. The question was raised as to whether the dose values given in the DER were in terms of mg/kg diet/day (concentration) or in terms of mg/kg body weight/day (dose). The study reports indicate that the values are in terms of dose (mg/kg/day). The concentrations were adjusted periodically in order to maintain a constant dose to the animals.

83-1b Chronic Feeding Study - Dog, MRID 42355601 (original DER is in HED Doc # 010271)

The HED RfD/Peer Review Committee (RfDC) determined that the NOEL of 25 mg/kg/day and LEL of 80 mg/kg/day in the original DER could not be supported by the data. The changes observed at 80 mg/kg/day (altered absolute adrenal weight and decreased inorganic phosphorous) were not considered to be of biologic significance since they were not corroborated with other toxicologic endpoints such as histopathology or relative adrenal weight decrease. However the decreased absolute adrenal weight in males at 250 mg/kg/day may be treatment related since it was seen in a six month study at 500 mg/kg/day (but not at 150 mg/kg/day) in females. The conclusions stated in this reevaluation of the study supersede those of the original DER.

EXECUTIVE SUMMARY - In a chronic oral study, 4 beagle dogs per dose per sex, received 0, 25, 80 or 260 mg fenoxycarb/kg/day by capsule (technical a.i. 96.6%, white powder) for 52 weeks.

Systemic toxicity was observed at 260 mg/kg/day and included decreased body weight gain in males (87 % less than controls) and females (94 % less than controls), decreased feed consumption in males, decreased absolute brain weight in males (11 % less than controls). The systemic LEL of 260 mg/kg/day is based on decreased body weight gain in males and females along with decreased food consumption and decreased absolute brain weight in males. The NOEL is 80 mg/kg/day.

This study is classified as Core-Guideline Data and satisfies the guideline requirement for a chronic oral study in dogs (83-1b).

83-3a Developmental Study - Rat, MRID #00131346 (Original DER is

in HED Doc # 004178).

The HED RfD/Peer Review Committee (RfDC) determined that the NOEL of 25 mg/kg/day and LEL of 80 mg/kg/day in the original DER could not be supported by the data. The changes observed at 80 mg/kg/day (altered absolute adrenal weight and decreased inorganic phosphorous) were not considered to be of biologic significance since they were not corroborated with other toxicologic endpoints such as histopathology or relative adrenal weight decrease. The conclusions stated in this reevaluation of the study supersede those of the original DER.

EXECUTIVE SUMMARY - In a developmental (teratology) study, 20 Fu-Albino rats per dose group received 0, 50, 150 or 500 mg fenoxycarb/kg/day by gavage from gestation days 7 through 16, inclusive. Each female was mated with one randomly selected male.

Maternal toxicity was not observed at any dose. The LEL for Maternal Toxicity is therefore greater than 500 mg/kg/day and the NOEL for maternal toxicity equal to or greater than 500 mg/kg/day.

Developmental toxicity was not observed at any dose. The LEL for Developmental Toxicity is therefore greater than 500 mg/kg/day and the NOEL for developmental toxicity equal to or greater than 500 mg/kg/day.

The study is classified as Core-Minimum Data even though there is no overt maternal toxicity tested (due to the high doses selected) and satisfies the requirement (Guideline 83-3a) for a developmental toxicity (teratology) study in rats.

83-3b Developmental Study - Rabbit, MRID #00153125 (supplemental DER attached)

This supplemental DER is intended to validate and, where necessary, supplement the original review of this study. The conclusions stated in this reevaluation of the study supersede those of the original DER.

EXECUTIVE SUMMARY - In a developmental (teratology) study, 20 Swiss hare rabbits per dose group received 0, 30, 100 or 300 mg fenoxycarb/kg/day by gavage (technical a.i. 98%, white powder) from gestation days 7 through 19, inclusive (Study A). A second study (B) was initiated with 35 Swiss hare rabbits per dose group which received 0 or 200 mg fenoxycarb/kg/day by gavage as above (Study B). Each female was mated sequentially with two randomly selected males from

a breeding stock of the same strain, then randomly assigned to dosing groups.

Maternal toxicity was observed at 200 and 300 mg/kg/day as reduced body weight gain during treatment (24% and 20% less than controls, respectively; not statistically significant). Weight gain showed a rebound at 300 mg/kg/day during the rest of gestation. **The LEL for Maternal Toxicity is therefore 200 mg/kg/day based on decreased maternal body weight gain during treatment. The NOEL for maternal toxicity is 100 mg/kg/day.**

Developmental toxicity was observed at the high dose as slightly increased incidence of spina bifida of the sacral region (3 fetuses in 3/20 litters vs. 0 in either control group, total 53 litters) and possibly increased incidence of hypoplastic tail (4 fetuses in 3/20 litters vs 1 per control group, or 2/53 litters). The incidence at 300 mg/kg/day was stated to be outside historical control range but historical control data was not provided in the study report. **The LEL for Developmental Toxicity is therefore 300 mg/kg/day based on slightly increased incidence of fetal malformations (spina bifida and possibly hypoplastic tails). The NOEL for developmental toxicity is 200 mg/kg.**

The study is classified as **Core-Minimum Data** and satisfies the requirement (Guideline 83-3b) for a developmental toxicity (teratology) study in rabbits.

83-4b Reproduction Study - Rat, MRID 40376903, 42343811, 42343812 (original DER is in HED Doc # 008101, 010721) (supplement 2)

The HED RfD/Peer Review Committee (RfDC) determined that the Reproductive DNOEL of 40 ppm and LEL of 200 ppm in the original and supplement # 1 DER could not be supported by the data. The changes in pup weight observed on day 21 at 200 or 600 ppm were not considered to be of biologic significance since they were of low magnitude and not consistent over time and litters. The delayed pinna unfolding and eye opening were also not attributed to treatment. The conclusions stated in this reevaluation of the study supersede those of the original DER.

EXECUTIVE SUMMARY: In a two generation reproduction study, Fenoxycarb was administered in the diet to male and female (30 per sex for the f₁ and 25 for to f₂ generations) Sprague-Dawley rats, at dose levels of 0, 200, 600 or 1800 ppm (approximately 0, 16, 47 and 140 mg/kg/day) for two generations.

Maternal toxicity was observed at 600 and 1800 ppm as liver

effects, including increased absolute and relative organ weight. At 1800 ppm there was also increased incidences of slight focal necrosis and hypertrophy (0 % controls, 43-96 % high dose) however, low and mid dose livers were not examined histologically. The systemic LEL and NOEL could not be determined since livers were not evaluated at all doses.

Reproductive/Systemic toxicity was observed at 1800 ppm as a decrease in pup weight (decrement ranging from 10-21 % depending on generation/litter). The reproductive/Systemic LEL is 1800 ppm based on decreased pup weight at day 21. The NOEL is 500.

This study is classified as Core-Minimum Data and satisfies the guideline requirement for a reproduction study (83-4) in rats.

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Developmental Study (83-3)

EPA Reviewer: Linnea J. Hansen, Ph.D.

Review Section IV, Toxicology Branch I (7509C)

EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 1-27-94

Marion P. Copley, Date 2/17/94

SUPPLEMENTAL DATA EVALUATION RECORD
(Original DER Doc. #4319)

STUDY TYPE: Developmental Study - Rabbit (83-3b)

TOX. CHEM. NO.: 652C

P.C. CODE: 125301

ACCESSION NO.: 073304 / MRID# 00153125

TEST MATERIAL: Phenoxycarb

SYNONYMS: Ethyl[2-p(p-phenoxyphenoxy) ethyl] carbamate; Ro 13-5223/000; Logic

STUDY NUMBER: B-104 700

SPONSOR: Maag Agrochemicals, Research and Development, HLR Sciences, Vero Beach, CA

TESTING FACILITY: F. Hoffmann-La Roche and Co. Ltd., CH-Basle, Switzerland

TITLE OF REPORT: Embryotoxicity Study in Rabbits With Oral Administration of Ro 13-5223/000

AUTHORS: Dr. H. Hummler and B. McKinney

REPORT ISSUED: February 13, 1984

EXECUTIVE SUMMARY - In a developmental (teratology) study, 20 Swiss hare rabbits per dose group received 0, 30, 100 or 300 mg fenoxycarb/kg/day by gavage (technical a.i. 98%, white powder) from gestation days 7 through 19, inclusive (Study A). A second study (B) was initiated with 35 Swiss hare rabbits per dose group which received 0 or 200 mg fenoxycarb/kg/day by gavage as above (Study B). Each female was mated sequentially with two randomly selected males from a breeding stock of the same strain, then randomly assigned to dosing groups.

Maternal toxicity was observed at 200 and 300 mg/kg/day as reduced body weight gain during treatment (24% and 20% less than controls, respectively; not statistically significant).

Weight gain showed a rebound at 300 mg/kg/day during the rest of gestation. **The LOEL for Maternal Toxicity is therefore 200 mg/kg/day based on decreased maternal body weight gain during treatment. The NOEL for maternal toxicity is 100 mg/kg/day.**

Developmental toxicity was observed at the high dose as slightly increased incidence of spina bifida of the sacral region (3 fetuses in 3/20 litters vs. 0 in either control group, total 53 litters) and possibly increased incidence of hypoplastic tail (4 fetuses in 3/20 litters vs 1 per control group, or 2/53 litters). The incidence at 300 mg/kg/day was stated to be outside historical control range but historical control data was not provided in the study report. **The LOEL for Developmental Toxicity is therefore 300 mg/kg/day based on slightly increased incidence of fetal malformations (spina bifida and possibly hypoplastic tails). The NOEL for developmental toxicity is 200 mg/kg.**

The study is classified as Core-Minimum Data (Acceptable) and satisfies the requirement (Guideline 83-3b) for a developmental toxicity (teratology) study in rabbits.

1. VALIDATION OF ORIGINAL DER: This supplemental DER is intended to validate and, where necessary, supplement the original review of this study. The conclusions stated in this reevaluation of the study supersede those of the original DER (attached, Appendix 1).
2. MATERIALS AND METHODS: A copy of the materials and methods section from the study report is included in Appendix 2 for reference since some details were not included in the study report. The purity of the test compound was 98% a.i. (information not contained in this study report but was obtained from the 6-month dog study in same HED document). The vehicle used was also not specified (called "standard solvent vehicle") in this report but was described in the rat developmental toxicity study (Accession no. 071780; reviewed in HED Doc. no. 4178) as 4% carboxymethyl-cellulose, 0.9% sodium chloride, 0.5% benzyl alcohol and 0.4% Tween 80 in distilled water.

The range-finding study was discussed in the study report and the original DER; however, details of the study results such as maternal body weight gain and number of pregnant females, litters and fetuses were not given in the study report.

3. COMPLIANCE: The study was conducted prior to initiation of EPA Good Laboratory Practice and there was no Quality Assurance Statement, but a Good Laboratory Practices Statement stating that it was conducted under FDA GLP was present.
4. RESULTS: Data tables from the study report showing maternal body weight gain, cesarean parameters and developmental effects are appended to this DER (Appendix 3) to support the conclusions drawn from this study.

Maternal toxicity: Maternal body weight gain data is shown in Table 1, Part 1, A and B

of Appendix 3. TB-I agreed with the study authors and the original DER that a maternal NOEL of 100 mg/kg/day and a LOEL of 200 mg/kg/day were observed in this study, based on decreased body weight gain at 200 and 300 mg/kg. Although the decreased mean body weight gain at these doses was not statistically significant, TB-I considers this a treatment-related effect since the decrease at 200 and 300 mg/kg/day was 24% and 20% lower than controls, respectively and was consistent with the decrease reported at 300 mg/kg/day in the range-finding study (magnitude of decrease not indicated in the study report).

There were no apparent clinical signs of toxicity observed in this study. Alopecia, excitement or inactivity following treatment were observed sporadically.

Developmental Toxicity: Cesarean parameter data is shown in Table 1, Parts 1 and 2, Study A and B in Appendix 3. TB-I agreed with the study authors and the DER that there were no treatment-related effects observed on cesarean parameters. No increases in fetal resorption or decreased fetal viability were observed.

Summaries of fetal malformations are shown in Table 3, Part 1, Study A and B and below in Table A:

TABLE A: Malformations

Observations	Control A	Control B	30 mg/kg/day	100 mg/kg/day	200 mg/kg/day	300 mg/kg/day
#Pups(litters) examined	122 (18)	261 (35)	101 (20)	109 (17)	234 (33)	126 (20)
#Pups(litters) affected:						
Spina bifida	0	0	0	1	0	3 (3)*
Hypoplastic tail	1	1	1	0	0	4 (3)
Missing tail	0	1	1	2 (2)	0	0
L. eyelid open	0	1	0	1	0	0
Bil. eyelids open	0	0	0	0	0	1
Ectopy of organs	0	2 (2)	0	0	0	0
Diastasis, rect. abdom. mus.	0	0	0	0	1	1
Anasarca	0	0	0	0	1	0
Omphalocele	0	1	0	0	0	1

(*) fetal [litter] incidence

The study authors concluded that there were no treatment-related fetal variations or

malformations, and the original DER agreed with this conclusion. However, at this time TB-I considered the slightly increased incidence of spina bifida, and possibly of hypoplastic tail, observed at 300 mg/kg/day to be treatment-related. The study report stated that at 100 mg/kg/day incidences of these defects were comparable to controls but were slightly higher at 300 mg/kg/day. The increases at high doses were not considered treatment-related because no abnormalities were seen at 200 mg/kg/day in Study B and none in the range-finding study at 300 mg/kg/day (number of litters/fetuses in the range-finding study was not indicated). Two litters with missing tails at 100 mg/kg/day did not appear to be treatment-related.

Males that were mated with females bearing litters with malformations are written into Table 3 in Appendix 3. Three of the four fetuses with spina bifida were from litters of females mated with males 101 or 108. It could not be determined whether the defects were related to particular males since each female was mated with 2 males; however, TB-I considers it unlikely to be due to mating procedures since the same males mated with does bearing fetuses with malformations were also mated with females which produced normal litters in Study A and Study B (200 mg/kg/day).

5. DISCUSSION: TB-I agreed with the original DER that the LOEL for maternal toxicity in this study was 200 mg/kg/day, based on decreased maternal body weight gain during treatment. The NOEL for maternal toxicity was 100 mg/kg/day and that there were no treatment-related effects observed on cesarean parameters.

TB-I disagreed with the original DER (and the study report) that the developmental NOEL was 300 mg/kg/day and considered the slightly increased incidence of malformations (spina bifida and possibly hypoplastic tail) at 300 mg/kg/day to be treatment-related. The study report stated that the increases at 300 mg/kg/day were slightly greater than historical control but considered them sporadic based on the lack of effects at 200 mg/kg/day in Study B and in the range-finding study at 300 mg/kg/day. However, there was no indication how many litters were examined in the range-finding study and historical control incidence was not provided. Because of the lack of incidence of spina bifida among all 53 control litters and at 30 mg/kg/day, and only a single incidence at 100 mg/kg/day (within historical control range), TB-I considered this a treatment-related effect. The lack of increased incidence of malformations at 200 mg/kg/day may simply indicate that higher doses are required to cause an increase of this defect. The slight increase in hypoplastic tail at 300 mg/kg/day may have been due to treatment. Although it cannot be ruled out, it appeared unlikely that the malformations were due to mating procedures.

STUDY DEFICIENCIES: study not conducted under EPA GLP or with Quality Assurance, historical control data not provided.

CORE CLASSIFICATION: Core-Minimum. This study is considered acceptable for regulatory purposes.

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Developmental Study (83-3)

APPENDIX 1



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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Petition No. 3P2941. Fenoxycarb: Review of
Teratogenicity Study, Rabbits; Hoffmann-LaRoche
Report No. -104 700.

Tox Chem. No. 652C

FROM: David G. Van Ormer ^{15 Feb 85}
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Adam Heyward, PM Team #17
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

The subject teratogenicity study is acceptable.

The six-month dog study (Hoffmann-LaRoche No. R-104 927)
is also acceptable, and the results are as follows:

NOEL = 150 mg/kg/day

LEL = 500 mg/kg/day (reduced weight gain in females)

Teratogenicity Study, Rabbit; Hoffmann-LaRoche (Basle) Report
No. R-104 700. February 13, 1984. Accession No. 073304.
Tox Chem. No. 652C.

The test material was fenoxycarb (Code No. R013-5223/000),
Batch No. 18, stated to be stable under conditions of the study.
Treatment was by daily oral gavage on gestation days 7 thru
19 at levels of 0, 30, 100 and 300 mg/kg in a volume of 5
ml/kg to dosage groups of 20 pregnant randomized rabbits. A
supplementary study (Study B) utilized dosages of 0 and 200
mg/kg administered to 35 rabbits per dosage group. The test
material was formulated in the vehicle fresh each week.

The test animals were Swiss hare rabbits (Inst. for Biological
and Medical Research, Fullinsdorf), with initial body weight
range 2440 to 3530 g. The Swiss hare strain was selected on
the basis of available background data at the laboratory.
Housing was one animal per cage under controlled ambient
conditions, with water and diet (Nafag 814 cubes) ad libitum.
Body weights were obtained on days 1, 7, 20 and 30. Observation
was daily.

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After sacrifice on day 30 the uteri were removed and examined for implantations and resorptions. The corpora lutea in each ovary were counted. Fetuses were weighed, examined macroscopically and submitted to crown-rump measurement. A 24-hour viability test was performed in an incubator at 34°C, following which the sacrificed fetuses received gross examination of the viscera. Fetuses for which skeletal examination by x-ray was inadequate were stained (Alizarin Red S) and preserved for subsequent inspection. Fetal heads were fixed in formalin/acetic acid for examination by a modified Julsingha and Bennett method.

Results:

Dose levels in the main study were based on results of a preliminary range-finding study, in which dosages of 100 and 300 mg/kg/day were generally well tolerated with a moderately reduced bodyweight at the top dose. The report states there was no evidence of either embryotoxic or teratogenic effects in the preliminary study.

Contrary to results of the range-finding study the main study produced incidences (at the mid and high dose groups) of malformations such as missing tail, open eye, and spina bifida. The study states that since the same malformations appear frequently in historical controls, a supplementary study using a dose level of 200 mg/kg (and a larger number of treated and control animals) was conducted in order to attempt to reproduce these malformations of "questionable significance." The results from both the main and supplementary study (Study B) were presented in figures and tables separately.

Maternal weight gain was reduced 20% at top dose (300 mg/kg/day, main study) and reduced 24% at 200 mg/kg/day in Study B.

Tabulated data show no treatment-related effects on the reproductive, fetal, or litter parameters (live and dead fetuses, sex ratio, percent resorptions, litter weight, bodyweight of live fetuses, crown-rump length, and 24-hour survival).

Malformations in the main study appear to show a dose-related effect, which the Report states to be an artifact for the reasons as follows:

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1. The incidence and type of malformations presented by the control group of Study B are similar ("analogous") to those found in the high dose group of the main study.
2. There was no pattern of association (in malformations) between the 200 mg/kg group of Study B and the 300 mg/kg group (top dose) of the main study.
3. The malformations at the top dose (main study) are the same type as often observed in historical controls, and are particularly similar to those observed among controls in Study B.
4. Malformations were not presented by fetuses at either 100 or 300 mg/kg in the range-finding study.

Toxicology Branch accepts the above discussion to support a lack of significant treatment-related terata in the data of the studies.

Tabulation of Wilson screening (examination of fetal heads) reveals similar incidences and variations in soft tissue structure among all groups (including controls) of both the principle and supplementary study. The main study presented no variations which do not occur in historical controls, according to the Report.

Skeletal examination of neonates with the aid of either x-rays or staining showed no treatment-related effects in any group (including controls) from either the principle or the supplementary study.

Conclusion: Minimum Data

Terata not observed up to 300 mg/kg/day (HDT)

Embryotoxicity not observed up to 300 mg/kg/day (HDT)

NOEL, maternal toxicity = 100 mg/kg/day

LEL, maternal toxicity = 200 mg/kg/day (supplementary study;
weight gain 24% less than controls).

OPP:HED:TOX:VAN ORMER:sb 2/14/85 X73713 #12-D11

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Developmental Study (83-3)

APPENDIX 2

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Page _____ is not included in this copy.

Pages 15 through 25 are not included.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients.
- ☐ Identity of product impurities.
- ☐ Description of the product manufacturing process.
- ☐ Description of quality control procedures.
- ☐ Identity of the source of product ingredients.
- ☐ Sales or other commercial/financial information.
- ☐ A draft product label.
- ☐ The product confidential statement of formula.
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- ☒ FIFRA registration data.
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