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**DATE STAMPED: 11/05/96**

**MEMORANDUM**

SUBJECT: RfD/Peer Review Report of Oxamyl [Oxamimidic acid, N', N'-dimethyl-N-((methylcarbamoyl)oxy)-1-thio-methyl ester]

CASRN: 23135-22-0
EPA Chem. Code: 103801
Caswell No.: 561A

FROM: Rick J. Whiting
Science Analysis Branch
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Chief, Registration Support Branch
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Insecticide-Rodenticide Branch
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The Health Effects Division-RfD/Peer Review Committee met on August 15, 1996 to discuss and evaluate the toxicology data submitted in support of Oxamyl reregistration and to assess the Reference Dose (RfD), carcinogenicity and developmental toxicity for this chemical.

The Reference Dose (RfD) for this chemical was previously assessed by the Health Effects Division RfD Committee on October 24, 1986. The RfD was verified by the Agency RfD/RfC Work Group on December 9, 1986. The RfD was based on a no-observable effect level (NOEL) of 2.5 mg/kg/day for decreased body weight gain and food consumption observed at 5 mg/kg/day in a 2-year feeding/carcinogenicity study in rats. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.025 mg/kg/day.

Material available for review consisted of data evaluation records (DERs) for two chronic toxicity/carcinogenicity studies in rats **(83-5**

**or 83-1a and -2a)**, three chronic toxicity studies in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a multi-generation reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats (83-1a) and rabbits **(83-1b)**, and a battery of mutagenicity studies **(84-2)**.

**A. <u>Chronic and Subchronic Toxicity</u>:**

The Committee considered the following studies:

1) 2-Year Feeding/Carcinogenicity Study in Rats (83-5, MRID No. 41963101. HED Doc. No. 010038. Core grade Minimum). The Committee considered the chronic toxicity phase of this study to be acceptable and the DER to be adequate. The NOEL/LEL for systemic toxicity are 50 ppm (1.97 and 2.69 mg/kg/day for males and females, respectively) and 100 ppm (4.19 and 6.73 mg/kg/day for males and females, respectively) based on the following effects: 1) An increase in the incidence of hyperactivity, swelling of legs/paws, and skin sores in males and females; 2) A decrease in mean body weights and mean body weight gains in males and females and 3) A statistically significant decrease in plasma cholinesterase activity in males at all measuring intervals (a similar decrease was also seen in females during the 1 month measuring interval).

2) 2-Year Feeding Study in Rats (83-1a, MRID No. 00083352. HED Doc. No. 005858. Core grade Supplementary). The Committee concurred with the study classification and considered the DER to be adequate. The NOEL/LEL for systemic toxicity are 50 ppm (2.5 mg/kg/day) and 100 ppm (5 mg/kg/day), respectively based on decreased body weight gain and food consumption.

3) 2-Year Feeding/Carcinogenicity Study in Mice (83-2b, MRID No. 0076813. HED Doc. No. 005858. Core grade Minimum). The Committee considered the chronic toxicity phase of this study to be acceptable and the DER to be adequate. The NOEL/LEL for systemic toxicity are 25 ppm (3.75 mg/kg/day) and 50 ppm (7.5 mg/kg/day), respectively, based on decreased body weights.

4) 1-Year Feeding Study in Dogs (83-1b, MRID No. 41697901. HED Doc. No. 009351. Core grade Supplementary). The Committee concurred with the study classification and considered the DER to be adequate. Based on the decrease in cholinesterase activity in plasma and brain in all treated male dogs and an increase in the incidence of tremors in all treated female dogs, a NOEL for chronic toxicity could not be established. The LEL for chronic toxicity is 50 ppm (1.56 and 1.46 mg/kg/day for males and females, respectively).

5) 1-Year Feeding Study in Male Dogs (83-1b, MRID No. 42052701. HED Doc. No. 009351. Core grade supplementary). The Committee concurred with the study classification and considered the DER to be adequate. This study was specifically designed and executed to determine if the data from the previous dog study (see above) were reproducible and to establish an NOEL for chronic toxicity in dogs. There were serious deficiencies in the design and the report of the study which prevented

appropriate evaluation and establishment for a NOEL for chronic toxicity.

6) 2-Year Feeding Study in Dogs (83-1b, MRID No. 00083352. HED Doc. No. 005858. Core grade Supplementary). This study was not reviewed by the Committee since it contained many deficiencies and has been superseded by the new chronic dog study.

**B. <u>Carcinogenicity</u>:**

The Committee considered the following studies:

1) 2-Year Feeding/Carcinogenicity Study in Rats (83-5, MRID No. 41963101. HED Doc. No. 010038. Core grade Minimum). The Committee considered the carcinogenicity phase of this study to be acceptable and the DER to be adequate. Study results indicated that Oxamyl did not induce an increase in any tumor incidence. The highest dose tested was considered to be adequate for carcinogenicity testing based on 1) decreased body weight and body weight gains in males and females, 2) increased incidence of hyperactivity, swelling of legs/paws, and skin sores in males and females and 3) decrease in plasma ChE in males.

2) 2-Year Feeding/Carcinogenicity Study in Mice (83-2b, MRID No. 0076813. HED Doc. No. 005858. Core grade Minimum). The Committee considered the carcinogenicity phase of this study to be acceptable and the DER to be adequate. The highest dose tested was considered to be adequate for carcinogenicity testing based on decreased body weight and survival. Concern was expressed by one Committee member that there was an increase in pulmonary tumors in treated female mice (see Table 1).

Table 1* Incidence of Pulmonary Tumors in Female CD-1 Mice

| Tumor Type | Control | 25 ppm | 50 ppm | 75 ppm |
|---|---|---|---|---|
| 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%) | 15/75 (19.7%) |

(Memorandum: W. Greear to T. Farber; June 17, 1985)

After a lengthy discussion, the Committee concluded that Oxamyl did not cause a biologically significant increase in tumor incidence. The Committee's reasoning is as following:

(1) Data on the incidence of pulmonary tumors in control animals from seven studies that were conducted during the same period of time as the Oxamyl study indicated that pulmonary tumors are relatively common in both the male and female CD-1 mouse. In the female mouse, the incidence ranged from 6% to 31% with a mean of 17.7%.

(2) Additional information on the incidence of pulmonary tumors in the

CD-1 mice was also available from the Food and Drug Administration. The incidence of pulmonary adenomas in female mice ranged from 0% to 24.2% with a mean of 9%. The incidence of pulmonary carcinomas ranged from 0.8% to 15.8% with a mean of 6.5%. When combined, the incidence of pulmonary tumors ranged from 6.5% to 26.7% with a mean of 15.5%. (Memorandum: W. Greear to T. Farber; June 17, 1995)

(3) The tumor incidence of the high-dose females (19.7%) was comparable to that of the low-dose females (15.2%). There was not a dose-related response.

(4) 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 higher than that of the controls.

The Committee, therefore, recommended that Oxamyl be classified as a **"Group E"**, i.e. the chemical is **Not likely** to be carcinogenic to humans via relevant routes of exposure.

This weight of the evidence judgement is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

**C. <u>Reproductive and Developmental Toxicity</u>:**

The Committee considered the following studies:

1) 2-Generation Reproduction Study in Rats (83-4, MRID No. 41660801. HED Doc. No. 009390. Core grade Minimum). The Committee considered the study to be acceptable and recommended the following changes to the DER: 1) Replace the term parental toxicity with systemic/developmental and 2) change the NOEL/LEL for reproductive toxicity to 75 and 150 ppm, respectively, and 3) a new executive summary should be written. The NOEL/LEL for systemic/developmental toxicity are 25 ppm (1.7 and 2.0 mg/kg/day for males and females, respectively) and 75 ppm (5.2 and 6.6 for males and females, respectively) based on significantly decreased food consumption, body weight, and body weight gain. The NOEL/LEL for reproductive toxicity are 75 ppm (6.6 mg/kg/day) and 150 ppm (15.8 mg/kg/day) based on significantly decreased number of live pups per litter during lactation and the viability index.

2) Developmental Toxicity Study in Rats (83-3a, MRID No. 4089201. HED Doc. No. 007099. Core grade Minimum). The Committee considered the study to be acceptable and recommended a new executive summary be written for the DER. The NOEL/LEL for maternal toxicity are 0.5 and 0.8 mg/kg/day, respectively, based on significant dose-related

decreases in body weight gains and food consumption and an increase in the incidences of tremors. NOEL/LEL for developmental toxicity are 0.2 and 0.5 mg/kg/day, respectively, based on a statistically significant decrease in fetal body weight.

3) Developmental Toxicity Study in Rabbits (83-3b, MRID No. 00063009. HED Doc. No. 005858. Core grade Minimum). The Committee considered the study to be acceptable and recommended a new executive summary be written for the DER. The NOEL/LEL for maternal toxicity are 1 and 2 mg/kg/day, respectively, based on statistically significant decreases in mean body weight. NOEL for developmental toxicity is 4 mg/kg/day, the highest dose tested.

**D. Acute and Subchronic Neurotoxicity:**

There were no acute (81-8) or subchronic (82-7) neurotoxicity studies in rats available for review by the Committee. However, the Committee was informed that the registrant is currently performing these studies and will be submitting them to the Agency in the near future. Thus, these studies are still outstanding for reregistration purposes.

**E. Mutagenicity:**

The Committee considered the following mutagenicity studies:

**GENE MUTATIONS**

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 40606509. HED Doc. No. 006891, 007077): The test is negative in all strains up to the highest dose tested (10,000 μg/plate) with or without S9 activation.

2) Chinese hamster ovary (CHO) HGPRT forward gene mutation assay (MRID No. 40606510. HED Doc. No. 006891, 007077): The test is negative in independently performed trials up to concentrations causing a ≤80% decreases in cell viability (1200 μM -S9; 700 μM +S9).

**CHROMOSOME ABERRATIONS**

3) In vitro CHO cell chromosome aberration assay (MRID No. 40606507. HED Doc. No. 006891, 007077): The test was negative up to cytotoxic concentrations (≤70 μg/mL -S9; 700 μg/mL +S9).

**OTHER MUTAGENIC MECHANISMS**

4) DNA damage/repair in Bacillus subtilis rec assay (MRID No. 00040594): The test is negative up to the highest dose tested (2000 μg/disc -S9).

5) In vitro unscheduled DNA synthesis in primary rat hepatocytes (MRID No. 41096001. HED Doc. No. 006891, 007595): The test is

negative up to cytotoxic concentrations (≤5 mM).

Other Information (e.g. GeneTox printout, published studies): An unacceptable but negative S.typhimurium/E.coli reverse gene mutation assay (MRID No. 00040594) and an unacceptable but negative mouse host mediated assay with S. typhimurium G46 (MRID No. 00040594) were included in the oxamyl mutagenicity study package. Since acceptable studies have been identified for this category of genetic toxicology testing, the data from these two unacceptable studies are not required to draw meaningful conclusions.

CONCLUSIONS: The acceptable studies satisfy the pre-1991 mutagenicity initial testing battery guidelines. Based on the findings of the acceptable studies, there is no concern for mutagenicity at this time.

**F. Reference Dose (RfD):**

It should be noted that Oxamyl acts by inhibiting cholinesterase and that this inhibition is readily reversible. The Committee felt that in order for a study to adequately address the toxicity of Oxamyl, test animals should receive a daily single oral dose with clinical observations and blood samples taken within three hours of dosing. There are only two studies which provide useful results that could be used in establishing an RfD. The first study is the 1-year feeding study in dogs (MRID No. 41697901) where the animals were observed immediately after feeding and the blood samples for cholinesterase inhibition assay were collected three hours after dosing. In this study, the lowest tested dose (1.56 mg/kg/day) was found to significantly inhibit brain and plasma cholinesterase activity and cause cholinergic signs (tremors). The second study is the developmental toxicity study in rats (MRID No. 40859201) where the test animals received Oxamyl by gavage (see below).

The Committee recommended that an RfD for this chemical be established based on the Developmental Toxicity Study in rats (MRID No. 40859201). In this study, groups of pregnant rats received Oxamyl by gavage at doses of 0, 0.2, 0.5, 0.8 and 1.5 mg/kg/day from gestation days 7 to 16. At doses of 0.8 mg/kg/day and above, maternal toxicity was indicated by significant dose-related decreases in body weight gains and food consumption. In addition, there were increases in the incidences of tremor, salivation, diarrhea, eye discharge, and wet fur in various areas of the body in animals receiving 1.5 mg/kg/day. An increase in the incidence of tremors was also observed at 0.8 mg/kg/day. These clinical signs were related to cholinesterase inhibition. Based on these findings, the NOEL and LEL for maternal toxicity are 0.5 and 0.8 mg/kg/day, respectively. A statistically significant decrease in fetal body weight was observed in males and females of the 0.5, 0.8 and 1.5 mg/kg/day dose groups. Based on this finding, the NOEL and LEL for developmental toxicity are 0.2 and 0.5 mg/kg/day, respectively.

In selecting the rat developmental toxicity study, the Committee noted that the LEL for maternal toxicity (0.8 mg/kg/day) was only 3-fold less

than the LD50 (2.5 mg/kg for females) from an acute oral toxicity study. In the acute oral toxicity study (MRID No. 00063011. HED Doc. No. 000844. Core grade Minimum) the oral LD50 for males was 3.1 mg/kg and for females was 2.5 mg/kg based on tremors, fasciculations, exophthalmos, salivation, chromodacryorrhea, stained faces and perineal areas, and slight weight loss.

An uncertainty factor of 1000 was applied to account for inter-species extrapolation (10x), intra-species variability (10x) and for the lack of neurotoxicity studies and the lack of an established NOEL (decreased brain and plasma cholinesterase activity in males and tremors in females were observed at the lowest dose tested) in the 1990 1-Year dog feeding study (MRID No. 41697901) (10x). **On this basis, the RfD for Oxamyl was calculated to be 0.0002 mg/kg/day.**

Oxamyl has also been reviewed by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) in 1989 and an Acceptable Daily Intake (ADI) of 0.03 mg/kg/day has been established. In establishing the ADI, the WHO/FAO Joint Committee considered two studies on Oxamyl: 1) a chronic rat feeding study with an NOEL of 2.5 mg/kg/day and 2) a chronic dog feeding study with an NOEL of 2.5 mg/kg/day. In these studies, Oxamyl produced decreased body weights in rats and liver effects in dogs. Therefore, the ADI was based on these two studies to which a safety factor of 100 was applied yielding an ADI of 0.03 mg/kg/day. It should be noted that the NOEL of 2.5 mg/kg/day from the chronic rat feeding study used by JMPR in establishing the ADI is equal to the oral LD50 for female rats (MRID No. 00063011).

**G. Individuals in Attendance:**

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), Karl Baetcke, (Chief, TB I), Stephen Dapson, Brian Dementi, Karen Hamernik, Paul Lewis, Guruva Reddy, Esther Rinde, Clark Swentzel and Rick Whiting.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Whang Phang _____

James Rowe _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Mike Ioannou _____

CC: Stephanie Irene
Albin Kocialski
Whang Phang
James Rowe
Mike Ioannou
Beth Doyle
Paul Lewis
Amal Mahfouz (OW)
RfD File
Caswell File

**H. Material Reviewed:**

1. Malley, L. (1991) Combined Chronic Toxicity/Oncogenicity Study With Oxamyl (IN D1410-196): Long-Term Feeding Study in Rats. MRID No. 41963101. HED Doc. No. 010038. Classification: Core minimum data. This study satisfies data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. 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. MRID No. 00083352. HED Doc. No. 005858. Classification: Core supplementary data. This study does not satisfy data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

3. Adamik, E.R.; Criswell, M.K.; Mahler, S.C.; et al. (1981) Long Term Feeding Study in Mice with Oxamyl. MRID No. 00076813. HED Doc. No. 005858. Classification: Core minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Mebus, C. (1990) Chronic Toxicity Study with Oxamyl (IN D1410-196): One-Year Feeding Study in Dogs. MRID No. 41697901. HED Doc. No. 009351. Classification: Core supplementary data. This study does not satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

5. Dickrell, L. (1991) 52-Week Dietary Toxicity Study with IND-1410 (Oxamyl) in Male Dogs. MRID No. 42052701. HED Doc. No. 009351. Classification: Core supplementary data. This study does not satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

6. 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. MRID No. 00083352. HED Doc. No. 005858. Classification: Core supplementary data. This study does not satisfy data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

7. Hurtt, M. (1990) Reproductive and Fertility Effects with Oxamyl (IN D1410): Multigeneration Reproduction Study in Rats. MRID No. 41660801. HED Doc. No. 009390. Classification: Core minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

8. Rickard, L. (1988) Teratogenicity Study of IN D1410-196 in the Rat. MRID No. 40859201. HED Doc. No. 007099. Classification: Core minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental

toxicity testing in rats.

9. Hoberman, A.M.; Mossburg, P.A.; Wolfe, G.W.; et al. (1980) Teratology Study in Rabbits: Oxamyl. MRID No. 00063009. HED Doc. No. 005858. Classification: Core minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

10. Dashiell, O.L.; Hinckle, L. (1980) Oral LD50 Test in Rats--EPA Proposed Guidelines. MRID No. 00063011. HED Doc. No. 000844. Classification: Core minimum data. This study satisfies data requirement 81-1 of Subpart F of the Pesticide Assessment Guideline for acute oral toxicity testing in rats.

11. Vanrell, B. (1989). Bacterial Reverse Mutation Assay. MRID No. 43145417, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

12. Loquet, C. (1987). Chromosomal Analysis in vitro in CHO Chinese Hamster Cells. MRID No. 43032614, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

13. Molinier, B. (1989). Chromosomal Analysis of Chinese Hamster Bone Marrow Cells. MRID No. 43145419, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

14. Loquet, C. (1987). Micronucleus Test in Mice. MRID No. 43145420, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

15. Loquet, C. (1987). DNA Repair: Differential Growth Inhibition of DNA Repair Proficient and Deficient Bacteria. MRID No. 43032615, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

16. Molinier, B. (1990). HPRT Gene Mutation Assay in V79 Chinese Hamster Cells. MRID No. 43145418, HED Doc. No. 011966. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.