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

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MAR 30 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Oxamyl (Vydate) Data Review.
Tox Chem No. (Caswell No.) 561 A
HED Project No. 1-1684

From: Dan W. Hanke, Ph. D. Dan W Hanke 25 March 1992
Review Section III
Toxicology Branch II (HFASB)
Health Effects Division (H7509C)

To: Mr. Larry Schnaubelt
Product Manager, Team 72
Special Review and Reregistration Division (H7508W)

Thru: James N. Rowe, Ph. D. James N. Rowe 3/25/92
Head, Review Section III
Toxicology Branch II (HFASB)
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph. D. M van Gemert 3/26/92
Chief, Toxicology Branch II (HFASB)
Health Effects Division (H7509C)

ACTION:

E. I. du Pont de Nemours and Company Agricultural Products has submitted a two generation reproductive toxicity study in rats in support of re-registration of oxamyl, a nematocide. The results of a review of this study are summarized below.

SUMMARY:

Reproductive and Fertility Effects (§83-4). Oxamyl, Technical 97.1 % pure.
MRID NO. 416608-01.
In a two-generation reproduction study, Crl:CD^{R}BR rats were fed oxamyl in the diet at dosage levels of 0, 25, 75, or 150 ppm (approximately 0, 1.7, 5.2, and 11.6 mg/kg/day for males and 0, 2.0, 6.6, and 15.8 mg/kg/day for females). Parental toxicity was observed in both sexes and generations at 75 and 150 ppm as significantly decreased food consumption, body weight, and body weight gain and at 150 ppm as significantly increased incidences of clinical signs

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(hyperactivity, skin sores, and alopecia). Based on these results, the NOEL for parental toxicity was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females respectively).

Reproductive toxicity was observed at 75 and 150 ppm in both generations as significantly decreased body weight during lactation in both generations. In addition, at 150 ppm, the number of live pups per litter during lactation and the viability index were significantly decreased. Based on these results, the NOEL for reproductive toxicity was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females respectively).

A signed quality assurance statement was present.

Core Classification: Minimum

This study satisfies the guideline requirements (§83-4) for a Reproductive and Fertility Effects Study.

DOC920086

FINAL

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DATA EVALUATION REPORT

OXAMYL

Study Type: Reproductive Toxicity in Rats

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Pia Lindström Date 3/10/92
Pia Lindström, D.P.H.

Independent Reviewer Sanju Diwan Date 3/10/92
Sanju Diwan, Ph.D.

QA/QC Manager Sharon A. Segal Date 3/11/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-49
Clement Number: 91-162
Project Officer: James Scott

EPA Reviewer: Dan Hanke, Ph.D. Signature: Dan h Hanke
Toxicologist, Toxicology Branch II/HED Date: 25 March 1992

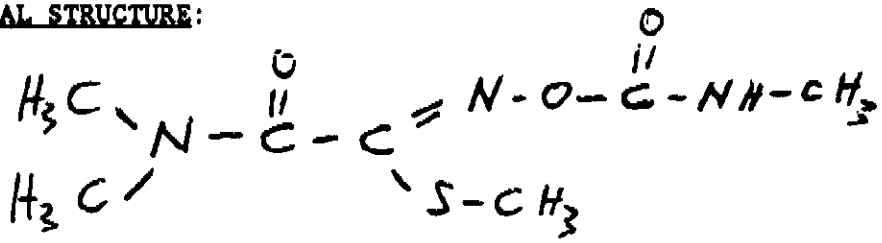
EPA Section Head: James N. Rowe, Ph.D. Signature: James N. Rowe
Toxicology Branch II/HED Date: 3/25/92

DATA EVALUATION REPORT 009390

STUDY TYPE: Reproductive toxicity in rats (§ 83-4)

EPA IDENTIFICATION NUMBERS:

CHEMICAL STRUCTURE:



HED PROJECT NUMBER: 1-1684

TOX CHEM. NUMBER: 561A

C.A.S. NUMBER: 2135-22-0 or 23135-22-0

MRID NUMBER: 416608-01

TEST MATERIAL: Ethanimidothioic acid, 2-(dimethylamino)-N-[[(methylamino) carbonyl]oxy]-2-oxo-, methyl ester; 97.1% pure

SYNONYMS: Oxamyl, IND-1410-196, IN D1410, DPX 1410, Vydate

SPONSOR: Agricultural Products, E.I. du Pont de Nemours and Company, Wilmington, DE

STUDY NUMBER: HLR 423-90

PROJECT NUMBER: 8433-88-001

TESTING FACILITY: Haskell Laboratories for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE

TITLE OF REPORT: Reproductive and Fertility Effects with Oxamyl (IN D1410), Multigeneration Reproduction Study in Rats

AUTHOR: Hurtt, M.E.

REPORT ISSUED: October 16, 1991

CONCLUSIONS: In a two-generation reproduction study, Crl:CD®BR rats were fed oxamyl in the diet at dosage levels of 0, 25, 75, or 150 ppm (approximately 0, 1.7, 5.2, and 11.6 mg/kg/day for males and 0, 2.0, 6.6, and 15.8 mg/kg/day for females). Parental toxicity was observed in both sexes and generations at 75 and 150 ppm as significantly decreased food consumption, body weight, and body weight gain and at 150 ppm as significantly increased incidences of clinical signs (hyperreactivity, skin sores, and alopecia). Based on these results, the NOEL for parental toxicity was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

Reproductive toxicity was observed at 75 and 150 ppm in both generations as significantly decreased body weight during lactation in both generations. In addition, at 150 ppm, the number of live pups per litter during lactation and the viability index were significantly decreased. Based on these results, the NOEL for reproductive toxicity was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

CLASSIFICATION: Core Guideline Data. This study meets all requirements set forth under Guideline 83-4 for a two-generation reproductive toxicity study in rats.

A. MATERIALS

Test Compound Oxamyl

Source:	E.I. du Pont de Nemours and Company, Wilmington, DE
Purity:	97.1% (reported by supplier) 99.5% (mean analytical purity)
Description:	White crystalline solid
Solubility:	Soluble in water, methanol, ethanol, acetone, and toluene
Melting point:	100° - 102°C
Lot/notebook numbers:	7577-46, 6689-176-5, 5103-173
Contaminants:	Not reported

Vehicle: None used; the test material was administered in the diet.

Test Animals

Species:	Rat
Strain:	Crl:CD®BR
Source:	Charles River Laboratories, Inc., Raleigh, NC
Age:	F_0 males--46 days upon arrival F_0 females--43 days upon arrival
Weight:	F_0 males--172-203 g upon arrival F_0 females--133-170 g upon arrival

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B. STUDY DESIGN

This study was designed to assess the potential of oxamyl to cause reproductive toxicity when administered continuously in the diet for two successive generations. A copy of the protocol is presented in Appendix A.

The animals were housed individually in rooms at a temperature of 23°C ± 2° and a relative humidity of 50% ± 10%. The light/dark cycle was 12 hours

Mating: After 15 days of acclimatization followed by 74 days of oxamyl dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating was obtained (intravaginal or extruded copulation plug) or for a maximum of 3 weeks. The day on which mating was confirmed was designated day 0 of gestation. The F_1 animals were mated in a similar fashion following 105 days (postweaning) on the test diet. Sibling matings were avoided.

Group Arrangement: F_0 and F_1 parental animals were divided into four groups (using computerized stratified randomization based on body weight) as follows:

Test Group	Dietary Level (ppm)	Number Assigned per Group			
		F_0		F_1	
		Males	Females	Males	Females
Control	0	30	30	30	30
Low dose	25	30	30	30	30
Mid dose	75	30	30	30	30
High dose	150	30	30	30	30

Dosage Administered: The test material was administered continuously in the diet (irradiated Purina Certified Rodent Chow #5002) for two consecutive generations. The test diets were prepared weekly by adding oxamyl to the diets and then mixing for three minutes in a high-speed mixer. The diets were refrigerated until used. The purity of the test material was analyzed before and after the study. Homogeneity, stability (after 7 and 14 days at 23°C ± 2°), and concentration analyses of the test material in the diet were conducted on samples from each dosage level from the first batches. Additional concentration analyses were conducted on samples from feed jars in the F_0 generation once and in the F_1 generation twice.

Dosage Rationale: The dosage levels were selected based upon results from a 90-day feeding one-generation reproduction study (HLR 307-69) and a three-generation reproduction study (HLR 313-71 and 37-72) both conducted at dosage levels of 0, 50, 100, or 150 ppm. In these studies, parental toxicity was manifested as reduced body weight gain at 100 and 150 ppm; reproductive toxicity was manifested as reduced litter sizes at 100 and 150 ppm and decreased pup body weight at all dosage levels.

Observations: Cage-site observations for mortality, moribundity, and overt signs of toxicity were conducted at least once a day. A more detailed clinical examination was performed weekly. Body weight of males and females was recorded weekly during the premating period and body weight of females was recorded on gestation days (GD) 0, 7, 14, and 21 and lactation days 0, 7, 14, and 21. Terminal body weight was recorded for all animals. Food consumption was recorded weekly during the premating period for all animals and on GD 0, 7, and 14 for females.

The following data were recorded for each litter.

- Number of dead pups on lactational day 0
- Number of live pups, sex, and pup weight (collectively by sex) on lactational days 0, 4, 7, and 14
- Number of live pups, sex, and individual pup weight on lactational day 21
- Individual abnormal behavior and appearance on lactational days 0, 4, 7, 14, and 21

On lactational day 4, pups were culled to 4/sex/litter; culled pups were sacrificed and discarded. Pups found dead or moribund were necropsied. Pups were weaned on day 21, and 30 male and 30 female F_1 pups were randomly selected as F_1 parental animals. Of the remaining F_1 pups, 20 pups/sex/group were given a gross pathological examination; the rest were sacrificed and discarded. Twenty F_2 pups/sex/group were also selected for a full post mortem examination. All gross lesions were preserved.

Following selection of the F_1 parental animals, the F_0 males and females (after 125-128 and 118-136 days, respectively, on the test diet) were sacrificed by chloroform anesthesia and exsanguination and subjected to a gross pathological examination. Evaluation of F_1 parental animals (males after 168-188 days; females after 150-189 days) and animals sacrificed prior to schedule or found dead was similar to that of F_0 parental animals. The following tissues (when present) were preserved in fixative:

- Pituitary
- Seminal vesicles
- Prostate
- Uterus
- Ovaries
- Gross lesions
- Testes (organ weight also recorded)
- Epididymides
- Vagina
- Coagulating gland

All gross lesions and the above tissues from the control and high-dosage groups were histologically evaluated.

Statistical Analysis: The following analyses were conducted.

- Parental body weight and weight gain, food consumption and efficiency, and gestation length--ANOVA and Dunnett's test

- Organ weight--Bartlett's test for variance homogeneity and, if significant, nonparametric procedures

- Clinical observations, gross and microscopic lesions, indices of mating, fertility, and gestation, and litter survival--Fisher's Exact test with a Bonferroni correction factor

- Pup numbers, survival, weights, viability index, and lactation index--Mann-Whitney U test

- Except for Bartlett's test, all significance was judged at alpha=0.05

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated October 19, 1990, was provided

- A signed Statement of Compliance with EPA GLPs, dated October 10 and 19, 1990, was provided

- A signed Quality Assurance Statement, dated October 10, 1990, was provided

- A signed Flagging Statement, dated October 10 and 19, 1990, was provided

C. RESULTS

1. Test Material Analysis

The purity of the test material was 100% and 99% as determined by HPLC analysis before the start of the study and after study completion, respectively. Concentrations of the test material in the diets ranged from 83% to 106% of the nominal values. Homogeneity analyses revealed concentrations ranging from 85% to 107% of nominal values. Analyses for stability of the test material in the diet after 14 days, either at room temperature or in the refrigerator, revealed concentrations ranging from 88% to 113% of nominal values. Test material was not detected in the control diet.

2. Parental Toxicity

Mortality: No compound-related mortality was observed. In the F_0 generation, one female at 150 ppm was found dead on study day 115; necropsy revealed enlarged pale kidneys. In the F_1 generation, one male at 150 ppm was found dead on day 6; cause of death could not be determined. Two additional males at 150 ppm were found dead on days 35 and 168; necropsies revealed atrophy of the liver and thymus in one animal and atrophy of the spleen in the other animal. These deaths were considered unrelated to the test compound since there was no discernable pattern regarding time of death and sex.

Clinical Observations: A summary of selected clinical signs during premating is presented in Table 1. Compound-related clinical signs (skin sores, hyperreactivity, and alopecia) were observed at 150 ppm. At this dosage level, the incidence of skin sores was increased in F_0 males (significantly) and in F_1 males and females (nonsignificantly). In addition, the incidence of hyperreactivity was increased in F_1 males (significantly) and females (nonsignificantly). Although frequently occurring in both sexes and generations at all dosage levels, the incidence of alopecia was increased in F_0 females (nonsignificantly) and in F_1 males (nonsignificantly) at 150 ppm and in F_1 females (significantly) at both 75 and 150 ppm. Likewise, for females during gestation and lactation, alopecia was increased at 150 ppm (significantly during gestation for F_1 females). The significantly increased incidence of crooked teeth, observed in F_0 males at 150 ppm, was not considered to be related to treatment.

Body Weight: Summaries of body weight from selected time intervals are presented in Tables 2, 3, and 4. Compound-related effects were consistently observed at 75 and 150 ppm in both sexes and generations. Detailed results are presented in the text; complete summary tables of body weight and weight gain have been copied from the CBI and may be found in Appendix B.

In the F_0 generation (Table 2), body weight for males and females was significantly decreased at 75 ppm (5%-9%) and 150 ppm (10%-18% for males and 10%-12% for females) during the entire premating phase (70 days on test material diet). Body weight gain during premating in males was significantly decreased at 75 ppm on days 0-21, 28-35, 49-56, and 0-70 and at 150 ppm on days 0-21, 28-42, 49-63, 0-70, and 70-119 (CBI p. 67). In females, body weight gain during premating was significantly decreased at 75 ppm on days 0-7 and 0-70 and at 150 ppm on days 0-7, 35-49, and 0-70 (CBI p. 69). For pregnant females, body weight was significantly decreased at 75 and 150 ppm during the entire gestation (Table 3) and lactation (Table 4) periods. Body weight gain was significantly decreased at 150 ppm on days 14-21 and 0-21 during gestation (CBI p. 74) and significantly increased at 75 and 150 ppm on days on days 14-21 and 0-21 during lactation (CBI p. 76).

In the F_1 generation (Table 2), body weight for males and females was significantly decreased at 75 ppm (7%-20%) and 150 ppm (17%-37%) during the entire premating phase (105 days postweaning). An incidental, but significant, decrease was noted at 25 ppm in females on day 7. Body weight gain during premating (data not shown) in males was significantly decreased at 75 ppm on days 0-35, 42-49, 63-70, and 0-105 and at 150 ppm on days 0-49, 56-70, 77-84, and 0-182 (CBI p. 68). In females, body weight gain during premating was significantly decreased at 75 ppm on days 0-14 and 0-105 and at 150 ppm on days 0-14, 28-35, 77-84, and 0-105 (CBI p. 72). For pregnant females, body weight was significantly decreased at 75 and 150 ppm during the entire gestation (Table 3) and lactation (Table 4) periods. Body weight gain was significantly decreased at 150 ppm on days 0-7, 14-21, and 0-21 during gestation (CBI p. 74) and

TABLE 1. Selected Clinical Signs During the Premating Period for Rats Fed Oxamyl for Two Successive Generations[a,b]

Observation	Dietary Level (ppm) 0	25	75	150
F_0 generation - males				
Alopecia	8	9	7	10
Colored discharge, eye(s)	0	2	4	5
Colored discharge, nose	1	0	2	1
Hyperreactive	5	1	3	7
Skin sore[c]	2	3	4	10*
F_0 generation - females				
Alopecia	7	4	4	14
Colored discharge, eye(s)	1	1	2	0
Hyperreactive	0	2	0	1
Skin sore	2	0	3	3
Stained fur	0	0	0	2
F_1 generation - males				
Alopecia	10	7	6	14
Colored discharge, eye(s)	4	7	4	4
Colored discharge, nose	3	6	7	2
Hyperreactive[c]	5	8	12	14*
Skin sore	11	12	7	19
F_1 generation - females				
Alopecia	2	5	10*	20*
Colored discharge, eye(s)	3	2	1	5
Hyperreactive	2	2	4	7
Skin sore	2	1	3	8

[a]Data were extracted from study no. HLR 423-90, Tables 29-32

[b]Includes incidences that occurred in two or more animals in any group

[c]Significant trend

*Significantly different from control (p=0.05)

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TABLE 2. Mean Body Weight (g ± S.D.) During the Premating Period in Rats Fed Oxamyl for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	25	75	150
F_0 males				
0	324 ± 14	320 ± 20	317 ± 14	319 ± 17
14	409 ± 26	410 ± 28	383 ± 19*	360 ± 30*
28	481 ± 30	472 ± 46	443 ± 24*	414 ± 39*
42	532 ± 36	532 ± 45	489 ± 29*	451 ± 45*
56	574 ± 39	574 ± 50	524 ± 31*	485 ± 50*
70	604 ± 42	606 ± 53	556 ± 36*	507 ± 55*
F_0 females				
0	211 ± 16	208 ± 12	206 ± 13	207 ± 11
14	248 ± 22	249 ± 16	228 ± 14*	221 ± 14*
28	274 ± 25	266 ± 20	254 ± 17*	244 ± 13*
42	294 ± 28	288 ± 23	267 ± 20*	259 ± 14*
56	305 ± 30	302 ± 25	279 ± 22*	271 ± 18*
70	312 ± 30	315 ± 29	286 ± 26*	282 ± 19*
F_1 males				
0	60 ± 7	58 ± 8	56 ± 8*	45 ± 6*
14	171 ± 14	163 ± 17	140 ± 16*	107 ± 12*
28	295 ± 24	288 ± 28	252 ± 25*	201 ± 21*
42	403 ± 31	394 ± 39	350 ± 30*	284 ± 25*
56	471 ± 40	461 ± 45	411 ± 35*	340 ± 30*
70	526 ± 49	512 ± 53	456 ± 39*	373 ± 45*
105	606 ± 61	599 ± 64	531 ± 45*	430 ± 53*
F_1 females				
0	58 ± 8	55 ± 7	50 ± 6*	44 ± 5*
14	143 ± 9	138 ± 12	118 ± 12*	98 ± 9*
28	200 ± 16	198 ± 17	176 ± 18*	158 ± 15*
42	246 ± 24	242 ± 20	214 ± 23*	196 ± 16*
56	277 ± 27	269 ± 23	242 ± 25*	228 ± 19*
70	300 ± 29	287 ± 27	264 ± 29*	247 ± 23*
105	329 ± 38	319 ± 32	284 ± 29*	268 ± 23*

[a]Data were extracted from study no. HLR 423-90, Tables 2, 3, 6, and 7

*Significantly different from controls (p=0.05)

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TABLE 3. Mean Body Weight (g ± S.D.) During Gestation in Rats Fed Oxamyl for Two Successive Generations[a]

Gestational Day:	Dietary Level (ppm) 0	25	75	150
F_0 generation - F_1 litters				
0	317 ± 31	318 ± 29	293 ± 24*	280 ± 23*
7	348 ± 30	353 ± 28	322 ± 24*	304 ± 21*
14	380 ± 34	383 ± 28	353 ± 22*	331 ± 26*
21	470 ± 36	469 ± 35	441 ± 34*	398 ± 37*
F_1 generation - F_2 litters				
0	335 ± 23	326 ± 31	291 ± 28*	270 ± 22*
7	368 ± 25	363 ± 36	319 ± 27*	294 ± 17*
14	393 ± 31	392 ± 39	347 ± 30*	317 ± 22*
21	483 ± 30	484 ± 45	424 ± 39*	384 ± 21*

[a]Data were extracted from study no. HLR 423-90, Table 10

*Significantly different from controls (p=0.05)

TABLE 4. Mean Body Weight (g ± S.D.) During Lactation in Rats Fed Oxamyl for Two Successive Generations[a]

Lactational Day:	Dietary Level (ppm) 0	25	75	150
F_0 generation - F_1 litters				
0	358 ± 32	351 ± 30	330 ± 23*	304 ± 16*
7	364 ± 31	354 ± 22	340 ± 22*	314 ± 17*
14	373 ± 29	372 ± 23	349 ± 26*	328 ± 16*
21	353 ± 37	357 ± 34	346 ± 19	328 ± 20*
F_1 generation - F_2 litters				
0	377 ± 29	372 ± 39	331 ± 33*	296 ± 24*
7	371 ± 33	370 ± 44	337 ± 28*	307 ± 25*
14	375 ± 28	373 ± 40	341 ± 33*	312 ± 23*
21	370 ± 30	357 ± 28	342 ± 25*	316 ± 22*

[a]Data were extracted from study no. HLR 423-90, Table 12

*Significantly different from controls (p=0.05)

significantly increased at 75 and 150 ppm on days 0-21 during lactation (CBI p. 76).

Food Consumption: Summaries of food consumption (g/animal/day) from selected time intervals are presented in Tables 5 and 6. Compound-related effects were observed at 75 and 150 ppm in both sexes and generations. Detailed results are presented in the text.

In the F_0 generation, daily food consumption (g/animal) among males significantly decreased during the entire premating phase (Table 5) at 75 and 150 ppm. For females during premating, food consumption decreased significantly at 75 ppm on days 0-7 and at 150 ppm on days 0-7, 21-35, 42-63, and 0-70.

Food efficiency (g weight gain/g food consumed) significantly decreased for males at 75 ppm on premating days 14-21, 49-56, and 0-70 and at 150 ppm on premating days 0-21, 35-42, 49-63, and 0-70 (CBI p. 79). For females, food efficiency decreased significantly at 75 ppm on premating days 0-7 and 0-70 and at 150 ppm on premating days 0-7, 35-42, and 0-70 (CBI p. 83). During gestation, food efficiency decreased significantly on days 7-14 and 0-14 (CBI p. 86).

In F_1 generation males, daily food consumption (g/animal) decreased significantly during the entire premating phase (Table 5) at 75 and 150 ppm. For F_1 females during premating, food consumption decreased significantly at 75 ppm on days 0-7 and at 150 ppm during the entire premating period.

Food efficiency (g weight gain/g food consumed) decreased significantly for males at 75 ppm on premating days 0-14 and at 150 ppm on premating days 0-35, 63-70, 77-84, and 0-105 (CBI p. 80). For females, food efficiency decreased significantly at 75 ppm on premating days 0-105 and at 150 ppm on premating days 0-7, 28-35, 63-70, 77-84, and 0-105 (CBI p. 84). During gestation, food efficiency decreased significantly on days 0-7 and 0-14 (CBI p. 86).

Compound Intake: In the F_0 generation, mean daily compound intake during premating was 0, 1.43, 4.22, and 8.74 mg/kg/day for males and 0, 1.74, 5.69, and 12.8 mg/kg/day for females at 0, 25, 75, and 150 ppm, respectively. During gestation for females it was 0, 1.74, 5.41, and 12.2 mg/kg/day for the respective dosage groups.

In F_1 generation, daily compound intake during premating was 0, 1.97, 6.17, and 14.5 mg/kg/day for males and 0, 2.28, 7.48, and 18.8 mg/kg/day for females at 0, 25, 75, and 150 ppm, respectively. During gestation for females it was 0, 1.77, 5.43, and 14.4 mg/kg/day for the respective dosage groups.

Gross and Microscopic Pathology: A summary of selected organ weights is presented in Table 7. No significant compound-related macroscopic or microscopic findings (including effects on organ weights) were observed for any sex or generation.

TABLE 5. Mean Food Consumption (g/day ± S.D.) During the Premating Period in Rats Fed Oxamyl for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	25	75	150
F_0 males				
0 - 7	26.7 ± 2.0	25.9 ± 2.2	22.5 ± 2.0*	18.4 ± 3.6*
14 - 21	28.2 ± 2.1	28.0 ± 2.5	25.8 ± 1.9*	25.5 ± 3.5*
35 - 42	28.8 ± 2.4	28.9 ± 2.3	26.8 ± 2.1*	26.4 ± 3.0*
49 - 56	28.9 ± 2.1	28.8 ± 2.2	26.4 ± 2.1*	26.9 ± 4.1*
63 - 70	28.9 ± 2.2	28.7 ± 2.1	27.3 ± 2.2*	26.6 ± 3.4*
0 - 70	28.6 ± 1.9	28.4 ± 2.2	26.0 ± 1.8*	25.1 ± 2.9*
F_0 females				
0 - 7	19.2 ± 2.8	19.1 ± 2.0	16.4 ± 4.1*	14.9 ± 5.0*
14 - 21	19.8 ± 2.1	18.8 ± 2.7	20.0 ± 4.8	21.7 ± 4.1
35 - 42	20.9 ± 3.8	19.2 ± 1.3	19.3 ± 3.2	21.0 ± 2.4
49 - 56	20.1 ± 2.8	19.4 ± 2.3	19.8 ± 4.2	22.8 ± 5.7*
63 - 70	19.8 ± 5.7	20.4 ± 5.9	20.0 ± 3.9	22.7 ± 4.7*
0 - 70	19.7 ± 2.1	19.3 ± 1.8	19.5 ± 3.7	21.4 ± 2.3*
F_1 males				
0 - 7	15.8 ± 3.6	15.3 ± 2.1	14.9 ± 4.3	12.4 ± 2.3*
14 - 21	25.4 ± 2.5	26.2 ± 2.8	22.8 ± 2.7*	21.4 ± 3.2*
35 - 42	30.5 ± 2.8	30.5 ± 2.6	27.7 ± 2.9*	27.1 ± 3.5*
63 - 70	31.0 ± 3.2	30.4 ± 3.3	27.7 ± 2.8*	26.5 ± 4.4*
91 - 98	29.9 ± 2.8	30.3 ± 3.1	25.9 ± 2.3*	25.2 ± 3.9*
0 - 105	28.3 ± 2.4	28.1 ± 2.2	25.5 ± 1.9*	24.3 ± 2.8*
F_1 females				
0 - 7	14.9 ± 2.0	14.2 ± 1.6	12.4 ± 2.5*	11.2 ± 1.8*
14 - 21	20.8 ± 1.9	21.1 ± 2.1	20.0 ± 3.1	21.4 ± 4.0
35 - 42	22.0 ± 2.7	22.2 ± 2.2	21.4 ± 3.2	27.0 ± 6.1*
63 - 70	22.3 ± 2.7	21.1 ± 2.3	21.7 ± 3.6	25.8 ± 5.6*
91 - 98	22.1 ± 3.1	21.1 ± 2.1	20.9 ± 3.8	25.4 ± 3.4*
0 - 105	21.2 ± 1.8	20.7 ± 1.7	20.2 ± 2.3	23.6 ± 2.8*

[a]Data were extracted from study no. HLR 423-90, Tables 14, 15, 18, and 19

*Significantly different from controls (p=0.05)

TABLE 6. Mean Food Consumption (g/day ± S.D.) During Gestation in Rats Fed Oxamyl for Two Successive Generations[a]

Gestational Days	Dietary Level (ppm) 0	25	75	150
F$_0$ generation - F$_1$ litters				
0 - 7	24.5 ± 2.9	24.9 ± 2.2	23.3 ± 3.7	24.8 ± 4.1
7 - 14	26.0 ± 4.7	26.1 ± 2.8	25.2 ± 4.9	27.1 ± 6.4
0 - 14	25.2 ± 3.4	25.5 ± 2.2	24.2 ± 3.8	25.6 ± 4.7
F$_1$ generation - F$_2$ litters				
0 - 7	25.1 ± 3.1	26.0 ± 3.2	23.5 ± 3.5	30.6 ± 6.4*
7 - 14	26.8 ± 2.4	27.4 ± 2.9	24.4 ± 2.1	27.2 ± 6.2
0 - 14	25.9 ± 2.6	26.7 ± 2.9	24.0 ± 2.4	28.9 ± 5.6

[a]Data were extracted from study no. HLR 423-90, Table 22

*Significantly different from controls (p=0.05)

TABLE 7. Mean Testes Weight (± S.D.) for Parental Rats Fed Oxamyl for Two Successive Generations[a]

Organ	Dietary Level (ppm) 0	25	75	150
F_0 generation				
Absolute (g)	3.91 ± 0.24	3.93 ± 0.34	3.91 ± 0.32	3.81 ± 0.40
Relative (to BW, %)	0.58 ± 0.05	0.58 ± 0.07	0.62 ± 0.06*	0.69 ± 0.07*
F_1 generation				
Absolute (g)	4.05 ± 0.47	3.90 ± 0.45	3.98 ± 0.30	3.69 ± 0.46
Relative (to BW, %)*	0.58 ± 0.09	0.56 ± 0.07	0.65 ± 0.09*	0.77 ± 0.13*

[a]Data were extracted from study no. HLR 423-90, Tables 44 and 46

*Significantly different from control (p=0.05)

In the F_0 generation, spontaneous gross pathologic observations occurring in more than one animal at any dosage level included teeth deformity in three males and four females and epididymal nodules in three males (CBI p. 113-115). Relative (to body weight) testicular weight (Table 7) was significantly increased at 75 and 150 ppm; an effect caused by the decreased body weight at these dosages. Microscopic observations (CBI p. 119-122) occurred only as single events or at rates similar to the control group and were not considered to be compound related.

In the F_1 generation, a significant increase in the incidence of nodules in the tail was observed at 150 ppm in males (CBI p. 116-118). These nodules were associated with the animals' identification tattoos and were not considered to be a result of the test compound. Additional gross findings, considered to be spontaneous and occurring in more than one animal at any dosage level, included stained skin, alopecia, periocular chromodacryorrhea, teeth deformity, and renal pelvis dilatation. Relative (to body weight) testicular weight was significantly increased at 75 and 150 ppm; an effect caused by the decreased body weight at these dosages. Microscopic observations (CBI p. 123-126) occurred only as single events or at rates similar to the control group and were not considered to be compound related.

3. Reproductive Toxicity

The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 8 and 9. Fertility, mating, and gestation indices and gestation length were not affected by treatment in any generation at any dosage level. However, compound-related decreased pup survival and decreased pup body weight were observed in both generations at 75 and 150 ppm. Detailed results are presented in the text.

In the F_1 offspring (Table 8), the number of live pups/litter was significantly decreased at 150 ppm on lactation days 0 and 4 preculling. As a consequence, the viability index was significantly decreased at 150 ppm. Pup body weight was significantly decreased at 75 and 150 ppm during the entire lactation period. No significant effects were noted in pups regarding clinical observations and gross pathologic findings (CBI p. 129-131).

In the F_2 offspring (Table 9), the number of live pups/litter was significantly decreased at 150 ppm from lactation day 4 preculling through lactation day 21. As a consequence, the viability index was significantly decreased at 150 ppm. Pup body weight was significantly decreased at 75 and 150 ppm during the entire lactation period. Clinical observations of 'small body weight' and 'no milk spot' in pups of oxamyl treated groups were consistent with reduced body weights. No effects were noted in pups regarding gross pathologic findings (CBI p. 132-135).

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TABLE 8. Summary of Effects of Dietary Administration of Oxamyl on F_0 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	25	75	150
No. matings (F_0 parents)	30	30	30	30
No. pregnancies	29	29	30	30
Fertility index (%)[b]	90	79	90	87
Mating index (%)[c]	97	97	100	100
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.4	22.7	22.4	22.7
Total no. dead pups, day 0	13	6	4	14
Total no. live pups[e]				
Day 0	348	303	372	291
Day 4 precull	347	294	363	223
Day 4 postcull	200	173	205	166
Day 21	200	173	202	163
Mean no. live pups/litter				
Day 0	13.4	13.2	14.3	11.2*
Day 4 precull	13.3	12.8	14.0	8.6*
Day 21	7.7	7.9	7.8	7.1
Live birth index (%)[f]	96	98	99	95
Viability index (%)[g]	99	94	98	78*
Lactation index (%)[h]	100	100	99	98
Pup body weight (g)				
Day 0	6.9	6.9	6.4*	6.0*
4 precull	11.8	11.7	10.1*	9.6*
14	38.2	36.8	33.4*	29.5*
21	59.9	58.6	52.9*	44.9*
Sex ratio (% male)	46	47	51	47

[a]Data were extracted from study no. HLR 423-90, Tables 37, 38, and 40 and Appendix R

[b]Fertility index was calculated as: $\frac{\text{No. of pairs producing litters}}{\text{No. of pairs copulating}} \times 100$

[c]Mating index was calculated as: $\frac{\text{No. of pairs copulating}}{\text{No. of pairs cohoused}} \times 100$

[d]Gestation index was calculated as: $\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[e]Calculated by the reviewers

[f]Live birth index was calculated as: $\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[g]Viability index was calculated as: $\frac{\text{No. of pups alive on day 4 precull}}{\text{No. of pups born alive}} \times 100$

[h]Lactation index was calculated as: $\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4 postcull}} \times 100$

*Significantly different from controls ($p=0.05$)

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TABLE 9. Summary of Effects of Dietary Administration of Oxamyl on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	25	75	150
No. matings (F_1 parents)	30	30	30	30
No. pregnancies	23	27	29	29
Fertility index (%)[b]	70	81	72	69
Mating index (%)[c]	77	90	97	97
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.7	22.5	22.3	22.6
Total no. dead pups, day 0	13	7	0	22
Total no. live pups[e]				
Day 0	203	310	261	214
Day 4 precull	196	296	234	106
Day 4 postcull	123	176	156	83
Day 21	123	176	146	78
Mean no. live pups/litter				
Day 0	12.7	14.1	12.4	10.7
Day 4 precull	12.2	13.5	11.1	5.3*
Day 21	7.7	8.0	7.0	5.6*
Live birth index (%)[f]	95	98	100*	90
Viability index (%)[g]	95	96	91	54*
Lactation index (%)[h]	100	100	93	89
Pup body weight (g)				
Day 0	7.1	6.9	6.6	5.7*
4 precull	12.4	11.6	10.2	8.4*
14	38.6	37.8	32.3*	28.1*
21	63.2	61.8	51.5*	43.8*
Sex ratio (% male)	51	47	49	47

[a]Data were extracted from study no. HLR 423-90, Tables 37, 39, and 41 and Appendix R

[b]Fertility index was calculated as: $\frac{\text{No. of pairs producing litters}}{\text{No. of pairs copulating}} \times 100$

[c]Mating index was calculated as: $\frac{\text{No. of pairs copulating}}{\text{No. of pairs cohoused}} \times 100$

[d]Gestation index was calculated as: $\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[e]Calculated by the reviewers

[f]Live birth index was calculated as: $\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[g]Viability index was calculated as: $\frac{\text{No. of pups alive on day 4 precull}}{\text{No. of pups born alive}} \times 100$

[h]Lactation index was calculated as: $\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4 postcull}} \times 100$

*Significantly different from controls (p=0.05)

C. REVIEWERS' DISCUSSION/CONCLUSIONS

1. Test Material Analyses

Purity of the test compound was confirmed. Homogeneity and stability of the test compound in the diet were confirmed. Concentrations of the test compound in the diet were within ±13% of nominal concentrations.

2. Parental Toxicity

Compound-related parental toxicity was observed at 75 and 150 ppm. Significant decreases were present in food consumption and body weight throughout the study for both sexes and generations at 75 and 150 ppm. Frequently, body weight gain was significantly decreased at these dosage levels as well. In addition, at 150 ppm incidences of selected clinical observations (skin sores, alopecia, and hyperreactivity) were significantly increased.

Based on these results, the systemic (parental) toxicity NOEL was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

3. Reproductive Toxicity

Fertility, mating, and gestation indices and gestation length were not affected by oxamyl. However, in both generations, pup body weights were significantly decreased at 75 and 150 ppm during the entire lactation period. In addition, the number of surviving pups during lactation was significantly decreased at 150 ppm in both generations which, as a result, significantly affected the viability index.

Based on these results, the NOEL for reproductive toxicity was 25 ppm (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); the LOEL was 75 ppm (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

4. Study and Reporting Deficiencies

No deficiencies were noted in the design/report of this study or in the submission of individual animal data for data verification.

D. CLASSIFICATION

Core Guideline Data. This study satisfies guideline requirements (83-4) for a multi-generation reproduction study in rats.

Parental Toxicity NOEL - 25 ppm (approximately 1.7 mg/kg/day for males; 2.0 mg/kg/day for females)

Parental Toxicity LOEL = 75 ppm (approximately 5.2 mg/kg/day for males and 6.6 mg/kg/day for females; decreased body weight and food consumption, increased clinical signs)

Reproductive Toxicity NOEL = 25 ppm (approximately 1.7 mg/kg/day for males; 2.0 mg/kg/day for females)

Reproductive Toxicity LOEL = 75 ppm (approximately 5.2 mg/kg/day for males and 6.6 mg/kg/day for females; decreased number of live pups/litter, decreased pup body weight)

E. RISK ASSESSMENT

Not applicable

END