DATE STAMPED: 10/25/96

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methomyl [S-Methyl N-[(methylcarbamoyl)oxy]thioacetimidate]

CASRN: 16752-77-5
EPA Chem. Code: 090301
Caswell No.: 549C

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Health Effects Division (7509C)

THRU: William Burnam
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Fungicide-Herbicide Branch
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Chief, Reregistration Branch
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The Health Effects Division-RfD/Peer Review Committee met on September 5, 1996 to discuss and evaluate the existing or recently submitted toxicology data in support of Methomyl reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, a chronic toxicity study 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)**, subchronic toxicity studies in rats and dogs **(82-1a and -1b)**, metabolism studies in rats and monkeys **(83-x)**, and a battery of mutagenicity studies **(84-2)**.

1/8

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 00078361) to be acceptable, and the data evaluation record (HED Doc. No. 001040, 007238, 000000) to be adequate. The systemic toxicity NOEL/LOEL for both males and females were considered to be 100 ppm (5 mg/kg/day) and 400 ppm (20 mg/kg/day), respectively, based on body weight gain depression.

A subchronic toxicity study in rats (82-1a, MRID No. 00007190, HED Doc. No. 000922, 000924, 000000) was available for review by the Committee. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The NOEL/LOEL were considered to be 125 ppm (6.25 mg/kg/day) and 250 ppm (12.5 mg/kg/day), respectively, based on body weight gain depression in both sexes and erythroid hyperplasia in the bone marrow of males.

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 00007091, 00009012) to be acceptable and the data evaluation record (HED Doc. No. 000924, 000000) to be adequate with minor changes suggested. The NOEL/LOEL were considered to be 100 ppm (2.5 mg/kg/day) and 400 ppm (10.0 mg/kg/day), respectively, based on kidney effects. The Committee questioned the lack of cholinesterase inhibition in this study with this carbamate compound although tremors and convulsions, typical cholinergic symptoms, were observed at 1000 ppm (40 mg/kg/day). The Committee attributed the absence of cholinesterase inhibition in this study to, possibly, inappropriate techniques in handling the specimens.

There was a subchronic toxicity study in dogs (82-1b, MRID No. 00009010, HED Doc. No. 000922, 000000) available for review by the Committee. The study was considered to be unacceptable (for lack of information on purity and stability of the test chemical and many tissues were not examined microscopically for pathology) and the data evaluation record was considered to be adequate. The NOEL was considered to be 400 ppm (14.68) mg/kg/day, the highest dose level tested.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the combined chronic toxicity/carcinogenicity studies in rats (83-2a, MRID No. 00078361) to be acceptable, and the data evaluation record (HED Doc. No. 001040, 007238, 000000) to be adequate. However, the Committee determined that the animals could have tolerated higher doses than the highest dose level used in this study.

The Committee considered the carcinogenicity study in mice (83-2b, MRID No. 00078423) to be acceptable and the data evaluation records (HED Doc. No. 001040, 007238, 000000) to be adequate. The highest dose level tested in this study was considered to

be adequate for carcinogenicity testing based on increased mortality.

The treatment did not alter the spontaneous tumor profile in these strains of rat and mouse under the testing conditions. The Committee, therefore, recommended that Methomyl 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 judgment 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.

It should be noted that the Committee was aware of the fact that methomyl is a metabolite and structurally-related to Thiodicarb, another pesticide that was classified as B2 carcinogen.

It should be noted also that the RfD Committee in their meeting of April 13, 1994 was requested to address the release of acetamide, a suspected carcinogen, as a possible metabolite for Methomyl. In that meeting, the Committee concluded that the ingestion of the anticipated levels of Methomyl and acetamide in the diet should not represent a significant carcinogenic hazard to consuming public based on the following: 1) the conversion rate of methomyl to acetamide is low , approximately 2-3 percent, therefore, residue levels of acetamide should be low, 2)carcinogenicity studies with methomyl in two rodent species indicated no increase in any type of tumors under the testing conditions, 3) the product is comprised of 98.7 percent syn-isomer and 0.092 percent anti-isomer, syn-isomer must be converted to anti-isomer before acetamide is formed, and 4) acetamide induced liver tumors in rats only when administered at a very high dosage, i.e. more than 1000 mg/kg/day. Acetamide, itself, was evaluated by the HED-CPRC and classified as a "Group C", possible human carcinogen, but it was recommended that no low dose extrapolation model was to be used for risk assessment.

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

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 43250701) to be acceptable. The data evaluation record (HED Doc. No. 011811) was considered to be adequate. The NOEL/LOEL for systemic toxicity were considered to be 75 ppm (3.75 mg/kg/day) and 600 ppm (30 mg/kg/day), respectively, based on decreased body weights and food consumption and altered hematological parameters. The NOEL/LOEL for reproductive toxicity were considered to be 75 ppm (3.75 mg/kg/day) and 600 ppm (30 mg/kg/day), respectively, based on decreased the mean number of live pups and mean body weights of offspring.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00008621) to be acceptable and the data evaluation record (HED Doc. No. 000920, 000000) to be adequate. The maternal toxicity NOEL/LOEL were considered to be 100 ppm (9.4 mg/kg/day) and 400 ppm (33.9 mg/kg/day), respectively, based on decreased body weight gain and food consumption during gestation. The developmental toxicity NOEL was considered to be 400 ppm (33.9 mg/kg/day), the highest dose level tested.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 00131257) to be acceptable and the data evaluation record (HED Doc. No. 003522, 007238, 000000) to be adequate. The maternal toxicity NOEL/LOEL were considered to be 6 and 16 mg/kg/day, respectively, based on mortalities and clinical signs. The Developmental toxicity NOEL was considered to be 16 mg/kg/day, the highest dose level tested.

D. Acute and Subchronic Neurotoxicity:

There was no acute neurotoxicity study (81-8) or subchronic neurotoxicity study (82-7) available for review by the Committee.

The Committee recommended that acute and subchronic neurotoxicity studies with cholinesterase measurements be submitted. Signs of cholinesterase inhibition were seen in the feeding study in dogs and the metabolism study in monkeys. It should be noted that during the course of discussion of the toxicology data base for this chemical, the Committee repeatedly questioned the lack of cholinesterase inhibition prompting the need for a thorough investigation of this parameter.

E. Mutagenicity:

There were several mutagenicity studies (84-2) available for review by the Committee including gene mutation assay, chromosomal aberration testing, and testing for other genotoxic mechanisms. The Committee considered the following mutagenicity studies to be acceptable:

1) Chinese hamster ovary (CHO) cells HGPRT forward gene mutation assay (MRID No. 00161887, HED Doc. No. 003850, 007238): The test is negative up to cytotoxic levels ($\geq$40 mM = 6.5 mg/mL -S9; $\geq$150 μM = 0.24 mg/mL +S9).

2) Mouse micronucleus assay (MRID No. 44047703, HED Doc. No. 000000): This study has not been formally reviewed and a DER should be prepared. A preliminary evaluation of the data indicate that the study is Acceptable and the test is negative in ICR mice up to an overtly toxic dose (12 mg/kg) administered once by oral gavage. There was, however, no evidence of a cytotoxic effect on the target tissue.

3) In vivo bone marrow cytogenetic assay (MRID No. 00161888, HED Doc. No. 003850, 007238): The test is negative in Sprague Dawley rats up to an overtly toxic level (20 mg/kg) administered once by oral gavage. Target tissue cytotoxicity was not observed.

The Committee further indicated that Methomyl was found to be inactive in a series of USEPA-sponsored mutagenicity studies which included: Salmonella typhimurium/Escherichia coli reverse gene mutation assays, DNA damage studies in bacteria, yeast and human lung fibroblasts, and a Drosophila melanogaster sex-linked recessive lethal assay (MRID No. 00124901). Although the actual treatment levels used in the above assays were not available for this review, all of these studies were adequately conducted according to established protocols and the studies have been classified as Acceptable.

The Committee concluded that 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):

The Committee recommended that the RfD for this chemical be based on a two-year feeding study in dogs with a NOEL of 2.5 mg/kg/day. Kidney effects were observed at the next higher dose level of 10 mg/kg/day.

An uncertainty factor (UF) of 100 was applied to account for both inter-species extrapolation and intra-species variability. An additional uncertainty factor of 3 was applied to account for the lack of acute and subchronic neurotoxicity studies; metabolism studies demonstrated cholinergic signs at 5 mg/kg/day, a dose level that is sligtly higher than the NOEL established for systemic toxicity in the critical study. On this basis, the RfD was estimated to be 0.008 mg/kg/day.

It should be noted that this chemical has been reviewed by the FAO/WHO Joint Committee Meeting on Pesticide Residue (JMPR) and that an acceptable daily intake (ADI) of 0.03 mg/kg/day has been established by that Committee in 1989.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Albin Kocialski (Senior Science Advisor, HED), Mike Ioannou (Acting Chief, TB II), Nancy McCarroll, Guruva Reddy, James Rowe, William Sette, Henry Spencer, and Rick whiting. In attendance also were John Redden of RCAB/HED and Linda Taylor of TB II/HED as observers.

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

Yung G. Yang _____

Clark Swentzel _____

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

Mike Ioannou _____

CC: Stephanie Irene
Albin Kocialski
Mike Ioannou
Clark Swentzel
Mike Ioannou
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Kaplan, A. M. et al (1981). Long-term feeding Study in Rats with S-Methyl N-(Methylcarbamoy) oxy) thioacetimidate (methomyl; INX-1179): MRID No. 00078361. HED Doc. No. 001040, 007238. Classification: Core minimum data. This study satisfies data requirement 83-5 (or 83-1a and -2a) of Subpart F of the pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Hazelton Laboratories America. (1981). 104-1eek Chronic Toxicity and Carcinogenicity Study in Mice: MRID No. 00078423. HED Doc. No. 001040, 007238. Classification: Core minimum data. This study satisfies data requirement 83-2b of Subpart F of the pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Busey, W. M. (1968). Two-year Dietary Administration--Dogs: MRID No. 00007091, 00009012. HED Doc. No. 000924. Classification: Core minimum data. This study satisfies data requirement 83-1b of Subpart F of the pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Lu, C. C. (1983). Nudrin Two-Generation Reproduction Study in Rats. MRID No. 43250701. HED Doc. No. 011811. Classification: Acceptable. This study satisfies data requirement 83-4 of Subpart F of the pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Rogers, A. S. et al. (1978). Oral Teratogenic Study in Rats with Lannate(R=) (INX-1179): MRID No. 00008621. HED Doc. No. 000920. 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.

6. Feussner, E. et al. (1983). Embryo-Fetal Toxicity and Teratogenicity Study of Methomyl in the Rabbit: MRID No. 00131257. HED Doc. No. 003522, 007238. Classification: Core minimum data. This study satisfies data requirement 83-3b of Subpart F of the pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Paynter, O. E. (1966). Final Report: Three-Month Dietary Administration--Rats: MRID No. 00007190. HED Doc. No. 000922, 000924. Classification: Core minimum data. This study satisfies data requirement 82-1a of Subpart F of the pesticide Assessment Guideline for subchronic toxicity testing in rats.

8. Sherman, H. (1967). Three-Month Feeding Study on Dogs with S-Methyl N-[methylcarbamoyl) oxyl] thioacetimidate [lannate

(R)=Methomyl Insecticide; INX-1179]: MRID No. 00009010. HED Doc. No. 000922. Classification: Core Supplementary data. This study does not satisfy data requirement 82-1b of Subpart F of the pesticide Assessment Guideline for subchronic toxicity testing in dogs.

10. Cortina, Y. et al. (1984). In vivo Bone Marrow Chromosome Study in Rats: MRID No. 00161888. HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the pesticide Assessment Guideline for mutagenicity testing.

12. Bentley, K. (1995). Mouse Bone Marrow Micronucleus Assay of DPX-X1179-394. MRID No. 44047703, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the pesticide Assessment Guideline for mutagenicity testing.

13. McCooey, K. (1984). CHO/HGPRT Assay for Gene Mutation: Ethanimidothioic acid N- (methylamino)carbpmylooxyo-methyl ester: MRID No. 00161887. HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the pesticide Assessment Guideline for mutagenicity testing.

14. Blevins, R. D. et al. (1977). Mutagenicity screening of five methyl carbamate insecticides and their nitroso derivatives using mutants of Salmonella typhimurium LT2. Mutation Research 56: 1-6. MRID No. 00008623. HED No. 000000. Classification: Supplementary data.

15. Simmon, V. et al. (1977). Evaluation of Selected Pesticides as Chemical Mutagens: In vitro and In vivo Studies. MRID No. 00124901, HED Doc. No. 000000. Classification: Supplementary data.