1-15-87

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

005858

Caswell # 561A

MEMORANDUM

Subject: Oxamyl: Toxicology Chapter of the Registration Standard

JAN 15 1987

To: Dennis Edwards, PM
Registration Division (TS- 767c)

From: Whang Phang, Ph.D.
Pharmacologist
Review Section III
Toxicology Branch, HED (TS-769c)

1/8/87

1/9/87

Through: Robert P. Zendzian, Ph.D.
Registration Standard Coordinator
Toxicology Branch

William Burnam, Deputy Chief
Toxicology Branch, HED (TS-769c)

1/14/87

Attached is the Toxicology Chapter of the Registration Standard for Oxamyl.

cc:

Coberly
Rispin
Zendzian

1/110

005858

Toxicology Chapter

of the

Oxamyl

Registration Standard

Prepared by

Khang Phang, Ph.D.
Pharmacologist
Review Section III
Toxicology Branch, HED

005858

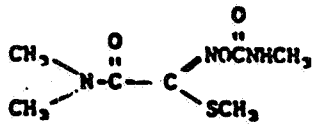
TOXICOLOGY CHAPTER

Table of Contents

005858

A. Toxicology Summary

Oxamyl is registered as a nematicide/insecticide. The chemical is a carbamate, and its stucture and chemical name are shown below:

	Name	Structure
Oxamyl;	Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate	

Oxamyl is acutely toxic as shown in both acute oral and inhalation toxicity studies, toxicity category I. For acute dermal toxicity, primary eye irritation, and skin irritation; the toxicity category could not be adequately determined at this time because those studies have deficiencies. The clinical signs of acute toxicity are primarily those of cholinesterase inhibition.

Available subchronic studies are all considered as supplementary data, and additional studies are needed.

Chronic rodent feeding studies showed that Oxamyl consistently caused decreases in body weights of treated mice and rats, and no additional compound-related effects were observed. The tumor incidences in treated rats and mice were comparable to those of the corresponding controls. A Core Supplementary chronic dog study did not show any adverse effects in treated animals relative to the controls.

A teratology study with rabbits did not show any structural or functional abnormalities besides decreases in maternal body weights. A Core Supplementary 3-generation reproduction study with rats found a decrease in body weights of weanlings in two generations.

An acceptable mutagenicity assay for DNA damage showed that Oxamyl did not cause DNA damage in the bacteria. Acceptable gene mutation and chromosomal aberration assays are still needed.

Properly conducted metabolism studies are needed to evaluate absorption, distribution, metabolism, and excretion of Oxamyl.

B. Toxicology Profile

§ 81 Series Acute Toxicity and Irritation Studies

81-1 Acute Oral

Sufficient data are available to demonstrate that Oxamyl (technical grade) has high acute oral toxicity to mammals. The acute oral LD_{50} for male rats is 3.1 mg/kg; female rats, 2.5 mg/kg (MRID No. 53011). Toxicity Category I.

The Oxamyl treated animals presented clinical signs of cholinesterase inhibition; atropine was shown to be an antidote in both rats and monkeys (MRID No. 113396 and 13397).

81-2 Acute Dermal

The acute dermal toxicity studies with technical Oxamyl are considered supplementary studies. The data derived from these studies are insufficient for evaluating the dermal toxicity of the test agent (MRID No. 66896 and 66898). Another study is required.

81-3 Acute Inhalation

Sufficient data are available to demonstrate that Oxamyl is extremely toxic when inhaled. With 1 hr of exposure by the inhalation route, the acute LC_{50} for male rats is 0.17 mg/L; female, 0.12 mg/L. With 4 hr exposure the acute LC_{50} for male rats is 0.064 mg/L (MRID No. 66902 and 66903). Toxicity Category I.

81-4 Primary Eye Irritation

The limited data indicate that Oxamyl produced some eye irritation which was reversible and caused marked pupillary constriction which was primarily due to cholinesterase inhibition (MRID No. 66894). The available data are considered supplementary and are inadequate for evaluating the possible eye irritation capability of the test agent. Another study is needed.

81-5 Primary Skin Irritation

The available data show that Oxamyl (technical grade) caused severe systemic effects and some dermal irritation; however, the studies are supplementary (MRID No. 66900). An additional study is required.

81-6 Dermal Sensitization

The limited data show that Oxamyl is not a dermal sensitizer, but the study is supplementary (MRID No. 66900). Another study is required.

81-7 Acute Delayed Neurotoxicity

An acute delayed neurotoxicity study was carried out, and the limited data showed no compound-related changes. However, the study was classified as invalid (MRID: 66893). This study is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Oxamyl is not an organophosphate; therefore, another study is not required.

§82 Series Subchronic Testing

82-1 Subchronic Oral

Available data are not adequate for assessing the subchronic oral toxicity of Oxamyl (MRID No's. 66911 and 66912). The 90-day rat study is considered invalid, and the 13-week dog study provides only supplementary data. Studies are required in a rodent and non-rodent species.

82-2 Subchronic Dermal (21-day)

No subchronic 21-day dermal toxicity study is available for Oxamyl. A study is required.

82-3 Subchronic Dermal (90-day)

No subchronic 90-day dermal toxicity study is available for Oxamyl. This study is not required under the present use pattern.

82-4 Subchronic Inhalation

No subchronic inhalation study is available for Oxamyl. This study is not required under the present use pattern.

82-5 Subchronic Neurotoxicity

This study is not needed at this time since Oxamyl is not an organophosphate and has not shown neurotoxicity in mammalian species.

§ 83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

Available data are insufficient to satisfied the data requirements on chronic oral toxicity studies in two species rodents and and non-rodent.

Rats (30/sex/dose) were fed diets containing Oxamyl in concentrations of 50, 100, and 150 ppm for 2 years. Oxamyl at concentrations of 100 and 150 ppm caused decreases in body weights of both males and females. Histopathological changes in treated animals were comparable to those of the controls. The NOEL for chronic toxicity was 50 ppm; LOEL, 100 ppm. The study is classified Supplementary (MRID: 83352).

Beagle dogs (3-4 dogs/sex/dose) were administered Oxamyl at dietary concentrations of 50, 100, and 150 ppm. There were no adverse effects observed. However, the highest dose in this study had not approached the maximum tolerated dose. Another study is required (MRID: 83352).

83-2 Oncogenicity

Chronic mice and rat studies (MRID: 83352) indicate that tumor incidence in treated animals was comparable to that of the controls, but the chronic rat study needs to be repeated in order to satisfied the data requirements.

Mice were orally dosed with 25, 50, and 75 ppm of Oxamyl for 2 years. Decreased body weights were observed in 50 and 75 ppm animals, and no other histopathological changes were found. The NOEL for chronic toxicity in mice is 25 ppm; LOEL, 50 ppm. Increased tumor incidence was not found among the treated animals relative to the controls (MRID: 76813). The study is classified Minimum.

83-3 Teratology

The available data only partially satisfy the data requirements for teratology. The study with rabbits meets the study requirements (MRID: 63009), but that with rats does not (MRID: 66909). Therefore, a teratology study with rats is required.

Oral administration of Oxamyl to pregnant rabbits (17/dose) at doses of 1, 2, and 4 mg/kg/day did not produce developmental toxicity, but in 2 and 4 mg/kg Oxamyl treated animals there were decreases in body weights. The developmental NOEL is 4 mg/kg (HDT). The maternal LOEL is 2 mg/kg; NOEL, 1 mg/kg. The study is classified Minimum (MRID: 63009).

Groups of female rats (26-28/dose) were fed Oxamyl at dietary concentrations of 50, 100, 150, and 300 ppm from day 6 through day 15 of the gestation period. The limited data did not show any structural or functional abnormalities, but the report contains only summary data. The study is classified Supplementary (MRID: 66909).

83-4 Reproduction and Fertility Effects

The available data are not sufficient to satisfy the data requirements for a reproduction and fertility effects study in the rodent (MRID: 83352). A new study is required.

The experimental animals of this 3-generation reproduction study were periodically taken from the chronic feeding study. The number of animals used in this study was not specified in Method section. The dose used in this study were 50, 100, and 150 ppm. The limited results indicate that Oxamyl caused only a decrease in body weights in the weanlings of mid and high dose groups in both F_1 and F_2 generations. However, the study has many deficiencies which preclude appropriate evaluation of the reproductive and fertility effects of Oxamyl. The study is classified Supplementary (MRID: 83352).

§ 84 Series Mutagenicity Testing

84-2 Mutagenicity Testing

DNA Damage

A differential toxicity assay using B. subtilis indicate that Oxamyl did not cause DNA damage (MRID: 40594). This study is acceptable.

Chromosomal Aberration

No chromosomal aberration assays have been submitted; an acceptable study is required.

Gene Mutation

An Ames assay using S. typhimirium and E. coli showed that Oxamyl did not cause gene mutation (MRID: 40594). Similar results were obtained in a host-mediated assay using S. typhimirium (MRID: 40594). However, both studies were unacceptable. An acceptable study is required.

§ 85 Series Special Studies

85-1 Metabolism

Available studies are not acceptable (MRID: 40498 and 28729). Additional studies are required.

85-2 Domestic Animal Safety

Studies are not required at this time.

85-3 Dermal Absorption

Dermal absorption studies are not required at this time.

Information on Human Effects

No reports are available at this time.

C. Data Gaps

Oxamyl is registered for use on food crops and has food tolerances. The following Guideline toxicology studies can be required for this registration:

§ 81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity
81-3 Acute Inhalation Toxicity
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

§ 82-1 Subchronic Oral Dosing (2 Species rodent and non-rodent)
82-2 Suhchronic Dermal (21-day)
82-3 Subchronic Dermal (90-day)
82-4 Subchronic Inhalation

§ 83-1 Chronic Toxicity (2 species rodent and non-rodent)
83-2 Oncogenicity in (2 species)
83-3 Teratology (2 species)
83-4 Reproduction and Fertility Effects

§ 84-2 Mutagenicity

§ 85-1 Metabolism

Based on this assessment of the toxicology data the following Guideline toxicology studies have been identified as data gaps and are required.

§ 81-2 Acute Dermal Toxicity
81-4 Primary Eye Irritation
81-5 Primary Skin Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral Toxicity (2 species rodent and non-rodent)

83-1 Chronic Feeding Study (2 species rodent and non-rodent)
83-2 Oncogenicity (rat)
83-3 Teratology (rat)
83-4 Reproduction and fertility Effects

84-2 Mutagenicity (gene mutation and chromosomal aberration assays)

85-1 Metabolism

At this time no non-guideline studies are required.

D. Tolerances and Tolerance Reassessment

Tolerances for Oxamyl have been approved for the RACs listed in Table I. An ADI has been approved by the RFD committee of EPA based on a 2-year rat feeding study (MRID: 83352). Compound related effects were decreases in body weights in both mid and high dose rats of both sexes. The NOEL in this study was 50 ppm (2.5 mg/kg). Utilizing a safety factor of 100, the ADI was set at 0.025 mg/kg/day which is equivalent to a MPI of 1.5 mg/day for a 60 kg person. The TMRC of Oxamyl in the daily diet based on the total tolerances listed in Table I and a daily food intake of 1.5 kg is 0.886 mg/day. Under these conditions 59.1% of the ADI has been utilized.

Based on the re-evaluation of the data base, it is necessary to reconsider the ADI. The 2-year rat feeding study is now considered supplementary. Nevertheless, the PADI should be based on the same study with the same safety factor until all data gaps are filled.

E. Toxicological Issues

There are no specific toxicological issues at this time; however, the toxicology data gaps must be filled for a complete evaluation.

Table I

005858

TOXICOLOGY BRANCH ADI PRINTOUT Date: 12/04/86

Oxamyl (Vydate) 2yr feeding- rat ADI = 0.025000 mg/kg/day
Caswell #561A NOEL = 2.5000 mg/kg Safety Factor = 100
CFR No. 180.303 LEL = 5.0000 mg/kg
Status: TOX complete 10/24/86. ORD not scheduled. WHO last reviewed 1984.

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
2	Apples	2.000		2.53	0.075900
7	Bananas	0.300	3E2833	1.42	0.006390
23	Cantaloupe	2.000		0.52	0.015600
28	Celery	3.000		0.29	0.013050
33	Citrus fruits	3.000		3.81	0.171450
41	Cottonseed (oil)	0.200		0.15	0.000450
47	Cucumbers, not inc. pickles	2.000		0.34	0.010200
52	Eggplant	2.000		0.03	0.000900
71	Honeydew melons	2.000		0.03	0.000900
115	Peanuts	0.200		3.36	0.001080
116	Pears	2.000		0.26	0.007800
120	Peppers	3.000		0.12	0.005400
123	Pineapple	1.000		0.30	0.004500
131	Pumpkin, including squash	2.000	322912	0.11	0.003300
138	Root crop vegetables	0.100		11.00	0.016500
148	Soybeans (oil)	0.200		0.92	0.002760
155	Summer squash	2.000		0.03	0.000900
163	Tomatoes	2.000		2.87	0.086100
169	Watermelon	2.000		1.43	0.042900
171	Winter squash	2.000		0.03	0.000900
193	Mint	10.000		0.03	0.004500

TMRC % ADI
0.007858 mg/kg/day (60kg BW, 1.5kg diet) 31.432000

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
9	Beans	3.000		2.04	0.391800000
22	Cabbage, sauerkraut	2.000		0.74	0.022200000
49	Cucurbits	2.000		2.84	0.085200000
56	Escarole/endive	10.000		0.03	0.004500000
67	Grapes, not including raisins	2.000		0.45	0.013500000
68	Corn, grain (field corn)	0.050		1.00	0.000750000

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
84	Lettuce	10.000		1.31	0.196500000

TMRC % ADI
0.014766 mg/kg/day (60kg BW, 1.5kg diet) 59.062000

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No new tolerances are listed in the file.

TMRC % ADI
0.014766 mg/kg/day (60kg BW, 1.5kg diet) 59.062000

F. TOXICOLOGY SUMMARY TABLES

TABLE A
GENERIC DATA REQUIREMENTS FOR

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	A	Yes	MRID:63011	No
81-2 - Acute Dermal -	TGAI	A	No		Yes
81-3 - Acute Inhalation Rat	TGAI	A	Yes	MRID: 66902 & 66903	No
81-4 Eye Irritation Rabbit	TGAI	A	No		Yes
81-5 - Dermal Irritation - Rabbit	TGAI	A	No		Yes
81-6 - Dermal Sensitization - Guinea Pig	TGAI	A	No		Yes
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	A	No		No 4/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	A	No		Yes 8/
Non-rodent	TGAI	A	No		Yes 8/

TABLE A
GENERIC DATA REQUIREMENTS FOR

a Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
58.135 Toxicology (Cont.)					
32-2 - 21-Day Dermal-	TGAI	A	No		Yes 6/
32-3 - 90-Day Dermal-	TGAI	A	No		No 7/
32-4 - 90-Day Inhalation -	TGAI	A	No		No 7/
32-5 - 90-Day Neurotoxicity-	TGAI	A	No		No 4/
CHRONIC TESTING:					
33-1 - Chronic Toxicity -					
Rodent	TGAI	A	No		Yes 8/
Non-rodent	TGAI	A	No		Yes 8/
33-2 - Oncogenicity Study -					
Rat	TGAI	A	No		Yes 8/
Mouse	TGAI	A	Yes	MRID: 76813	No
33-3 - Teratogenicity -					
Rat	TGAI	A	No		Yes 5/
Rabbit	TGAI	A	Yes	MRID: 63009	No
33-4 - Reproduction -	TGAI	A	No		Yes 9/

005858

TABLE A
GENERIC DATA REQUIREMENTS FOR

ta Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
58.135 Toxicology (continued)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A	No		Yes 10/
84-2 - Chromosomal Aberration	TGAI	A	No		Yes 10/
84-2 - Other Mechanisms of Mutagenicity (DNA Damage)	TGAI	A	Yes	MRID: 40594	No
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	A	No		Yes 11/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, RAdiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.

2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.

3/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard this standard.

4/ This study is not required since the test article is not an organophosphate.

5/ Data must be submitted no later than 12 months after the publication of this standard.

6/ Data must be submitted no later than 7 months after the publication of this standard.

005858

7/ Additional data are not required because of the nature of the expposure pattern.

8/ Data must be submitted no later than 42 months after the publication of this standard.

9/ Data must be submitted no later than 20 months after the publication of this standard.

10/ Data must be submitted no later than 10 months after the publication of this standard.

11/ Data must be submitted no later than 14 months after the publication of this standard.

005858

G. Bibliography

MRID No.

00028729 Han, J.C.Y.; Jackson, R.A.; Harvey, J., Jr. (1976) Metabolism of Oxamyl in the Rat. (Unpublished study received Jun 14, 1976 under 352-372; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:097651-B)

00040498 Belasco, I.J. (19??) Liver Microsomal Metabolism of Oxamyl. (Unpublished study received Jul 21, 1977 under 352-372; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 096301-I)

00040594 Shirasu, Y.; Moritani, M.; Watanabe, K. (1976) Oxamyl Mutagenicity Study Using Bacteria. (Unpublished study received Oct 21, 1976 under 6F1696; prepared by Institute of Environmental Toxicology, Toxicity Dept., submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:095326-C)

00063009 Hoberman, A.M.; Mossburg, F.A.; Wolfe, G.W.; et al. (1980) Teratology Study in Rabbits: Oxamyl: Project No. 201-545; HLO-0801-80. Final rept. (Unpublished study received Nov 21, 1980 under 352-371; prepared by Hazleton Laboratories America, Inc., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 099754-B)

00063011 Dashiell, O.L.; Hinckle, L. (1980) Oral LD50 Test in Rats--EPA Proposed Guidelines: Haskell Laboratory Report No. 775-80. (Unpublished study received Nov 21, 1980 under 352-371; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:099754-D)

00066893 Lee, K.P. (1970) Oral ALD and Delayed Paralysis Test (White Leghorn Chickens): Haskell Laboratory Report No. 234-70. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-E)

00066894 Reinke, R.E. (1968) Eye Irritation Test: Haskell Laboratory Report No. 263-68. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-F)

00066896 Colburn, C.W. (1970) Acute Skin Absorption Toxicity Tests on Rabbits: Haskell Laboratory Report No. 282-70. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-H)

00066898 Hood, D.B.; Ellis, C.B. (1970) Acute Skin Absorption Toxicity Test on Rabbits: Haskell Laboratory Report No. 103-70. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-J)

00066900 Wells, L.A. (1968) Primary Skin Irritation and Sensitization Tests: Haskell Laboratory Report No. 146-68. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-L)

00066902 Tayfun, F.O. (1969) Acute Dust Inhalation Toxicity: Haskell Laboratory Report No. 280-69. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-M)

00066903 Tayfun, F.O. (1969) One-hour Inhalation Toxicity: Haskell Laboratory Report No. 281-69. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-O)

00066909 Culik, R.; Sherman, H. (1971) Teratogenic Study in Rats with S-Methyl-1-dimethylcarbamoyl-N-[(methylcarbamoyl)oxy] Thioformimidate (IMD-1410): Haskell Laboratory Report No. 5-71. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-U)

00066912 Sherman, H. (1971) Three-generation Reproduction Study in Rats with 1-(Dimethylcarbamoyl)-N-(methylcarbamoyloxy)-thioformimidic Acid, Methyl Ester [IMD-1410]: Haskell Laboratory Report No. 313-71. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092249-X)

005858

00076813 Adamik, E.R.; Criswell, M.K.; Mahler, S.C.; et al. (1981) Long Term Feeding Study in Mice with Oxamyl: Project No. WIL-77033; HLO-252-81. (Unpublished study received May 29, 1981 under 352-372; prepared by WIL Research Laboratories, Inc., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:070136-A; 070137; 070138; 070139; 070140; 070141; 070142; 070143)

00083352 Sherman, H.; Snee, D.; Carroll, K.; et al. (1972) Long Term Feeding Study in Rats and Dogs with 1-(Dimethylcarbamoyl)-N-(methylcarbamoyloxy)-thioformimidic Acid, Methyl Ester (IND-1410: Haskell Laboratory Report No. 37-72). Final rept. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL:092248-A)

00113396 Sherman, H. (1969) Antidote Study: Haskell Laboratory Report No. 322-69. (Unpublished study received Jan 5, 1972 under unknown admin. no.; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, DE; CDL:123332-R)

00113397 Holsing, G. (1969) Insecticide 1410 Antidotal Study--Monkeys: Insecticide D-1410-8: Project No. 201-236. Final rept. (Unpublished study received Jan 5, 1972 under unknown admin. no.; prepared by TRW, Inc., submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, DE; CDL:123332-S)

H. ONEL-LINERS #561A

Tox Chem No. Oxamyl; IND-1401 File Last Updated _____ Current Date 12/29/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results· LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD_{50}-rat; Haskell Lab. #775-80; 7/24/80	97.1% a.i.	099754	Male LD_{50} = 3.1 mg/kg (fasted) Female LD_{50} = 2.5 (fasted) Doses tested: 2, 3, 4, and 5 mg/kg	I	Minimum
Acute Dermal LD_{50}-rabbit Haskell Lab.# 282-70 12/30/80	95% Technical	112157	Very toxic through abraded skin. 50% a.i. in water at 90 mg/kg caused death. Only male rabbits tested.		Supple-mentary
Acute Dermal LD_{50}-rabbit Haskell Lab.#103-70; 3/5/70	purity not specified	112157	LD_{50} (male) > 5000 mg/kg (unabraded skin)		Supple-mentary
Acute Dust Inhalation-rat; Haskell Lab.# 280-69; 9/22/69 (4 hrs exposure).	95% Technical	245474	LC_{50} (male) = 0.064 mg/L Symptoms: salavation, lacrimation, exophthalmous, and fasciculationd.	I	Minimum
Acute Inhalation-rat (1 hr. exposure); Haskell Lab.# 281-69; 9/22/69	95% Technical	245474	LC_{50} (male) = 0.17 mg/L LC_{50}(female)= 0.12 mg/L Symptoms: salvation, lacrimation, exophthamous, and fasciculation.	I	Minimum
Primary Eye Irritation-rabbits: Haskell Lab.# 263-68; 11/18/68	purity not specified	245474	Marked constrition of the eye and some irritations.		Supple-mentary
Primary Skin Irritation-guinea pig; Haskell Lab. # 146-68; 10/14/68	purity not specified	245474	Caused severe systemic effects after application. Minor erythema was also observed.		Supple-mentary
Dermal Sensitization-guinea pig; Haskell Lab. # 146-68; 10/14/68	purity not specified	245474	4/7 test animals died. Effect at exposure sites were slight. Extreme toxicity of the material makes the sensitization potential relatively unimportant. The report contains only summary data.		Supple-mentary

Tox Chem No. Oxamyl, IND-1410 File Last Updated _____ Current Date 12/29/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Delayed Neurotoxicity-hens;	purity not specified	112157	No individual hen data and lack of negative control.		Invalid
13-Week Feeding Study-dogs; Hazleton Lab.# 201-239, MR-1202; 10/10/69	purity assumed to be 100%	092248	Doses tested: 50, 100, & 150 ppm. NOEL = 150 ppm Insufficient data.		Supplementary
90-Day Feeding Study-rats; Haskell Lab.# 308-69; 1969	purity not specified	092248	The report has no individual animal and histopathology data.		Invalid
Chronic Feeding Study-rats; Haskell Lab.#37-72 2/2/72	95% a.i.	092248	Doses tested: 50, 100, & 150 ppm. NOEL = 50 ppm LOEL = 100 ppm (decreased body weights). Insufficient data.		Supplementary
Chronic Feeding Study-dogs; Haskell Lab. # 37-72; 2/2/72	95% a.i.	092248	Doses tested: 50, 100, & 150 ppm. NOEL = 150 ppm (HDT). MTD has not reached and insufficient data.		Supplementary
Oncogenicity Study-mice; WIL Res. Lab. Inc., # WIL 77033, HLO-252-81; 5/29/81	97.1% a.i.	070136 to 070413	Doses tested: 25, 50, and 75 ppm which was decreased from 100 ppm. NOEL (chronic toxicity) = 25 ppm LOEL (chronic toxicity) = 50 ppm (decreased body weights) Tumor incidence was not increased even at 75 ppm (HDT).		Minimum
Teratogenicity Study-rats; Haskell Lab. # 5-71; 1971	purity not specific	112157	Doses tested: 50, 100, 150, & 300 ppm Maternal NOEL = 50 ppm Materanl LOEL = 100 ppm (decreased body weights). Only summary data.		Supplementary
Teratogenicity Study-rabbits; Hazleton Lab. America, Inc., # 201-405 10/80	97.1% a.i.	099754	Doses tested: 1, 2, & 4 mg/kg NOEL (developmental toxicity) = 4 mg/kg (HDT) Maternal NOEL = 1 mg/kg Maternal LOEL = 2 mg/kg		Minimum

Tox Chem No. Oxamyl, IND-1410 File Last Updated _____ Current Date 12/29/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
3-Generation Reproduction Study-rats; Haskell Lab. # 37-72; 2/2/72	95% a.i.	092248	Doses tested: 50, 100, & 150 ppm The F_0 animals were taken from the Chronic Feeding Study. Fetoxic NOEL = 50 ppm Fetoxic LOEL = 100 ppm (decreased weanling body weights). Insufficient data amd number of litters.		Supple-mentary
Mutagenicity/Host Mediated Gene Mutation Assay with S. typhimiruim in mice. Institute of Environ. Tox.; Study No.: not reported. 1976	93.7% a.i.		Negative Doses tested: 1 and 2 mg/kg Insufficient data.		Unaccep-table
Mutagenicity/DNA Damage/ Repair Assays with B. subtilis; Inst. Environ. Tox.; Study No.: not reported. 1976	93.7% a.i.		Negative Doses tested: 20, 100, 200, 500, 1000, & 2000 ug/disk.		Acceptable
Mutagenicity/ Gene Mutation Assays with S. typhimirium and E. coli; Inst. Environ. Tox.; no study No.; 1976	93.7% a.		Negative Doses tested: 10, 100, & 1000 ug/plate Insufficient data.		Unaccep-table
Metabolism Study-rats; E.I.du Pont de Nemours; Study No.: 352-372; 1976	93.7%		Within 72 hrs. of dosing approximately 70% of the administered dose (1.0 mg; 3.74 uCi) was excreted in urine and feces. Insufficient # of test animals.		Supple-mentary
Metabolism - Rat Liver Homogenate; E.I. du Pont de Nemours; Study #: 352-372; 19??	93.7%		Dose tested: 0.5-1.0 gm of radio-Oxamyl was incubated. In-vitro metabolism study.		Supple-mentary

005858

I. Study Type: Acute Oral Toxicity
(Guideline § 81-1)

Citation: Dashiell, O. L.; Hinckle, L. (1980). Oral LD_{50} Test in Rats--EPA Proposed Guidelines: Haskell Laboratory No. 775-80. (unpublished study received Nov 21, 1980, under 352-371; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 099754-D)

EPA Identification No.: MRID No. 63011
Accession No. 099754
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 775-80

Study Date: July 24, 1980

Material Tested: An aqueous solution of 97.1% Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; (Oxamyl)

Test Animal: ChR-CD rats; 10 animals/sex/dose.

Reviewer: Whang Phang, Ph.D. 11/25/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 11.24.86
Section Head
Toxicology Branch/HED

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 000804), and currently validated by this reviewer. The conclusions drawn by this reviewer are similar to those of Backus. An excerpt of the Backus review is appended, and the following details are to be added to the previous review:

1). The test agent was administered by intragastric intubation to fasted rats.
2). Clinical signs resulting from cholinesterase inhibition were observed in all test animals.

005858
000844
005858

1. Oral LD50 in Rats. Haskell Laboratory Report No. 775-80. MR No. 0581-872. Date issued: September 29, 1980. Material tested: 97.1% active.

Procedure: After an initial range-finding study using dosage levels of 1.5-12 mg/kg (all rats receiving more than 3.4 mg/kg died), groups of 10M rats received dosage levels of 2.0, 3.0, 4.0 and 5.0 mg/kg of the technical administered as 0.01-0.03% solutions in water, while groups of 10F rats received dosage levels of 1.0, 2.0, 2.1, 2.4, 2.5 and 3.0 mg/kg, administered as 0.005-0.02% solutions in water. Animals were observed for 14 days.

Results:

Dose mg/kg	Mortalities M	F
1.0	-	0/10
2.0	1/10	0/10
2.1	-	0/10
2.4	-	4/10
2.5	-	7/10
3.0	3/10	8/10
4.0	9/10	-
5.0	10/10	-

Oral LD50 (male rats) = 3.1 mg/kg with 95% confidence limits of 2.6-3.5 mg/kg
Oral LD50 (female rats)=2.5 mg/kg with 95% confidence limits of 2.4-2.7 mg/kg.

Symptoms: tremors, fasciculations, exophthalmos, salivation, chromodacryorrhea, stained faces and perineal areas, slight weight loss.

Pathology: Lungs slightly heavy to heavy, moist, dull to dark red, hyperinflated with colored foci and mottling. Livers were dark red and slightly heavy to heavy in many rats. Seven males in highest dosage group showed heart that was in systole at time of death. 1M, 2F had corneal opacity in eyes. All deaths occurred within 2 days of dosage.

Study Classification: Core Minimum Data (some ambiguity as to correlation - if any - between pathological findings and dosage levels at which they occurred).

Product Classification: Tox. Cat. I (Expected oral LD50's for a 42% Vydate formulation would be 7.2 mg/kg for male rats and 5.8 for female rats).

005858

I. Study Type: Acute Dermal
(Guideline § 81-2)

Citation: Hood, D.B., Ellis, C.B. (1970). Acute Skin Absorption Toxicity Test on Rabbits: Haskell Laboratory Report No. 103-70. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-J).

EPA Identification No.: MRID No. 66898
Accession No. 245474
Caswell No. 561A

Sponsor: I. du Pont de Nemours & Co., Inc.
.mington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Delware 19711

Study No.: 103-70

Study Date: March 6, 1970

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate (Oxamyl); purity was not specified.

Test Animal: Male rabbits; number of experimental animals not reported.

Reviewer: Whang Phang, Ph.D. 11/25/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 11/21/86
Section Head
Toxicology Branch/HED

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The report of this study contained only summary-like data. The conclusions drawn by this reviewer are similar to those derived by Backus. An excerpt of the Backus review is appended.

3. Acute Skin Absorption Toxicity Test on Rabbits. Haskell Laboratory Report No. 103-70. MR No. 581. Dated March 6, 1970.

Procedure: Groups containing an unknown number of male rabbits (or perhaps consisting of individual male rabbits) received a 24-hr occluded dermal exposure (intact skin only) to dosage levels of 5,000, 1,500 or 450 mg/kg of the technical active, applied as either a 33.3 or 25% w/w mixture with "hydrophilic ointment," with subsequent 14-day observation.

Results: No mortalities. All dosage levels showed initial weight loss. Highest exposure group (or possibly individual animal) showed apprehension, inactivity, slow breathing, soft mucoid feces and other symptoms with recovery at 7 days.

Study Classification: Core Supplementary Data (only males were tested; no indication as to how many animals there were in each group; no data or information as to composition of "hydrophilic ointment," no dermally abraded subjects tested).

005858

I. Study Type: Acute Dermal
(Guideline § 81-2)

Citation: Colburn, C.W. (1970). Acute Skin Absorption Toxicity Tests on Rabbits: Haskell Laboratory Report No. 282-70. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-H).

EPA Identification No.: MRID No. 66896
Accession No. 245474
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 282-70

Study Date: Dec 30, 1970

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; 95% technical grade.

Test Animal: Male rabbits; number of experimental animals not identified.

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
12/4/86

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The report of this study contained insufficient information. The conclusions drawn by this reviewer are similar to those derived by Backus. An excerpt of the Backus review is appended.

4. Acute Skin Absorption Toxicity Tests on Rabbits. Haskell Laboratories Report No. 282-70. MR No. 581. Dated December 30, 1970.

Procedure: Male rabbits were given a 24-hr occluded dermal exposure to various dosage levels of the active, applied as either a 25% w/w mixture with "hydrophilic ointment," a 50% w/w mixture with water, or a 25% w/w mixture with propylene glycol. Rabbits with intact and abraded skin exposure sites were used, but at most only 1 of each was used at each dosage level for each mixture.

Results:

Composition of Test Material	Subjects with Intact or Abraded Skin	Highest Dosage Level at which a Subject Survived	Lowest Dosage Level at which a Subject Died.
25% active in "Hydrophilic Ointment."	Intact	3,400 mg/kg	5,000 mg/kg
25% active in "Hydrophilic Ointment."	Abraded	90 mg/kg	130 mg/kg
50% active in water.	Intact	1,500 mg/kg	2,250 mg/kg
50% active in water.	Abraded	1,000 mg/kg	90 mg/kg
25% active in propylene glycol.	Intact	200 mg/kg	130 mg/kg
25% active in propylene glycol	Abraded	90 mg/kg	60 mg/kg

"Animals treated with hydrophilic ointment, especially on abraded skin, showed more clinical sign... after washing than in the preceding 24-hour exposure. Evidently the compound in H.O. was not readily absorbed, but with the addition of water during washing, more of the compound was absorbed."

Symptoms and Pathology: consistent with anticholinesterase effects.

Study Classification: Core Supplementary Data

005858

I. Study Type: Acute Inhalation
(Guideline § 81-3)

Citation: Tayfun, F.O. (1969). Acute Dust Inhalation Toxicity: Haskell Laboratory Report No. 280-69. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-N).

EPA Identification No.: MRID No. 66902
Accession No. 112157
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 280-69

Study Date: Sept 22, 1969

Material Tested: 95% Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; (Oxamyl) (Technical grade)

Test Animal: ChR-CD rats; 6 males/dose.

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The conclusions drawn by this reviewer are similar to those of Backus. An excerpt of the Backus review is appended.

5. Acute Dust Inhalation Toxicity. Haskell Laboratory Report No. 280-69. MR No. 581. Dated September 22, 1969.

Procedure: Groups of 6M ChR-CD rats, 250-260 g, were exposed (heads only) for 4 hrs to concentration averages of 0.090, 0.077, 0.066, 0.053 and 0.020 mg/L of 95% active technical material. Particles had a mass median diameter of 3.5 u with a dispersion of 2.1. Some test subjects were subsequently observed for 14 days; others were used in serial sacrifices.

Results:

Measured Exposure Level (mg/L)	Mortality (Males only)
0.090	6/6
0.077	5/6
0.066	3/6
0.053	1/6
0.020	0/6

Inhalation LC50 (male rats) for 4-hr exposure = 0.064 mg/L, with 95% confidence limits of 0.057-0.072 mg/L.

Symptoms: Salivation, lacrimation, exophthalmous, fasciculations (typical of anticholinesterase activity).

Study Classification: Core Minimum Data (although only males were used, and exposure was for 4 hrs, the low LC50 for this material is such that this product can be classified; see also the study below).

Product Classification: Tox. Cat. I

005858

I. Study Type: Acute Inhalation
(Guideline § 81-3)

Citation: Tayfun, F.O. (1969). One-Hour Inhalation Toxicity: Haskell Laboratory Report No. 281-69. (Unpublished study received Nov 29, 1972 under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-0).

EPA Identification No.: MRID No. 66903
Accession No. ~~112157~~ 245474
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 281-690

Study Date: Sept 22, 1969

Material Tested: 95% Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; 95% a.i.

Test Animal: ChR-CD rats; 6 animals/sex/dose.

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
11.24.86

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by the reviewer. The conclusions drawn by this reviewer are similar to those of Backus. An excerpt of the Backus review is appended.

6. One-Hour Inhalation Toxicity. Haskell Laboratory Report No. 281-69. MR No. 581. Dated September 22, 1969.

Procedure: Groups of 6M (250-260 g) ChR-CD rats were exposed to measured concentrations of 0.21, 0.18, 0.13 and 0.14 mg/L (head exposure only). Groups of 6F (210-218 g) rats of the same strain were similarly exposed to concentrations of 0.14, 0.12 and 0.10 mg/L. Exposures were for 1 hr, with subsequent 14-day observation. Mass median diameter was 3.5 u, with a dispersion of 2.1.

Results:

Measured Exposure Level (mg/L)	Mortality M	F
0.21	5/6	-
0.18	4/6	-
0.16	2/6	-
0.14	0/6	5/6
0.12	-	4/6
0.10	-	1/6

LC50 (male rat) = 0.17 mg/L with 95% confidence limits 0.151-0.193 mg/L.
LC50 (female rat)=0.12 mg/L with 95% confidence limits 0.109-0.132 mg/L.

Most deaths occurred during exposure.

000844

Clinical signs: typical of a cholinesterase inhibitor.

Study Classification: Core Minimum Data

Product Classification: Tox. Cat. I (for a 95% product; in theory a product containing 42% active would have an inhalation LC50 of about 0.33 mg/L and ~~would~~ when be in toxicity category II. However, given the hazards of this material we can accept the applicant's toxicity category I labeling by this exposure route).

005858

I. Study Type: Primary Eye Irritation
(Guideline § 81-4)

Citation: Reinke, R.E. (1968). Eye Irritation Test: Haskell Laboratory Report No. 263-68. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-N).

EPA Identification No.: MRID No. 66894
Accession No. 245474
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 263-68

Study Date: Nov 18, 1968

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; (Oxamyl); the report did not identified the purity of the test agent.

Test Animal: Rabbits

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
11.28.86

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The report of this study contained only summary data. The conclusions drawn by this reviewer are similar to those derived by Backus. An excerpt of the Backus review is appended.

7. Eye Irritation Test. Haskell Laboratory Report No. 263-68, MR NO. 581. Study dated November 18, 1968.

Procedure: 10 mg of powder (95% technical) was instilled in one eye of each of 2 rabbits, with one eye subsequently washed out, the other remaining unwashed. Two additional rabbits each had one eye treated with 0.1 ml of a 10% w/v solution of technical dissolved in propylene glycol, with one eye subsequently washed, the other remaining unwashed. Ocular effects were observed at 15 minutes, 1, 2, 3, and 4 hrs, and 1, 2, 3 and 7 days.

Results: Eyes in which the powder was instilled showed marked constriction shortly afterwards, with effects lasting up to 1 day later. There was minimal redness 1 day after instillation, and eyes had apparently recovered by day 2. Marked constriction was also noted in eyes treated with 0.1 ml 10% solution, with recovery by 3 days.

Study Classification: Core Supplementary Data

005858

I. Study Type: Primary Skin Irritation
(Guideline § 81-5)

Citation: Wells, L.A. (1968). Primary Skin Irritation and Sensitization Tests: Haskell Laboratory Report No. 146-68. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-N).

EPA Identification No.: MRID No. 66900
Accession No. 245474
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 146-68

Study Date: Oct 14, 1968

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate (Oxamyl), whose purity was not identified in the report.

Test Animal: Guinea pigs (male)

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
11.24.86

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The conclusion drawn by this reviewer are similar to those derived by Backus. An excerpt of the Backus review is appended.

8. Primary Skin Irritation and Sensitization Tests. Haskell Laboratory Report No. 146-68. MR NO. 581. Dated October 14, 1968.

Procedure: Groups of 10M guinea pigs were exposed to 0.05 ml aliquots of either 50% w/v of the 95% technical in propylene glycol, 25% w/v of the 95% technical in propylene glycol, or 25% w/v of 95% technical in 1:1 acetone-dioxane containing 13% guinea pig fat. Aliquots were applied to both shaved and intact skin.

Results: Severe systemic effects were seen, particularly after application to abraded skin. Relatively minor erythema was observed at the sites.

Study Classification: Core Supplementary Data

000844

Byron T. Backus 8/24/81

Byron T. Backus
IRB/TSS

005858

005858

I. Study Type: Dermal Sensitization
(Guideline § 81-6)

Citation: Wells, L.A. (1968). Primary Skin Irritation and Sensitization Test: Haskell Laboratory Report No. 146-68. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-N).

EPA Identification No.: MRID No. 66900
Accession No. 245474
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 146-68

Study Date: Oct 14, 1968

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; (Oxamyl); purity of the test agent was not identified in the report.

Test Animal: Guinea pigs (male)

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
#2486

II. Conclusion:

This study was previously evaluated by B. T. Backus, IRB/TSS (Tox. Branch document No. 00084), and currently validated by this reviewer. The report of this study contained only summary data. The conclusions drawn by this reviewer are similar to those derived by Backus. An excerpt of the Backus review is appended.

8. Primary Skin Irritation and Sensitization Tests. Haskell Laboratory Report No. 146-68. MR NO. 581. Dated October 14, 1968.

Procedure:

In the sensitization study, a series of applications (~~probably 10~~) 9 of 25% technical were made to intact and abraded skin sites on each of ~~10~~ 7 guinea pigs. Another group of 5 guinea pigs received a series of 4 intradermal injections of 0.1 ml of 1.0% solution in propylene glycol.

Results:

4/~~10~~ 7 guinea pigs receiving the 25% material in the sensitization study, and 1/5 receiving the intradermal injections, died. Although statement is made that no sensitization was produced, there was moderate erythema for 4/6 animals in the topical study at abraded sites. However, the extreme toxicity of the material makes the sensitization issue relatively unimportant.

Study Classification: Core Supplementary Data

000844

Byron T. Backus 8/24/81

Byron T. Backus
IRB/TSS

005858

I. Study Type: Acute Delayed Neurotoxicity
(Guideline § 81-7)

Citation: Lee, K.P. (1970), Oral ALD and Delayed Paralysis Test (White Leghorn Chicken): Haskell Laboratory Report No. 234-70. (unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 099754-C).

EPA Identification No.: MRID No. 66893
Accession No. 112157
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Deleware 19711

Study No.: 234-70

Study Date: June 4, 1970

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate; (Oxamyl) (purity unspecified)

Test Animal: White Leghorn hens

Reviewer: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED
11/25/86

Secondary Reviewer: Marcia van Gemert, Ph.D.
Section Head
Toxicology Branch/HED
11.24.86

II. Conclusion:

This study was evaluated in 1972 and was not given any core classification An excerpt of the previous review is appended. This reviewer has re-evaluated this neurotoxicity study and found numerous deficiencies such as lack of negative control hens, individual hen data, and any indication of the purity of the test chemical. The study is found to be invalid.

Oral ALD and Delayed Paralysis (234-70) - The test material as a 1% suspension was administered in single doses directly into the crops of hens approximately 1 year old. A few minutes prior to dosing with the test compound, the chickens, except those used to determine the ALD, received IM injections of 0.5 mg/kg atropine. The ALD was found to be 40 mg/kg. The delayed paralysis test demonstrated the following signs: After administration of 20 and 40 mg/kg of test material with IM injection of 0.5 mg/kg atropine there was sudden depression, lethargy, ruffed feathers, slight respiratory difficulty, ataxia, and incoordination. After 12 hours no clinical signs of abnormality were observed, egg production was normal. There were no compound-related histopathological changes reported. Mortality ratio was 0/5 for both 20 mg and 40 mg/kg test levels.

005858

I. Study Type: Subchronic Oral
(Guideline § 82-1)

Citation: Holsing, G.C. and Voelker, R.W. (1969) 13-Week Oral Administration—Dog. Project No. 201-239. MR-1202. (Unpublished study received Nov 29, 1972, under 3G1316; prepared by TRW, Inc., submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-V).

EPA Identification No.: MRID No. 66912
Accession No. 092248
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Hazleton Laboratories, Inc. (A subsidiary of TRW,Inc.)
P.O.Box 30
Fall Church, VA 22046

Study No.: 201-239

Study Date: Oct 10, 1969

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate (Oxamyl), whose purity was assumed to be "100% active"

Test Animal: Beagle dogs

Reviewer: Whang Phang, Ph.D. 12/22/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 12-22-86
Section Head
Toxicology Branch/HED

II. Conclusion: Although dietary administration of Oxamyl to beagle dogs at concentrations of 50, 100, and 150 ppm has not demonstrated any compound related effects, the study has many deficiencies. (1) No brain or spinal cord were examined histologically. (2) No brain or blood cholinesterase levels were measured. (3) The test agent was never analyzed for its identy or purity, and it was assumed to be "100% active". (4) The test animals could have tolerated higher doses, and the maximum tolerated dose was not reached.

The study is classified as supplementary.

III. Materials and methods:

Oxamyl (white powder whose purity was assumed to be 100%) was orally administrated in diet to groups of beagle dogs (4/sex/dose) at nominal concentrations of 0, 50, 100, and 150 ppm for 13 weeks. During the study food consumption, body weight, and clinical observations were recorded. At the end of the study, gross necropsies were performed on all dogs. Various organs were weighed and examined. Clinical chemistry and hemotology studies were carried out. Histopathology was carried out according to the EPA guidelines for subchronic toxicity studies.

IV. Results:

Values of mean body weights and food consumptions of treated animals were comparable to those of the controls. No clinical signs of cholinesterase inhibition were reported. There were no changes in the parameters of clinical biochemistry and hematology in treated animals relative to controls. Histopathology examinations of different tissues did not show any consistent changes relative to the controls. Based upon the limited data derived from this study, the NOEL in dogs is 150 ppm (HDT). However, the test animals could have easily tolerated higher doses, and maximum tolerated dose had not been reached.

005858

I. Study Type: Subchronic Oral
(Guideline § 82-1)

Citation: Snee, D.A. and Sherman, H. (1969). 90-Day Feeding Study in Rats with 1-(Dimethylcarbamoyl)-N-(methylcarbamoyloxy)-thioformimidic acid, Methyl Ester IND-14101: Haskell Laboratory Report No. 308-69. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 092249-W).

EPA Identification No.: MRID No. 66911
Accession No. 092248
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Delware 19711

Study No.: 308-69

Study Date: 1969

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate (Oxamyl), whose purity was specified.

Test Animal: Rats (Charles River)

Reviewer: Whang Phang, Ph.D. 12/22/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 12/22/86
Section Head
Toxicology Branch/HED

II. Conclusion:

This study contains several deficiencies which include (1) no individual animal data, (2) no histopathology data, and (3) no specification on purity of the test agent. The absence of individual animal data and the histopathology data prelude appropriate evaluation of the study. This study is classified as invalid, and a detailed evaluation report will not be prepared.

42

005858

Reviewed by: Whang Phang, Ph.D. Whang Phang 12/17/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert Marcia van Gemert 12/17/86
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding in Rats TOX. CHEM. NO.: 561A

ACCESSION NUMBER: 092248 MRID NO.: 83353

TEST MATERIAL: Methyl N', N'-dimethyl-N-[(methtlcarbamoyl)oxy]thiooxamimidate

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): 37-72

SPONSOR: E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine Newark, Del

TITLE OF REPORT: Long Term Feeding Study in Rats and Dogs with 1-(Dimethyl-carbamoyl)-N-(methylcarbamoyloxy)-thioformimidic Acid, Methyl Ester (IND-1410)

AUTHOR(S): H. Sherman, D. Snee, K. Carroll, et al.

REPORT ISSUED: Feb 2, 1972

CONCLUSIONS:

Based upon the reported data, oral administration of Oxamyl at concentration of 100 and 150 ppm caused decreases in body weights of both male and female rats. Histopathologic changes in treated animals were comparable to those of the controls. The NOEL for chronic toxicity was 50 ppm; LOEL, 100 ppm.

Classification: Core-Supplementary. The study and has many deficiencies; for example, missing histopathology data and insufficient clinical chemistry study. The study can not be upgraded, and it must be repeated.

005858

INERT INGREDIENT INFORMATION IS NOT INCLUDED

A. MATERIALS:

1. Test compound: Oxamyl; Description: powder; Batch #: none given; Purity: 95.0%; contaminants: [redacted]

2. Test animals: Species: Rats; Strain: ChR-CD; Age: not given; however, judging from the body weights the animals were approximate 6 weeks old. body Weight: 140 gm; Source: Charles River.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months male	female	Interim Sac. 12 months male	female
1 Cont.	0	30	30	6	6
1A Cont.	0	30	30	6	6
2 Low (LDT)	50	30	30	6	6
3 Mid (MDT)	100	30	30	6	6
4 High(HDT)	150	30	30	6	6

2. Diet preparation

Diet was freshly prepared each week and stored in the refrigerator until used. The treated food was analyzed.

3. Animals received food and water ad libitum.

4. Statistics:

The report did not state any statistical procedure which was applied.

5. Quality assurance: No quality assurance statement was included in the report.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected "regularly" for signs of toxicity and mortality.

A). Toxicity:

Based upon the reported data, there were no signs of toxicity which could be attributed to the administration of Oxamyl.

B). Mortality (survival):

The data indicate that the survival rates of 100 and 150 ppm treated males and females were better than the corresponding controls (see attachment A).

2. Body weight

Animals were weighed once a week for 7 months and once every other week for the remainder of the first year. For the second year, the animals were weighed monthly. The average body weights and body weight gains of the test animals are presented in the following table.

Average Body Weights (gm) of Oxamyl Treated Animals

	Control I	Control IA	50 ppm	100 ppm	150 ppm
Male	799	806	745	748	678
Female	640	634	580	466	418

There were decreases in body weights of both treated male and female rats, and the decreases in mid and high dose females were statistically significant ($p < 0.05$) when compared to contols.

3. Food consumption and compound intake

Total Food and Compound Intake in Oxamyl Treated Animals

	Control I	Control IA	50 ppm	100 ppm	150 ppm
Food (gm)					
Male	17,888	17,298	17,760	17,972	16,695
Female	13,601	14,477	14,052	13,131	12,487
Compound (mg/kg/day)					
Male			1.64	3.30	5.07
Female			1.67	3.87	6.16

Total food consumption was also decreased in 150 ppm females relative to that of the controls.

4. Ophthalmalogical examinations

Ophthalmalogical examinations were not performed.

005858

5. Blood was collected before treatment and at 1, 3, 6, 9, 12, 18, and 12 months for hematology and clinical analysis from 5 males and 5 females. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
	Platelet count*		Reticulocyte count
	Blood Clotting Measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

The data did not indicate any difference between the control and the treated animals.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*		Blood urea nitrogen*
	Phosphorous*		Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	Enzymes		Total Bilirubin*
x	Alkaline phosphatase		Total Serum Protein*
x	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
	Serum alanine aminotransferase (also SGPT)*		
	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
# Should be required for OP
° Not required for subchronic studies

No meaningful difference in the levels of alkaline phosphatase between the control and treated animals were detected. The average cholinesterase activities were decreased at 4 days after treatment for 150 ppm males; 8 days, for 150 ppm females. Subsequently, no changes in cholinesterase activities were observed. Failure to detect changes in cholinesterase activities in the treated animals after the 8th day may be due to improper sampling. Clinical chemistry and hematology should be carried out at 24 months also.

6. Urinalysis°

Urine was collected from fasted animals at 1, 3, 6, 9, 12, 18, and 24 months. The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	x	Glucose*
x	Volume*		Ketones*
	Specific gravity*		Bilirubin*
x	pH	x	Blood*
	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

The data indicate no difference in the values of urine volume, protein, glucose, and blood were observed between the control and treated animals.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	.Aorta*	x	.Brain*†
x	.Salivary glands*	x	.Heart*	x	Periph. nerve*#
x	.Esophagus*	x	.Bone marrow*	x	Spinal cord (3 levels)*#
x	.Stomach*	x	.Lymph nodes*	x	.Pituitary*
x	.Duodenum*	x	.Spleen*	x	Eyes (optic n.)*#
	.Jejunum*	x	.Thymus*		Glandular
	.Ileum*		Urogenital	x	.Adrenals*
x	.Cecum*	x	.Kidneys*†	x	Lacrimal gland#
x	.Colon*	x	.Urinary bladder*	x	Mammary gland*#
	.Rectum*	x	.Testes*†	x	.Parathyroids*††
x	.Liver*†	x	Epididymides	x	.Thyroids*††
x	Gall bladder*#	x	Prostate		Other
x	.Pancreas*		Seminal vesicle	x	Bone*#
	Respiratory	x	Ovaries*†	x	Skeletal muscle*#
x	.Trachea*	x	.Uterus*		Skin*#
x	.Lung*				All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

005858

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight

The data of organ weights and organ to body weights are appended

b. Gross pathology
No gross pathological changes were observed in treated animals relative to controls

c. Microscopic pathology

Non-neoplastic and neoplastic:

No difference in histopathological changes were found between control and treated animals

Discussion:

Based upon the data, orally administering Oxamyl at concentrations of 50, 100, and 150 ppm to rats decreased body weights of both males and females at mid and high dose. No other changes were observed. The NOEL is 50 ppm; LOEL, 100 ppm. The study has many deficiencies which include:

1). The report stated that there were 6 rats/sex/dose were placed on interim study, and these animals were sacrificed at 24 months. However, the histopathology data are not reported; these data must be submitted.

2). The data of this study was mixed in two other studies and presented in a rather confusing fashion.

3) Insufficient clinical chemistry study.

OXAMYL

Page _____ is not included in this copy.

Pages 49 through 51 are not included in this copy.

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.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005858

Reviewed by: Whang Phang, Ph.D. 12/19/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. 12.19.86
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding Study in Dogs TOX. CHEM. NO.: 561A

ACCESSION NUMBER: 092248 MRID NO.: 83352

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (95% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): 37-72

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine Newark, Del

TITLE OF REPORT: Long Term Feeding Study in Rats and Dogs with 1-(Dimethyl-carbamoyl)-N-(methylcarbamoyloxy)-thioformimidic Acid, Methyl Ester (IND-1410)

AUTHOR(S): H. Sherman, D. Snee, K. Carroll, et al.

REPORT ISSUED: Feb 2, 1972

CONCLUSIONS:

Oral administration of Oxamyl in dietary concentrations of 50, 100, and 150 ppm to beagle dogs produced no adverse effects. However, the highest dose in this study had not approached maximum tolerated dose (MTD), the report did not have histopathology data on interim sacrificed animals, and the numbers of test animals in the control and high dose groups were insufficient. Clinical chemistry parameters measured were extremely aparse.

This study is classified as supplementary.

A. MATERIALS:

INERT INGREDIENT INFORMATION IS NOT INCLUDED

1. Test compound: Oxamyl, Description: wettable powder
Batch # was not specified , Purity 95 %, contaminants: [redacted]

2. Test animals: Species: Dog , Strain: Beagle , Age: 1-2 yrs,
Weight: 8-16 kg , Source: not reported.

005858

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months male	Main Study 24 months female	Interim Sac. 12 months male	Interim Sac. 12 months female
1 Cont.	0	3	3	1	1
2 Low (LDT)	50	4	4	0	0
3 Mid (MDT)	100	4	4	0	0
4 High(HDT)	150	3	3	1	1

2. Diet preparation

Diet was freshly prepared each week and stored in the refrigerator until used. Samples of treated food were not analyzed for either stability or concentration.

3. Animals received food (containing Oxamyl) and water ad libitum.

4. Statistics - The statistical procedures utilized in analyzing the numerical data were not specified in either the Results or Procedures sections.

5. Quality assurance statements were not given.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily for signs of toxicity and mortality.

Toxicity/Mortality (survival): No compound related toxicity was observed in in any of the test animals. None of the test animals died during the study.

2. Body weight

Animals were weighed weekly for 24 months. Values of mean body weights were comparable between treated and control (for example, controls. 12.9 kg: high dose, 12.6 kg).

3. Food consumption and compound intake

There was no difference in food consumption between the control and treated dogs.

005858

4. Ophthalmalogical examinations: The examinations were not performed on test animals.

5. Blood was collected before treatment and at 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months for hematology and clinical analysis from test animals. The CHECKED (X) parameters were examined.

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
	Platelet count*		Reticulocyte count
	Blood Clotting Measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

No hematological changes were observed in treated animals relative to controls.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorous*	x	Cholesterol*
	Potassium*		Globulins
	Sodium*	x	Glucose*
	Enzymes		Total Bilirubin*
x	Alkaline phosphatase	x	Total Serum Protein*
x	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
	Serum alanine aminotransferase (also SGPT)*		
	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

There was marginal increase in the alkaline phosphatase in 150 ppm female dogs relative to the controls at 24 months (control, 2.4 Bessy unit; 150 ppm, 3.6 Bessy unit). No changes were found in any other parameters.

5.1

005858

6. Urinalysis°

Urine was collected from animals at 12 and 24 months. The CHECKED (X) parameters were examined.

X		X	
	Appearance*	x	Glucose*
x	Volume*	x	Ketones*
	Specific gravity*	x	Bilirubin*
x	pH	x	Blood*
	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

There was an increase in the amount of protein excreted in the urine in 150 ppm females at 24 months (control, 35 g/24 hr; 150 ppm, 259 g/24 hr). No meaningful changes were found in any other measurements.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	.Aorta*	x	.Brain*†
x	.Salivary glands*	x	.Heart*	x	Periph. nerve*#
x	.Esophagus*	x	.Bone marrow*	x	Spinal cord (3 levels)*#
x	.Stomach*		.Lymph nodes*	x	.Pituitary*
x	.Duodenum*	x	.Spleen*	x	Eyes (optic n.)*#
	.Jejunum*	x	.Thymus*		Glandular
	.Ileum*		Urogenital	x	Adrenals*
x	.Cecum*	x	.Kidneys*†		Lacrimal gland#
x	.Colon*	x	.Urinary bladder*	x	Mammary gland*#
	.Rectum*	x	.Testes*†		.Parathyroids*††
x	.Liver*†	x	Epididymides	x	.Thyroids*††
x	Gall bladder*#	x	Prostate		Other
x	.Pancreas*		Seminal vesicle	x	Bone*#
	Respiratory	x	Ovaries*†	x	Skeletal muscle*#
x	.Trachea*	x	.Uterus*		Skin*#
x	.Lung*				All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

No consistent changes in organ weights were found in treated animals compared to controls. Ratios of organ to body weight were not reported.

b. Gross pathology: Findings of gross pathology were not reported.

c. Microscopic pathology:

1) Non-neoplastic: There seemed to be a marginal increase in the incidence of interstitial nephritis in 150 ppm females (controls, 0/3; 150 ppm, 2/3). However, the biological significance of this observation could not be determined because the number of dog in this dose group was so small (3 animals).

2). Neoplastic: No increase in neoplastic lesions were observed in treated animals.

D. DISCUSSION:

The experimental data indicate that orally administered Oxamyl to beagle dogs at concentrations of 50, 100, and 150 ppm did not produce biologically significant effects. The author of the report claimed that "there was a suggestion that IND-1410 may have had an effect on the liver at the highest dietary level, 150 ppm". According to the histopathology data (Table XLIII of the submission, MRID # 83353), there was no such effect at all. The liver lesions as presented in the report are the following:

	Male		Female	
	Control	150 ppm	Control	150 ppm
Liver				
Microgranuloma with hemosiderosis	0/3	1/3	1/3	[illegible]
Portal cellular infiltration	1/3	2/3	3/3	3/3

If there were any toxic effects, kidney lesion in high dose females (interstial nephritis: control, 0/3; high dose, 2/3) might be better supported because increased amounts of protein were found in the urine relative to the controls. However, due to small number of animals in both control and high dose groups, the biological significance of this finding is difficult to determine.

The study has several deficiencies.(1) Based upon the data on body weights, mortality, and other parameter, the highest dose used in this study has not approached maximum tolerated dose. (2) The report is lacking in histopathology data on the interim sacrificed animals. (3) The numbers of animals in the control and high dose groups were not sufficient (3 dogs/group). The "Core Study Guidelines" requires at least 4 dogs per dose. (4) The clinical chemistry parameters measured were extremely sparse.

Reviewed by: Whang Phang, Ph.D. 12/19/86
Section , Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III. Tox. Branch (TS-769C) 12.19.86

005858

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity Study in Mice TOX. CHEM. NO.: 561A

ACCESSION NUMBER: 070136-A - 070143 MRID NO.: 76813

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (97.1% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): WIL-77033; HLO-252-81

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: WIL Research Laboratories, Inc.,
3154 Exon Ave.
Cincinati, Ohio 45241

CITATION: Adamik, E.R.; Criswell, M.K.; Mahler, S.C.; et al. (1981) Long Term Feeding Study in Mice with Oxamyl: Project No. WIL-77033; HLO-252-81. (Unpublished study received May 29, 1981 under 352-372; prepared by WIL Research Laboratories, Inc., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 070136-A, 070137, 070138, 070139, 070140, 070141, 070142, 070143).

CONCLUSIONS:

Oral administration of Oxamyl at dietary concentrations of 25, 50, and 75 ppm to CD-1 mice decreased body weights of the treated mice. Other pathological changes were either comparable to those of the controls or not treatment related.

Based upon the data, the NOEL for chronic toxicity in mice is 25 ppm; LOEL, 50 ppm. Oxamyl at 75 ppm (HDT) did not cause increase in tumor incidence.

This study is classified as core minimum.

005858

A. MATERIALS:

1. Test compound: Oxamyl; description: white powder; batch # 1063, purity 97.1%; contaminants: not listed.

2. Test animals: species: mice; strain: CD-1; age: approximately 3 weeks; weight: avg. 17 gm; source: Charles River Breeding Laboratories, Inc. Portage, Michigan

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months male	Main Study 24 months female	Interim Sac. months male	Interim Sac. months female
1 Cont.	0	80	80		
2 Low (LDT)	25	80	81†		
3 Mid (MDT)	50	81†	84†		
4 High(HDT)	100/75*	86†	88†		

* Due to excessive death of the treated animals at 100 ppm, this concentration was lowered to 75 ppm.
† Extra animals were added at the early part of the study.

2. Diet preparation

Diet was freshly prepared weekly and stored in the refrigerator until used. Samples of treated food were analyzed, but the results were submitted under a separate cover.

3. Animals received food (containing Oxamyl) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the data: ANOVA; Dunnetts test, Kolnogorov-Smirnov test, and life table analysis.

5. Quality assurance: All phases of the study were inspected according to the GLP regulations. Quality Assurance Statement was also submitted.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity, mortality, and behavior changes.

Toxicity/Mortality (survival):

During the initial phase of the study, the animals at mid and high dose groups died. The concentration of Oxamyl was reduced from 100 to 75 ppm, and extra animals were added to the mid and high dose groups. The survival rates of 75 ppm males and females were decreased, but they are not significantly different from that of the controls.

Ratios of Number of Survivals to Total Number of Mice in the Study

	Control	25 ppm	50 ppm	75 ppm
Males	38/80	35/80	30/81	32/88
Females	34/80	34/81	31/84	31/88

2. Body weight

Animals were weighed weekly for the first 6 months, once every other week for the next 6 months, and once a month until termination of the study. During the early parts of the study, the body weights of male and female mice in 50 and 75 ppm groups were decreased. The body weight decrease in mid and high dose males was statistically significant. For example, at 11 weeks the mean body weights were:

	Control	25 ppm	50 ppm	75 ppm
Males	34.6	34.9	32.7*	32.7*
Females	28.2	27.7	26.6*	27.3

The decrease in body weights of females in 50 and 75 ppm was sporadic whereas that in males persisted through out the major portion of the study.

005858

3. Food consumption and compound intake

The amount of food consumed in treated mice were not significantly different from that of the controls.

4. Ophthalmalogical examinations were not performed on test animals.

5. Blood was collected before treatment and at 1, 3, 6, 12, 18 months for hematology and clinical analysis from 10 animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpuscular volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood Clotting Measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

No meaningful changes in the parameters of hematology in treated animals relative to controls.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*		Blood urea nitrogen*
	Phosphorous*		Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	Enzymes		Total Bilirubin*
	Alkaline phosphatase		Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
	Serum alanine aminotransferase (also SGPT)*		
	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies

Clinical chemistry study was not required for the chronic-mouse feedig study in the presence of an available chronic feeding study in rats.

005858

6. Urinalysis°

Urine was collected from fasted animals at _____ months. The CHECKED (X) parameters were examined.

X		X	
| |	Appearance*	| |	Glucose*
| |	Volume*	| |	Ketones*
| |	Specific gravity*	| |	Bilirubin*
| |	pH	| |	Blood*
| |	Sediment (microscopic)*	| |	Nitrate
| |	Protein*	| |	Urobilinogen

* Required for chronic studies
° Not required for subchronic studies

Urinalysis is also not required for the chronic mouse study in the presence of an available chronic mouse study.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
|x|	Tongue	|x|	.Aorta*	|x|	.Brain*†
|x|	.Salivary glands*	|x|	.Heart*	|x|	Periph. nerve*#
|x|	.Esophagus*	|x|	.Bone marrow*	|x|	Spinal cord (3 levels)*#
|x|	.Stomach*	|x|	.Lymph nodes*	|x|	.Pituitary*
|x|	.Duodenum*	|x|	.Spleen*	|x|	Eyes (optic n.)*#
|x|	.Jejunum*	|x|	.Thymus*		Glandular
|x|	.Ileum*		Urogenital	|x|	.Adrenals*
|x|	.Cecum*	|x|	.Kidneys*†	| |	Lacrimal gland#
|x|	.Colon*	|x|	.Urinary bladder*	|x|	Mammary gland*#
| |	.Rectum*	|x|	.Testes*†	|x|	.Parathyroids*††
|x|	.Liver*†	|x|	Epididymides	|x|	.Thyroids*††
|x|	Gall bladder*#	|x|	Prostate		Other
|x|	.Pancreas*	|x|	Seminal vesicle	|x|	Bone*#
	Respiratory	|x|	Ovaries*†	|x|	Skeletal muscle*#
|x|	.Trachea*	|x|	.Uterus*	|x|	Skin*#
|x|	.Lung*			|x|	All gross lesions and masses*
x	Nose°				
x	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight

Mean Organ Weights (gm) of Oxamyl Treated Mice

	Control	25 ppm	50 ppm	75 ppm
Males				
liver	2.617	2.464	2.027	2.188
kidneys	0.854	0.908	0.861	0.932
heart	0.242	0.257	0.236	0.248
Females				
liver	2.006	2.112	2.067	1.948
kidneys	0.632	0.629	0.606	0.604
heart	0.221	0.219	0.205	0.205

Values of the mean liver weights appaeared to be decreased in treated males and those of kidneys appeared to be increased in males and decreased in females relative to those of the corresponding controls, but the changes in these two organs weights have been shown not to be treatment related (Attachment A). Similarly, the corresponding changes in the ratios of organ to body weight were not compound related.

b. Gross pathology

Gross pathological changes were comparable between the treated and control animals.

c. Microscopic pathology

1) Non-neoplastic

There was an increase in the incidence of glomerulosclerosis in all treated male mice when compared to the concurrent controls. However, this increase has been shown not to be compound related (Attachment A).

Incidence of Glomerulosclerosis in Oxamyl Treated Mice

	Control	25 ppm	50 ppm	75 ppm
Males	3/79	9/78	13/80	11/79
Females	5/79	10/79	13/79	4/77

2) Neoplastic

The data indicate that there was a higher incidence of pulmonary tumors in treated female than that of the controls. Similarly, the increase in the incidence of pulmonary tumors also has been shown not to be compound related (Attachment A). The following table presents the incidence of pulmonary tumor in female mice.

	Control	25 ppm	50 ppm	75 ppm
Adenomas	3/79	12/79	6/79	13/76
Adenocarcinomas	0/70	0/79	1/79	2/76
Combined	3/79	12/79	7/79	15/76

005858

Discussion:

Oral administration of Oxamyl at dietary concentrations of 25, 50, and 75 ppm to CD-1 mice decreased body weights in 50 and 75 ppm mice. Other pathological changes were either comparable to those of the controls or not treatment related. This study has been evaluated previously by three other reviewers in Toxicology Branch, and the final conclusions are all similar.

The NOEL for chronic toxicity in mice is 25 ppm; LOEL, 50 ppm. The highest dose of Oxamyl used in this study (75 ppm) appeared to have approach maximum tolerated dose based upon the body weight and survival rat data. Oxamyl at 75 ppm (HDT) did not cause biologically significant increase in tumor incidence.

005858

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oxamyl-Response to the Scientific Issues Raised in Dr. Gross' Memorandum Dated March 20, 1985

FROM: William B. Greear William B. Greear 6/17/85
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Albin B. Kocialski, Ph.D., Section Head ABK 6/17/85
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

The intent of this memorandum is to impartially address the scientific issues raised by Dr. Gross in his memorandum of March 20, 1985, in which he expresses concern over certain conclusions drawn in a Toxicology Branch memorandum dated June 23, 1981. This memorandum was an evaluation of the results of the study identified as "Long Term Feeding Study in Mice with Oxamyl"- Project No. WIL-77033, conducted by WIL Research Laboratories, Inc. Each of the scientific issues that were raised by Dr. Gross will be addressed below to determine if his concerns are justified and should receive additional attention. (The arguments presented within are more of a toxicological nature rather than of a purely statistical nature. The statistical analysis is appended.)

Issue No. 1 - Concern is expressed that there was a dose-related increase in pulmonary tumors in treated female mice.

The incidence of pulmonary tumors in CD-1 mice in the oxamyl study is presented below in the following table.

Incidence of Pulmonary Tumors in CD-1 Mice

Sex	Tumor Type	Control	25 ppm	50 ppm	75 ppm
Female	Adenoma	3/79 (3.8%)	12/79 (15.2%)	6/79 (7.6%)	13/76 (17.1%)
	Adenocarcinoma	0/79 (0%)	0/79 (0%)	1/79 (1.3%)	2/76 (2.6%)
	Combined	3/79 (3.8%)	12/79 (15.2%)	7/79 (8.9%)	15/76 (19.7%)
Male	Adenoma	13/76 (17.1%)	9/78 (11.5%)	6/78 (7.7%)	9/75 (12.0%)
	Adenocarcinoma	1/76 (1.3%)	3/78 (3.8%)	0/78 (0%)	0/75 (0%)
	Combined	14/76 (18.4%)	12/78 (15.4%)	6/78 (7.7%)	9/75 (12.0%)

The data presented above show that all treated groups of female mice had a higher incidence of pulmonary tumors than the control group. There was also a slight increase in the number of female animals with malignant lung tumors (adenocarcinomas) in the 50 ppm and 75 ppm groups. In classical toxicology studies, it would be expected that a significantly greater response would be observed in the high-dose group than in the lowest dose group if the doses were well spaced. However, when the incidence of pulmonary tumors in females in the 75 ppm group is compared to the incidence in the 25 ppm group, no significant difference can be discerned. Additionally, the incidence of pulmonary tumors in the 50 ppm group is lower than that observed in the 25 ppm group and is not significantly different from the control group. This type of response, if a true compound-related response, is at least highly questionable. Therefore, the variability of these tumor types in this strain of mouse is further explored later in this text because this variability could very well account for this type of uneven response.

In treated male mice, there was a decrease in the incidence of pulmonary tumors when compared to control mice. It is also noted that malignant lung tumors occurred only in the male control and 25 ppm groups and not in the two higher dose groups. This is clearly not an oncogenic response. Of importance is the fact that the incidence of pulmonary tumors in these four groups of male mice varies considerably, i.e., between 7.7 percent and 18.4 percent. Therefore, it appears that (1) pulmonary tumors are relatively common in male mice, and (2) the incidence of pulmonary tumors in male mice varies considerably.

In order to supplement the above information obtained from the data presented in the study, additional information was sought on the background incidence of lung tumors in the female CD-1 mouse. It was considered that the use of historical control data would be quite useful as an aid in making the determination whether the response in treated female mice was excessively high, indicating a potentially oncogenic effect, or if the response in female control mice was unusually low.

Historical control data on the incidence of pulmonary tumors in the CD-1 mouse were submitted to R. B. Jaeger (Toxicology Branch/HED) for his evaluation of the oxamyl data base for the 1984 JMPR meeting. The information was transmitted in letters from Dr. P. W. Schneider, Jr. (Dupont) to R. B. Jaeger, dated August 29, 1984, and from Dr. W. D. Kerns (Haskell Laboratory) to J. C. Summers (Dupont) dated June 13, 1982. The data were obtained from seven Dupont studies conducted at IRDC and at Haskell Laboratory between September 26, 1977, and April 8, 1981. (The oxamyl mouse study was conducted between November 8, 1977, and November 17, 1979, at WIL Research Laboratories, Inc.) It would have been desirable to have obtained the historical control data from the laboratory that had conducted the study, but, this was either not done or the data were not obtainable, e.g., no studies may have been conducted at this laboratory using the CD-1 mouse during this period of time. It would have also been preferable to have had the incidence of each pulmonary tumor type provided rather than have the data categorized simply as "pulmonary tumors."

Data on the incidence of pulmonary tumors in control animals from the seven Dupont studies that were conducted during the same period of time as the oxamyl study are provided below.

Incidence of Pulmonary Tumors in Control CD-1 Mice

Study Date	Male	Female	Laboratory
9/26/77-9/25/79	16/80 (20%)	20/80 (25%)	IRDC
9/30/77-10/2/79	29/80 (36%)	25/80 (31%)	IRDC
1/25/79-2/3/81	19/79 (24%)	12/80 (15%)	Haskell
10/13/78-10/16/80	16/80 (20%)	12/79 (15%)	Haskell
9/30/78-9/12/80	13/79 (16%)	16/80 (20%)	Haskell
3/26/79-4/8/81	17/78 (22%)	9/79 (11%)	Haskell
6/27/78-7/2/80	9/80 (11%)	5/80 (6%)	Haskell

It is apparent from examining the contemporary historical control data that pulmonary tumors are relatively common in both the male and the female CD-1 mouse. In the female mouse, the incidence ranged from 6 percent to 31 percent and the mean was 17.7 percent.

Information on the incidence of pulmonary tumors in the CD-1 mouse is also available from the Food and Drug Administration which has, in the near past, required that lifetime feeding studies be conducted on a number of color additives in order to maintain their provisional listing. As a result, data on the incidence of tumors from 18 contemporary lifetime feeding studies using the CD-1 mouse have been compiled. In each study, two control groups containing 60 animals/sex/group were employed. Studies ranged from 22 to 25 months in duration and survival ranged from 18.5 percent to 52.1 percent with a mean of 38.9 percent at termination. Data on the incidence of pulmonary tumors were obtained on 2123 control female mice. The incidence of pulmonary adenomas ranged from 0 percent to 24.2 percent with a mean of 9.0 percent. The incidence of pulmonary carcinomas ranged from 0.8 percent to 15.8 percent with a mean of 6.5 percent. When combined, the incidence of pulmonary tumors ranged from 6.5 percent to 26.7 percent with a mean of 15.5 percent.

Additional information on the incidence of pulmonary tumors in the CD-1 mouse can be found in a number of journal articles. Homburger et al. (1975) reported on aging changes in 300 CD-1 HaM/ICR mice that were used as control animals in a 2-year carcinogenicity study. Mortality was 50 percent in females at 18 months. Useful necropsies were conducted on 102 females. The incidence of pulmonary adenomas and adenocarcinomas was 23.5 percent and 7.8 percent, respectively. The combined incidence of pulmonary adenomas and adenocarcinomas was 31.4 percent. More recently Sher et al. (1982) addressed the incidence of spontaneous tumors in Charles River CD-1 mice. The data were compiled from

24 groups of control CD-1 mice that were used in studies conducted on human drugs in the Department of Safety Assessment, Merck Sharp and Dohme Research Laboratories. Almost all studies were of 81 weeks duration. The total number of female mice necropsied was 1240. The incidence of pulmonary adenomas ranged from 0 percent to 41 percent with a mean of 14 percent. The incidence of pulmonary adenocarcinomas ranged from 0 percent to 12 percent with a mean of 3 percent. The combined mean incidence of pulmonary adenomas and adenocarcinomas was 17 percent. Gaunt et al. (1974) conducted a long-term toxicity study on Sunset Yellow FCF in the CD-1 mouse. The duration of the study was 80 weeks and female survival was 57 percent. The incidence of pulmonary adenomas in the female control mice was 12/47 or 25.5 percent.

Although statistical analysis of the data on the incidence of pulmonary tumors in oxamyl treated female mice (see attachment) indicates a dose-related trend, the biological significance of the data becomes questionable when the results are compared to those obtained in male mice, in which it was shown that the incidence of pulmonary tumors was relatively high and that the incidence varied considerably.

The response in female mice becomes less significant when the results are compared to historical control data on the incidence of pulmonary tumors in the female CD-1 mouse. The incidence of pulmonary tumors in the oxamyl female control mice is exceptionally low, i.e., 3.8 percent. The incidence is below the historical control range for studies conducted concurrently by the sponsor and is below the historical control range for studies conducted on color additives for the Food and Drug Administration. The incidence of pulmonary tumors in treated female mice, i.e., 17.1 percent, is not only well within the historical control range but also approximates the mean pulmonary tumor incidence for the historical control data.

After careful consideration of the information, it is concluded that it is unlikely that the apparent dose-related increase in pulmonary tumors in oxamyl treated female mice represents an oncogenic response. Rather, it appears that the incidence of pulmonary tumors in the control group was unusually low, by chance alone, creating the misconception that the incidence of pulmonary tumors in treated mice was high and compound induced.

Issue No. 2 - Concern is expressed that the incidence of glomerulosclerosis was increased in treated male mice in a dose-related manner.

The incidence of glomerulosclerosis in male and female mice is shown in the following table.

005858

Incidence of Glomerulosclerosis in CD-1 Mice

Sex	Control	25 ppm	50 ppm	75 ppm
Male	3/79 (3.8%)	9/78 (11.5%)	13/80 (16.3%)	11/79 (13.9%)
Female	5/79 (6.3%)	10/79 (12.7%)	13/79 (16.5%)	4/77 (5.2%)

As indicated in the table, the incidence of glomerulosclerosis is increased in all treated male groups when compared to the control group. Statistically, there is a dose-related trend in the incidence of glomerulosclerosis in males (see attachment). However, when the incidence of glomerulosclerosis in male animals in the 25 ppm group is compared to the incidence in the 75 ppm group, no significant difference is apparent. Further, males in the 50 ppm group have a higher incidence of glomerulosclerosis than those animals in the 75 ppm group. Once again, as in the case of the perceived increase in incidence of lung tumors in female mice, this type of response is unusual in that it would be expected that there would be a progressive increase in the incidence of glomerulosclerosis as the dose increased. When the data for female mice are examined, only the 25 ppm and 50 ppm groups appear to have an increase in the incidence of glomerulosclerosis. The incidence in the female 75 ppm group was actually less than the incidence in the control group. The incidence of glomerulosclerosis in female mice ranged from 5.2 percent to 16.3 percent. The data seem to indicate that glomerulosclerosis is relatively common in the CD-1 mouse, however, the incidence appears to be quite variable.

Another significant observation is that the number of males that died early and were diagnosed to have glomerulosclerosis were similar for each group. If the test material was responsible for the occurrence of glomerulosclerosis in the treated male mice, one would not only expect to see an increase in incidence, but also an increase in the extent and severity of the lesion which would be manifested as early deaths since glomerulosclerosis progressively leads to death. This did not occur.

Based on the above observations, it is concluded that it is unlikely that the increase in incidence of glomerulosclerosis in treated male mice is related to administration of the test material. Rather, the incidence of glomerulosclerosis was probably low in the control group, which can be attributed to normal variability of this lesion in the CD-1 mouse.

Issue Nos. 3 and 4 - Concern is expressed that there was a dose-related increase in the absolute and relative weight of the kidney in treated male mice.

The group mean values for the absolute and relative weight of the kidney are presented in the following table.

Kidney Weight of Male CD-1 Mice

Weight	Control	25 ppm	50 ppm	75 ppm
Absolute (g)	0.854	0.908	0.861	0.932
Relative (g/100 g BW)	2.2309 (2.2243)	2.3840 (2.3941)	2.3368 (2.3276)	2.4965* (2.4882)
Body (g)	38.2	38.0	36.8	37.3

* $p < 0.01$ (statistical analysis provided by the sponsor).

(There are minor differences between several of the mean organ weight values that were provided by the sponsor and those that have been calculated using data provided on individual animal pathology sheets. The calculated values appear within parentheses.)

Examination of the data on kidney weights reveals that in animals in the 75 ppm group the absolute weight of the kidney is marginally increased and the relative weight of the kidney is significantly (using the sponsor's statistical analysis) increased when compared to animals in the control group. However, there were no effects on kidney weight when analyzed by analysis of variance tests (see attachment). The absolute and relative weight of the kidneys in animals in the 50 ppm group are lower than those in the 25 ppm group. Additionally, the absolute weight of the kidneys in animals in the 50 ppm group is comparable to the absolute kidney weight of animals in the control group. The data do not appear to support the conclusion that there was a dose-related increase in the absolute and relative weight of the kidneys in treated animals that could be attributed to administration of the test substance. The response obtained for animals in the 75 ppm group does not therefore appear to be related to treatment.

Issue No. 5 - Concern is expressed that there was a dose-related decrease in the relative weight of the liver in treated male mice.

The group mean values for the absolute and relative weight of the liver are provided in the follcwing table.

Mean Liver Weight of Male CD-1 Mice

Weight	Control	25 ppm	50 ppm	75 ppm
Absolute (g)	2.617 (2.616)	2.464	2.027*	2.138
S.E.	.240	.192	.035	.083
Relative (g/100 g BW)	6.8603 (6.8147)	6.4318 (6.5004)	5.5149 (5.4818)	5.8707 (5.8410)
S.E.	.642	.437	.115	.221

* $p < 0.05$ (statistical analysis provided by the sponsor).

(There are minor differences between several of the mean organ weight values that were provided by the sponsor and those that have been calculated using data provided on individual animal pathology sheets. The calculated values appear within parentheses.)

On initial inspection of the data, there appears to be a general trend towards a decrease in the absolute and relative weight of the liver as the dose increases. Using the sponsor's statistical analysis, statistical significance is only achieved at the $p < .05$ level when the absolute weight of the liver for animals in the 50 ppm group are compared to those in the control group. When analyzed by analysis of variance tests, there are only marginal effects (significant at the $p = .08$ level) on liver weight (see attachment). It is also noteworthy that the standard errors for the mean liver weight of animals in the control and 25 ppm groups are relatively large in comparison to those obtained for the 50 ppm and 75 ppm groups. On examination of the individual liver weight data, it is clear that there are a few animals with abnormally high (greater than 6 g) liver weights. (It is also interesting to note that the next highest liver weight of 4.67 g occurs in control male number 6 which was diagnosed to have

reticulum cell sarcoma present in the liver.) All of these animals have significant pathological lesions of the liver, e.g., hepatocellular carcinoma, hepatoma or pericholangitis and microabscesses. These animals are numbers 10 and 38 (control group) and 204 and 227 (25 ppm group). Due to small group size (N = 30-38), the liver weights of these four animals contribute substantially to the mean liver weight of animals in the control and 25 ppm groups and make them appear to be increased in comparison to the mean liver weight of animals in the 50 ppm and 100 ppm groups. If these four animals were excluded from the calculations of the mean absolute and relative liver weights, there would be little difference among the groups as indicated in the following table.

Recalculation of Mean Liver Weight of Male CD-1 Mice

Weight	Control	25 ppm	50 ppm	75 ppm
Absolute (g)	2.302	2.234	2.027	2.188
Relative (g/100 g BW)	5.991	5.930	5.482	5.841

It seems likely that the presence of a couple of animals with pathologically large livers in each of the control and 25 ppm groups are responsible for the apparent dose-related decrease in the relative weight of the liver. In conclusion, the response obtained in males with respect to the apparent dose-related decrease in relative liver weight is probably not related to treatment.

Conclusion

1. The scientific issues raised by Dr. Gross concerning (1) the dose-related increase in the incidence of pulmonary tumors in treated female mice, (2) the dose-related increase in the incidence of glomerulosclerosis in treated male mice, (3) and (4) the dose-related increase in the absolute and relative weight of the kidney in treated male mice and (5) the dose-related increase in the relative weight of the liver in treated male mice do not appear to be of concern. Sufficient information is available to conclude that it is unlikely that these responses were related to treatment.

References

1. Dykstra, W. D. (1981). Long-term Feeding Study in Mice with Oxamyl. Memorandum to Jay Ellenberger, June 23, 1981.

2. Gaunt, I. F., Mason, P. L., Grasso, P., and Kiss, I. S. (1974). Long-term toxicity of Sunset Yellow FCF in mice. Food Cosmet. Toxicol. 12:1-10.

3. Gross, M. A. (1985). Oxamyl. Memorandum to Kevin Keany, March 20, 1985.

4. Homburger, F., Russfield, A. B., Weisburger, J. H., Lim, S., Chak, S. P., and Weisburger, E. K. (1975). Aging changes in CD-1 HaM/ICR mice reared under standard laboratory conditions.

5. Sher, S. R., Jensen, R. D., Bokelman, D. L. (1982). Spontaneous tumors in control F344 and Charles River-CD rats and Charles River CD-1 and B6C3HF1 mice. Toxicol. Letters 11(1-2):103-110.

6. WIL Research Laboratories, Inc. (1981). Long-term Feeding Study in Mice with Oxamyl. Project No. WIL-77033.

005858

I. Study Type: Teratogenicity Study in Rabbits
(Guideline § 83-3)

Citation: Hobermam, A.M.; Mossburg, P.A.; Wolfe, G.W.; et al.(1980). Teratology Study in Rabbits: Oxamyl: Project No. 201-545; HLO-0801-80. Pinal rept. (Unpublished study received Nov 21, 1980, under 352-371; prepared by Hazleton Laboratory America, Inc., submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.; CDL: 099754-B).

EPA Identification No.: MRID No. 63009
Accession No. 099754
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Hazleton Laboratory America, Inc.
9300 Leesburg Turnpike
Vienna, VA

Study No.: 201-405

Study Date: October, 1980

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamimidate (Oxamyl), 97.1% technical grade.

Test Animal: New Zealand White female rabbits

Reviewer: Whang Phang, Ph.D. 12/19/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 12.19.86
Section Head
Toxicology Branch/HED

II. Conclusion:

Based upon the reported data, orally administering Oxamyl at doses of 1, 2, and 4 mg/kg to pregnant rabbits did not produced developmental toxicity. The NOEL of developmental toxicity in rabbits is 4 mg/kg (HDT). The maternal LOEL is 2 mg/kg; NOEL, 1 mg/kg.

This study is classified as Core Minimum.

7

005858

III. Material and Methods:

Groups of New Zealand White female rabbits (17/dose) were artificially inseminated and orally administered Oxamyl (97.1% a.i.) at doses of 1, 2, and 4 mg/kg from day 6 through day 19. The day of insemination was designated as day 0. At day 29, the fetuses were delivered by cesaren section. The weight and length of each fetus were measeured. Each fetus was also examined for soft tissue and skeletal abnormalities. Gross pathology were carried out on the does. The number of corpora lutea per ovary, the number of implantation, resorption, live fetus, and dead fetus were recorded. A detailed description of the experimental procedures taken from the submission is appended.

IV. Results:

A). Maternal effects:

The data showed no treatment-related clinical signs in does. However, during the treatment period (days 6-19), does which received 2 and 4 mg/kg of Oxamyl showed statistically significant decreases in mean body weight changes when compared to controls (Table I).

TABLE I
Mean Maternal Body Weight and Weight Changes
in Oxamyl Treated Rabbits
(data taken from submission, MRID: 63009)

	Day(s)	Control	1 mg/kg	2 mg/kg	4 mg/kg
Mean Weight (gm)	0	3362.9 n = 17	3416.7 n = 15	3349.3 n = 15	3290.4 n = 13
	6	3420.9 n = 17	3482.7 n = 15	3409.0 n = 15	3403.5 n = 13
	19	3590.4 n = 17	3603.4 n = 14	3474.2 n = 15	3459.1 n = 13
	29	3728.8 n = 17	3747.5 n = 14	3631.3 n = 15	3677.7 n = 13
Mean weight changes (gm)	6-19	169.5	120.7	65.2*	55.6*

* statistically significant when compared to controls

The values of mean food consumption for mid- and high-dose groups were lower than that of the controls during the treatment period (control, 1.89 kg; mid dose, 1.68 kg; high dose, 1.64 kg), but they were not statistically different from that of controls. During the later part of the post treatment period the amount of food consumed among the controls and the treatment were comparable. In addition, the body weights of the treated animals were approaching those of the controls.

005858

B). Developmental Effects:

The data indicate that Oxamyl did not cause any increase in the incidence of soft tissue and skeletal abnomalities relative to controls. The report stated that there was a slightly higher incidence of resorptions in the mid- and high-dose groups when compared to control group (MRID: 63009)(Table II).

TABLE II
Mean Ovarian, Uterine and litter Data
in Oxamyl Treated Rabbits
(data taken from submission, MRID: 63009)

	Control	1 mg/kg	2 mg/kg	4 mg/kg
Number of does	17	17	17	17
Number of does pregnant	17	15	15	13
Mean number of:				
corpora lutea	11.1	9.9	11.1	9.8
implantations	7.4	7.0	7.0	7.0
resorptions	0.8	0.5	1.0	1.2
fetuses: -dead	0.0	0.0	0.1	0.0
-live	6.6	6.6	5.9	5.8
Indices calculated on per litter basis:				
mean implantation efficiency (%)	68.9	72.9	65.2	74.2
mean incidence of resorption (%)	10.4	8.7	15.9	24.8
Mean ovarian and uterine weights:				
-with fetuses	418.7	416.6	384.9	413.5
-without fetuses	62.4	62.3	59.7	53.3
Pre-implantation loss (%)†	33%	29%	37%	18%
Post-implantation loss (%)†	11%	7%	16%	17%

†: calculated by this reviewer from the submitted data

However, this slightly increased incidence of resoption was not be biologically significant. The reasons are as the following:

1). The increase in the high dose animals was largely contributed by two completely resorbed litters of which one litter had only one implantation and the doe of the other litter had consumed substantially less amount of food relative to the mean average food consumption of controls.

2). The values of mean number of resoption indicate very little difference between the treated and control animals (Table II)

3). The values of percent post-implantation loss also do not indicate a significant difference between treated and control rabbits.

Therefore, based upon the data presented above, the developmental toxcity NOEL is 4 mg/kg (HDT). The maternal LOEL is 2 mg/kg; maternal NOEL, 1 mg/kg.

OXAMYL

Page _____ is not included in this copy.

Pages 78 through 83 are not included in this copy.

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.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005858

I. Study Type: Teratogenicity Study in Rats
(Guideline § 83-3)

Citation: Culik, R. and Sherman, H. (1971). Teratogenic Study in Rats with s-Methyl-1-(Dimethylcarbamoyl)-N-(Methylcarbamoyloxy)-Thioformimidate, (IND-1410): Haskell Laboratory Report No. 5-71. (Unpublished study received Nov 29, 1972, under 3G1316; submitted by E. I. du Pont de Nemours & Co., Inc., Wilmington, Del. CDL: 092249-U).

EPA Identification No.: MRID No. 66909
Accession No. 112157
Caswell No. 561A

Sponsor: E. I. du Pont de Nemours & Co., Inc.
Wilmington, Del.

Testing Laboratory: Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road,
Newark, Delware 19711

Study No.: 5-71

Study Date: 1971

Material Tested: Methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamidate (Oxamyl), whose purity was specified.

Test Animal: Rats (ChR-CD)

Reviewer: Whang Phang, Ph.D. 12/19/86
Pharmacologist
Toxicology Branch/HED

Secondary Reviewer: Marcia van Gemert, Ph.D. 12.1986
Section Head
Toxicology Branch/HED

II. Conclusion:

This study contains several deficiencies. There were no individual animal data or analyses of the purity of the test agent and its stability in the diet. The test animals were from separate shipments at different times. Most importantly the report contains only summary data. These deficiencies prelude any accurate assessment for developmental toxicity of Oxamyl in rats. This study is classified as supplementary.

84

III. Materials and Methods:

Groups of female rats (26-28 animals/dose) were administered Oxamyl (95% a.i.) at nominal dietary concentrations of 0, 50, 100, 150, and 300 ppm from day 6 through day 15 of the gestation period. From day 16 to the end of the experiment (day 20), the Oxamyl treated animala were placed on control diet. Fetuses were delivered by cesarean section. The maternal uterine and ovarian tissues were examined. Approximately 2/3 of the fetuses from each litter were examined for skeletal abnormalities, and the remaining were examined for soft tissue anomalies.

IV. Results:

No clinical signs of toxicity were observed in any of the treated animals during the study. Based upon the limited data presented in the report, Oxamyl appeared to produced a decrease in average food consumptions and body weights in 100, 150, and 300 ppm Oxamyl treated dames.

No structural or functional abnormalities were observed in the fetuses. However, the study containes many deficiencies which preclude appropriate evaluateion of the developmental toxicity of Oxamyl in rats. The deficiencies include the following: (1) the report contains only summary data, (2) the test animals were from separate shipments and at different time intervals, (3) the purity and the stability of the test chemical were not analyzed, and (4) no gravid uterus weights were measured.

005858

Reviewed by: Whang Phang, Ph.D. 12/19/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) 12 1986

DATA EVALUATION REPORT

STUDY TYPE: 3-Generation Reproduction Study TOX. CHEM. NO.: 561A

ACCESSION NUMBER: 092248 MRID NO.: 83352

TEST MATERIAL: Methyl N', N'-dimethyl-N-[(methylcarbamoyl)oxy]thiooxamimidate (95% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): 37-72

SPONSOR: E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine Newark, Del

TITLE OF REPORT: The 3-generation reproduction was included in the following title: Long Term Feeding Study in Rats and Dogs with 1-(Dimethylcarbamoyl)-N-(methylcarbamoyloxy)-thioformimidic Acid, Methyl Ester (IND-1410)

AUTHOR(S): H. Sherman, D. Snee, K. Carroll, et al.

REPORT ISSUED: Feb 2, 1972

CONCLUSIONS:

The limited data indicate that Oxamyl caused only a decrease in body weights in the weanlings of mid and high dose groups. The study has many deficiencies which include insufficient number of litters, poorly written protocol, and insufficient data.

This study is classified as supplementary.

916

Materials and Methods:

Both male and female rats of the F_0 generation were taken periodically from the chronic feeding study (MRID: 83353). The number of animals used for mating in each generation was never stated in the report. These animals were then treated with Oxamyl for approximately 12 weeks. The females were housed with each of the three males (F_0) from the same treatment group of the chronic study for 5 days; after the females had been exposed to each male, the males were returned to the chronic study. The concentrations of the compound in the diet were 50, 100, and 150 ppm. After 21 day females were checked at least twice daily for birth of F_{1A} pups. The number of pups in each litter was reduced to 10. After approximately 1 week, the F_0 animals were mated as described above for a second time to produce F_{1B} litters. Then, all F_0 females were returned to the chronic study. F_{1A} pups were sacrificed after the F_{1B} litters were born. The F_{1B} litters litters were continued on the diets containing the test agent (no concentration levels were reported). When F_{1B} generation reached approximately 110 days, they mated as above to produce F_{2A} and F_{2b} litters. Similar process was repeated to yield F_{3A} and F_{3B} litters. At weaning 2 males and 2 females per litter in F_{3B} generation were selected from both control and highest concentration group for histopathology study. The protocol of the report is appended (Attachment A).

An additional study (diet-reversing) was carried out to ascertain whether the decrease in body weight was due to compound related or nutritional effects. At approximately weaning time, 20 male and 20 female pups were selected from five or more litters n the control group and high-dose dames. These animals were divided into two sub-groups (10/sex); one sub-group contiued on their respective diets. For the other sub-group, if the animals were selected from controls, they were placed on high-dose-Oxamyl diet while those selected from litters which received high-doseOxamyl diet were transferred to the control diets. The study was carried out for 8 weeks.

Results:

The indices of fertility, viability, gestation, and lactation as presented did not showed meaningful difference among controls and treated animals. Average body weights of weanlings of all generations in mid and high dose (100 ppm and 150 ppm) groups were decreased. The results from the diet-reversing study indicate that the decrease in male weanlings could be due to nutritional effects, but that with females was less convincing. The results are appended (Attachment B).

Discussion:

Although the limited data derived from this study appeared to indicate that Oxamyl caused only a decrease in body weights of the weanlings of 100 and 150ppm animals, numerous deficiencies in this study preclude any accurate assessement of the reproductive effect of Oxamyl. The deficiencies include, but no limited, to the following:

1). The information in the Procedure section of the report was extremely scanty; for example, the number of animals used in this study was not mentioned, and the statistical methods to be applied were not specified.

97

2). The data presented in the report are insufficient and poorly reported. Since the F_0 males and females used in this study were taken from the chronic study, the observations made on these animals should also be presented in the results of the reproduction study. Viability and lactation indices and average weight of the weanlings should be reported on the per litter basis.

3). The data on the growth rate of offspring between birth and weaning are lacking.

4). The number of litters in the study was not sufficient. A reproduction study, according to the "core study guidelines" requires at least 20 litters for proper evaluation of the reproductive effects.

99

OXAMYL

Page _____ is not included in this copy.

Pages 89 through 92 are not included in this copy.

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.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005858

005858

Reviewed by: Whang Phang, Ph.D. 12/19/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) M. van Gemert 12.19.86

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Study/Host-Mediated Gene Mutation Assay with S. typhimurium

TOX. CHEM. NO.: 561A

ACCESSION NUMBER: None

MRID NO.: 40594

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (93.7% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): Not given

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Institute of Environmental Toxicology

CITATION: Shirasu, Y.; Moritani, M.; Watanabe, K. (1976) Oxamyl Mutagenicity Study Using Bacteria. (Unpublished study received Oct 21, 1976 under 6F1696; prepared by Institute of Environmental Toxicology, Toxicity Dept., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 095326-C)
[Host Mediated Assay in Mice]

CONCLUSION: In this host-mediated assay using male ICR mice and S. typhimurium G 46 his, Oxamyl at doses of 2 and 4 mg/kg did not cause gene mutation. However, certain pieces of crucial information concerning the clinical signs of the treated mice and the data on the preliminary dose selection study are missing.

The study is classified as unacceptable.

MATERIAL AND METHODS: Groups of male ICR mice (5-6/group) were treated twice with Oxamyl at doses of 1 and 2 mg/kg 24 hrs apart by gavage (total dose, 2 and 4 mg/kg). Dimethylnitrosoamine (DMN) was use as a positive control administered orally as a single dose of 50 mg/kg. Subsequent to the second administration of the test compound, 2 ml of S. typhimurium (5.8×10^8/ml) was innoculated intraperitoneally into the mice. Three hrs later the animals were sacrificed. The peritoneal fluid was removed, plated on the agar plates (in triplicate), and incubated for 2 days at 37°C. The survivors and the revertant colonies were determined. For details of the study, an excerpt of the Methods section from the submission is appended (Attachment A).

93

RESULTS: With host-mediated assay, Oxamyl did not cause any increase in the number of revertant colonies relative to the control, but positive control, DMN, caused marked increase in the number of revertant colonies (Attachment B).

The study needs some important pieces of information. There are no clinical observations concerning the treated mice, and no data on the preliminary dose selection study with Oxamyl in mice. Hence, dose apparently is insufficient.

OXAMYL

Page _____ is not included in this copy.

Pages 95 through 97 are not included in this copy.

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.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005858

Reviewed by: Whang Phang, Ph.D. 12/19/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) 12.19.86

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Study/Gene Mutation Assay with S. typhimurium and E. coli

TOX. CHEM. NO.: 561A

ACCESSION NUMBER: None

MRID NO.: 40594

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (93.7% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): Not given

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Institute of Environmental Toxicology

CITATION: Shirasu, Y.; Moritani, M.; Watanabe, K. (1976) Oxamyl Mutagenicity Study Using Bacteria. (Unpublished study received Oct 21, 1976 under 6F1696; prepared by Institute of Environmental Toxicology, Toxicity Dept., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 095326-C)

CONCLUSION: Oxamyl was tested on S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100. The results were all negative in assays with and without metabolic activation. This study has deficiencies, for example: (1) the results were not confirmed in another independent study, and (2) the toxicity of Oxamyl was not tested on the bacteria in order to select the doses for the study.
The study is classified as unacceptable.

MATERIAL AND METHODS: S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 (histidine auxotrophs) and E. coli WP2 hcr^{-6} (which requires tryptophan for growth) were used in this study. The methods used were those of Ames et al. for assays with S. typhimurium and those of Legator and Malling for assays with E. coli WP2 hcr^{-6}. The bacteria were plated with Oxamyl at doses of 10, 100, or 1000 ug/plate with or without metabolic activation system derived from the S-9 fraction of Aroclor 1254 induced rat liver plus appropriate co-factors. The culture was incubated for 2 days at 37°C; then, the numbers of revertant colonies were counted.
For positive controls, 2-aminoanthracene, AF-2 [2-(2-furyl)-3-(5-nitor-2-furyl)acrylamide], beta-propiolactone, 9-aminoacridine, and 2-nitrofluorene were used.

RESULTS:

The positive chemicals, AF-2, beta-propiolactone, and 2-nitrofluorene produced marked increase in numbers of revertant colonies relative to DMSO controls. In the presence of the metabolic activation system, 2-aminoanthracene was also strongly mutagenic. However, Oxamyl in the presence or absence of the metabolic activation system did not increase the numbers of revertant colonies relative to the controls (Attachment).

OXAMYL

Page _____ is not included in this copy.

Pages 100 through 102 are not included in this copy.

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.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005858

Reviewed by: Whang Phang, Ph.D. 12/22/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) M. van Gemert 12.22.86

DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study in Rats TOX. CHEM. NO.: 561A

ACCESSION NUMBER: not given MRID NO.: 28729

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (93.7% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): 352-372

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Biochemicals Department Research Division, E.I. du Pont de Nemours, Wilmington, Del.

CITATION: J.C.Y.; Jackson, R.A.; Harvey, J., Jr. (1976) Metabolism of Oxamyl in the Rat. (Unpublished study received June 14, 1976, under 352-372; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 097651-B)

CONCLUSIONS: Orally administering radiolabelled Oxamyl to 2 male rats at a dose of 1.0 mg (3.74 uCi) resulted in rapid excretion of the radioactivity. Within 72 hrs of dosing, approximately 70% of the radioactivity was excreted in urine and feces. The amount of radioactivity excreted in the urine was substantially more than that in the feces during the first 24 hrs (Attachment A). Metabolites were found in urine and fece as conjugates of probably glucuronides or sulfates (Attachment B). The tissue distribution data indicate that skin (hide), carcass, and G.I. tract sequestered radioactivity more than liver, blood or any other organ examined (Attachment A).

This study was previous evaluated in 1976 in conjunction with other studies. The present conclusions are similar to those of that review; an excerpt of the 1976 review is appended (Attachment C).

This study is classified as supplementary because the study used only two male rats, and the metabolism of Oxamyl in females might be rather different. For future studies, at least 5 animals/sex/dose must be used.

(ATTACHMENT A)

TABLE II

Recovery of Radioactivity From Rats Treated with ^{14}C-Oxamyl

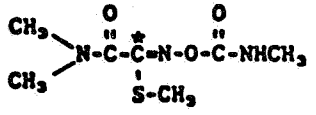
	% of Original Treatment	
External Fractions	Rat A	Rat B
Pre-furnace Gas Trap	0.00	0.24
Post-furnace Gas Trap	0.00	0.06
Sub-total	(0.00)	(0.30)
Urine, 0-24 hr.	47.33	36.15
Urine, 24-48 hr.	9.36	9.14
Urine, 48-72 hr.	4.55	3.06
Sub-total	(61.24)	(48.35)
Feces, 0-24 hr.	3.21	16.96
Feces, 24-48 hr.	2.41	4.11
Feces, 48-72 hr.	.80	1.93
Sub-total	(6.42)	(23.00)
Total Eliminated	67.66	71.65
Body Fractions		
Hide	6.98	12.55
Carcass	6.34	4.18
G.I. Tract	4.76	1.32
Liver	1.58	.20
Blood	1.55	2.13
Kidneys	.19	.27
Testes	.13	.09
Lungs	.11	.16
Heart	.11	.14
Muscle	.11	--
Spleen	.05	.06
Brain	.03	.36
Fat	.03	.08
Sub-total	(21.97)	(21.54)
Total Recovery	89.63	93.19

v - 6 %

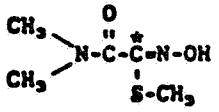
J. Lacl 2/23/91 Exhibit 2

ATTACHMENT B Exhibit C12

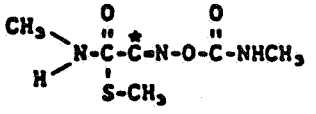
Structures



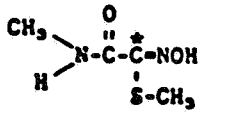
(I) Oxamyl
methyl N',N'-dimethyl-N-[(methyl-carbamoyl)oxy]-1-thiooxamimidate



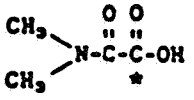
(II) Methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate



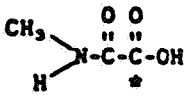
(III) Methyl N'-methyl-N-[(methyl-carbamoyl)oxy]-1-thiooxamimidate



(IV) Methyl N-hydroxy-N'-methyl-1-thiooxamimidate



(V) N,N-dimethyloxamic acid



(VI) N-methyloxamic acid

*denotes position of ^{14}C-label

107

ATTACHMENT C.

005858

Exhibit C. Metabolism of Oxamyl in the Rat. J. C-Y. Han, R.A. Jackson, and J. Harvey, Jr.

Procedure: Two adult male rats each received orally 1 mg oxamyl (methyl N',N'dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate), which contained C^{14} (the atom to which thio and imino groups are attached), after preconditioning with 50 or 150 ppm cold oxamyl in the diet. Each rat was placed in a metabolism cage, and expired air, urine, and feces were collected at intervals. Rats were killed at 72 hrs after dose.

Blood samples and tissues (brain, lungs, heart, liver, spleen, kidneys, testes, gastrointestinal (G.I.) tract, and portions of muscle and fat) were collected. Carcass minus hide was ground up. Fractions and samples collected were processed appropriately and radioactivity determined by liquid scintillation counting (lsc). Characterization of the radio-labelled compounds in various fractions was attempted.

Results: About 70% of radioactivity was excreted by each rat by 72 hrs, most of it in urine and none (< 0.3%) in respired air. About 18% was in hide, carcass, and G.I. tract. About 3% was in liver and blood. Remaining 1% accounted for was distributed evenly throughout other animal tissues.

On thin-layer chromatography (TLC) of fresh urine, no radioactivity migrated from the origin. Therefore, urine did not contain any of the following substances in free form: Oxamyl; its oxime (I); the N'-desmethyl oxime (II); N,N-dimethyl-1-cyanoformamide (DMCF); the S-oxide of oxamyl, the S-oxide of (I); the S,S-dioxide of oxamyl; or the S,S-dioxide of (I). In confirmation - each of these is soluble in ethyl acetate, but this solvent extracted less than 1% of radioactivity from either fresh urine or feces. Evidently, oxamyl is transformed and excreted in urine and feces only as very polar, water-soluble materials.

Gel permeation chromatography of urine showed the radioactive molecules to be larger than (I) and probably to be conjugates. Anion exchange chromatography showed them to be acidic in nature, suggesting glucuronides or sulfates, but treatment of urine with beta-glucuronidase-aryl sulfatase failed to liberate ethyl acetate-soluble radioactivity. However, acid (MeOH-HCl) did hydrolyze them, and TLC and GLC identified (I) and (II) as components of these conjugates. Cleavage by Lewis acid (BCl_3/$ClCH_2CH_2OH$) and TLC, corresponding identified N,N-dimethyloxamic acid (III) and N-methyloxamic acid (IV) as other components of the conjugates. About 75% of radioactivity of urine and feces was shown to be conjugates of these four oxamyl-related compounds.

Ethyl acetate extraction of blood, liver, skin, hair failed to remove radioactivity (< 1%); thus, neither oxamyl, (I), (II), nor DMCF were present in free form. Ethyl acetate extracted < 3% radioactivity from acid-hydrolyzed "tissues which contained....large amounts of radioactivity." Presumably, these compounds were not present in combined form, either, in the latter (unspecified) tissues. Note our question on this, under DISCUSSION.

About one-half of radioactivity originally present in rat skin/hair and rat blood was then shown to be incorporated into natural amino acids. [Samples were hydrolyzed (by refluxing with 6N HCl for 24 hrs), and amino acids were isolated (on an ion exchange column) and made into (N-butyl-trifluoroacety) derivatives, which were subjected to gas chromatography (GLC) (on a gas chromatograph equipped with a splitter, which sent part of the gas stream through for GLC analysis and retained

part for assay of radioactivity). This assay showed the radioactive substances to be amino acids, as did further GLC/mass-spectrum confirmation.]

Discussion:

Deficiency 2 of (7/13/76) reject letter, this PP, is now satisfied, but deficiences 3 and 4 remain unsatisfied.

Petitioner's rat metabolite studies on oxamyl (Exh. 1) and Metabolite A (Exh. 3) give some, but not wholly satisfying, information on Deficiencies 1 and 5. We elaborate on this below:

Exhibit I, this PP, now shows that most oxamyl is fairly rapidly excreted in urine and feces of the rat as polar, water-soluble conjugates of the oxamyl oxime (I), its desmethyl oxime (II), and the two oxamic acids (III and IV). What these oxamyl metabolites are conjugated with is unknown. It is suggested that the conjugates are acidic, but they were not cleaved by glucuronidase or aryl sulfatase.

It is noteworthy that neither the sulfone nor the sulfoxide of oxamyl or its oxime was excreted in urine. In contrast, the rat metabolizes aldicarb [2-methyl-2(methylthio)propionaldehyde-O-(methylcarbamoyl)oxime], a pesticide structurally related to oxamyl, to both the sulfoxide and the sulfone, which are potent anticholinesterase metabolites, and these latter are excreted in urine (Dorough, 1970).

In tissues examined (skin, hair, liver, blood), 72 hrs after dose, no free oxamyl or free oximes (I or II) or free DMCF occurred.

In some "tissues" no conjugated I, II, or DMCF are said to have occurred, either (Exh. 1, p. 14, 3rd para.). The tissues are not specified, and the "experimental" portion of Exh. 1 contains no mention of ethyl acetate extraction of any acid-hydrolyzed tissue. Petitioner is asked to explain this seeming discrepancy and, also, to specify which one of the "acid-hydrolyzed tissues" in Exh. 1 yielded "less than 3% radioactivity when extracted with ethyl acetate" (Exh. I, this PP, p. 14, para. 3).

In skin, hair, and blood, about one-half of radioactivity was identified as amino acids; like those which occur naturally in protein. Thus part of oxamyl is degraded and transformed into naturally-occurring substances. Liver, however, was not further examined. We presume from results of in vitro tests made previously (cf. our memo of 1/6/76, this PP) that oxamyl was metabolized in liver to I, II, III, and IV. These could then have been conjugated in liver and either stored and later excreted or excreted directly in urine and feces. However, no direct proof of either possibility is provided.

We would like to have had liver further examined for any conjugates of oxamyl metabolites which may have formed there, but this was not done. Nor were the excreted oxamyl-derived conjugates identified; although they appear not to have been glucuronides or sulfates - such other as carbamate pesticides often form (Dorough, 1970). Exhibit I, therefore, is judged deficient in showing where - in rat metabolism - oxamyl metabolites conjugate and with what. And a discrepaney in Exhibit I - as to what, if any, acid-hydrolyzed tissues were checked for presence of oxamyl metabolites (by ethyl acetate extraction) - needs to be explained (cf. above).

10

Distribution of Radioactivity in Amino Acids

Skin and Hair	Percentage of ^{14}C in Sample
Alanine & Valine	5.1
Glycine	9.1
Leucine	5.4
Proline & Methionine	3.2
Phenylalanine & Aspartic Acid	10.2
Glutamic Acid, Lysine & Arginine	10.2
Tryptophan	8.0
	51.2

Blood	
Alanine, Valine & Glycine	7.3
Leucine	9.4
Proline, Methionine, & Aspartic Acid	5.1
Glutamic Acid and Lysine	11.8
Arginine & Tryptophan	9.3
	42.9

005858

Reviewed by: Whang Phang, Ph.D. Whang Phang 12/22/86
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. Marcia van Gemert 12.22.86
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study of Oxamyl with Rat Liver Homogenate

TOX. CHEM. NO.: 561A

ACCESSION NUMBER: not given

MRID NO.: 40498

TEST MATERIAL: Methyl N', N'-dimethyl-N-[methylcarbamoyl)oxy]thiooxamimidate (93.7% a.i.)

SYNONYMS: Oxamyl; IND-1410

STUDY NUMBER(S): 352-372

SPONSOR: E.I. du Pont de Nemours & Co., Inc., Wilmington, Del.

TESTING FACILITY: Biochemicals Department Research Division, E.I. du Pont de Nemours, Wilmington, Del.

CITATION: Belasco, I.J. (19??) Liver Microsomal Metabolism of Oxamyl (Unpublished study received June 21, 1977, under 352-372; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 096301-I)

CONCLUSIONS: Radiolabelled Oxamyl (0.5-1.0 gm) was incubated with rat liver homogenate (supernatant from 15,000 xg homogenate) in the presence of co-factor NADPH and phosphate buffer. The reaction mixture was incubated for more than 2 hrs at 37°C. Oxamyl was rapidly converted to methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate (II) which was the major metabolite. Other minor metabolites formed are shown in Attachment A .

This study provides certain information, but it dose not meet the requirements for registration. The study is classified as supplementary. No detailed evaluation report would be prepared for this study.

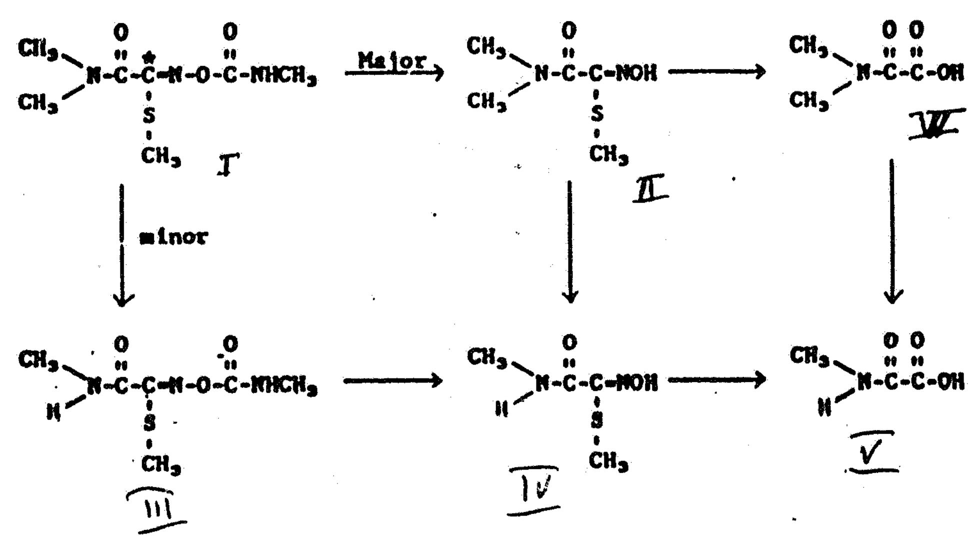
10

ATTACHMENT

Exhibit C68

Figure 3

Proposed Rat Liver Microsomal Metabolism of Oxamyl



005858

END