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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methyl Isothiocyanate (MITC)

CASRN. 556-61-6
EPA Chem. Code: 068103
Caswell No. 573

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

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

TO: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

Esther Saito, Chief
Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on February 9, 1995 to discuss and evaluate the existing and recently-submitted toxicology data in support of Methyl Isothiocyanate re-registration and to assess a Reference Dose (RfD) for this chemical.

The chemical is registered for use as a pre-planting soil fumigant for weeds, fungi, insects and nematodes in potatoes, tobacco, vegetables, and ornamentals. The chemical is applied to soil by injection.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity/carcinogenicity study in rats **(83-1a and -2a or 83-5)**, a carcinogenicity study in mice **(83-2b)**, a one-year oral toxicity study in dogs **(83-1b)**, a two-generation reproductive toxicity study in rats **(83-4)**, dermal developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a subchronic inhalation toxicity study in rats **(82-4)**, two subacute (one-month) dermal toxicity studies in rats **(82-2)**, and a battery of mutagenicity studies in the categories of gene mutation **(84-2a)**, structural chromosomal aberrations **(84-2b)**, and other genotoxic effects **(84-4)**.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity studies in rats (83-1a, MRID No. 00150078) and dogs (83-1b, MRID No. 41240701) to be unacceptable and not upgradable. In addition to other deficiencies mentioned in the data evaluation records, it was difficult to accurately ascertain the actual doses ingested by the animals because of the high volatility and instability of the test material.

The Committee considered the subacute (30-day) dermal toxicity study in rats (82-2, MRID No. 41221406) to be acceptable and the data evaluation record (HED Doc. No. 011275) to be adequate. The Committee discounted all systemic effects observed except the increased liver weight. All other systemic effects were considered, possibly, as secondary or compensatory mechanism to the skin effects. Therefore, the Committee recommended not to establish a NOEL based on these systemic effects. The Committee deferred to the respective toxicology branch to investigate the magnitude of liver weight changes and determine whether it could be considered a treatment-related or biologically significant effect. Subsequently, the scientific reviewer determined that the increase in absolute and/or relative liver weights at the dose level of 10 mg/kg/day were about 10%. The effect was not considered by the respective branch to be biologically significant. Consequently, the NOEL/LOEL were considered to be 10 and 100 mg/kg/day, respectively.

The Committee considered the subacute (one-month) dermal toxicity study in rats (82-2, MRID No. 00132815) to be Core-supplementary data.

The Committee considered the subchronic inhalation toxicity study in rats (82-4, MRID No. 41221407) to be acceptable and the data evaluation record (HED Doc. No. 011275) to be adequate. Females of the high dose group exhibited signs of hind limb dysfunction, skeletal muscle degeneration and decreased body weight gain. Males did not show any signs of toxicity that could be considered treatment-related.

The Committee considered the subchronic inhalation toxicity study in rats (82-4, MRID No. 40756901) to be acceptable and the data evaluation record (HED Doc. No. 011275) to be adequate. In this study the animals were exposed to the chemical for 4 hours daily, but the NOEL/LOEL were extrapolated from 4 hours to 6 hours exposure, thus lowering the NOEL/LOEL. The Agency Guideline required the NOEL/LOEL to be based on a four hour exposure period. Justifications for such an extrapolation were not provided.

B. Neurotoxicity:

No acute or subchronic neurotoxicity data (81-8 or 82-7) were

available for review by the Committee.

C. Carcinogenicity:

The Committee considered the carcinogenicity studies in both rats (83-2a, MRID No. 00150078) and mice (83-2b, MRID No. 00150075, 00151942) to be unacceptable and not upgradable. In addition to other deficiencies mentioned in the data evaluation records, it was difficult to accurately ascertain the actual doses ingested by the test animals because of the high volatility and instability of the test material. Furthermore, the dose levels tested in both studies were inadequate (too low) for carcinogenicity testing in either species.

C. Reproductive and Developmental Toxicity:

The Committee considered the two-generation reproductive toxicity study in rats (83-4, MRID No. 40974601, 40974602, 92114015) to be Core-supplementary, but upgradable, and the data evaluation record (HED Doc. No. 007145) to be adequate. The Committee indicated that the information needed to upgrade this study is not extensive; it is recommended that the registrant be requested to submit this information. The chemical was administered in drinking water at levels of 2, 10, or 50 ppm (equivalent to 0.2, 1, or 5 mg/kg/day). The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The Committee noted that the testing for developmental landmarks and functional neurotoxicity were conducted on the litters of both generations and were negative.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00150077) to be Core-supplementary, but upgradable, and the data evaluation record (HED Doc. No. 005414) to be adequate. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The Committee indicated that the significant decreases in mean fetal weight and crown-rump length values at the highest dose tested appear to be treatment-related. Tentative developmental NOEL/LOEL were set at 5 and 25 mg/kg/day, respectively. Nevertheless, because the fetal evaluation data are incomplete and because some unusual findings (e.g., lens opacities) require further explanation, the study was classified as Core-supplementary data.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 00150076) to be Core-supplementary and the data evaluation record (HED Doc. No. 005414) to be adequate. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The Committee agreed with the reviewer that the significant decrease in mean fetal weight and mean crown-rump length are not treatment-related effects based on the historical control data provided. The historical control data illustrate that these findings are artifacts related to an unusual

control group. The Committee indicated that the deficiencies noted are severe enough that the study could be categorized as not upgradable.

The Committee concluded that, based on the available data, there was no evidence of reproductive toxicity in rats at dose levels up to and including 5 mg/kg/day. In the developmental toxicity study in rats, reduced fetal body weights and crown-rump length were observed at a dose of 5 mg/kg/day, but adequate structural assessment of fetuses was not provided in the study report. No developmental toxicity was observed in the rabbit study; however, this study was inadequate and not upgradable.

E. Mutagenicity:

Several mutagenicity studies were available for review by the Committee in the categories of gene mutations (84-2a), structural chromosomal aberrations (84-2b), and other genotoxic effects (84-4).

The Committee considered the structural chromosomal aberration assay in V79 lung cells (84-2b, MRID No. 00150074) to be acceptable and the data evaluation record HED Doc. No. 005368 to be adequate. The study was positive in the presence of a metabolic activating system at concentrations as low as 1 µg/ml and in the absence of metabolic activation at concentrations as low as 2.5 µg/ml. The response increased slightly at 12 hours, but clearly increased at 28 hours after the initiation of treatment. The Committee recommended upgrading the study to acceptable. The data evaluation record should be revised to reflect the Committee's position on the acceptability of the study. The rationale for rejection of the study in the original data evaluation record was mainly based on dose selection. However, a positive response was obtained, therefore, the concentrations used in this study should be considered acceptable.

The Committee considered the gene mutation test in the Salmonella and E. coli WP2 uvrA gene mutation assays (84-2a, MRID No. 41221410) to be acceptable and the data evaluation record (HED Doc. No. 011275) to be adequate. The study was negative up to 100 µg/disc, the highest concentration tested. It should be noted that because of the high volatility of the test compound, a modified assay was performed using an impregnated disc placed on the inside lid of the plates which in turn were sealed in bags. Reduced number of revertant colonies, i.e. signs of cytotoxicity to the bacteria, indicated interaction of the testing organism with testing compound. There was a published Salmonella assay (Mut Res 116: 185-216, 1983) for gene mutation (84-2a) which was considered to be negative.

The Committee considered the unscheduled DNA synthesis (UDS) in primary rat hepatocytes (84-4, MRID No. 00150072) for other

genotoxic effects to be unacceptable and the data evaluation record HED Doc. No. 005368) to be adequate. The study was negative up to 15.2 μg/ml, the highest dose tested, but no raw data were provided to confirm the results. In addition there were also problems with the positive control.

The Committee considered the V79/hgprt assay for gene mutation (84-2a, MRID No. 00150073) to be unacceptable and the data evaluation record (HED Doc. No. 005368) to be adequate. The study was negative up to 1 μg/ml without metabolic activation and 2.5 μg/ml with metabolic activation, the highest concentrations tested. It was determined from the limited toxicities that higher concentrations could have been used.

The Committee considered the DNA damage assay in B. subtilis (84-4, MRID No. 41221410) to be unacceptable and the data evaluation record (HED Doc No. 011275) to be adequate. The study was negative up to 2000 μg/disc, the highest concentration tested. However, no toxicity was observed at the highest dose tested, no precautions were taken against compound loss (volatile compound), only single plates were used, and the chemical was not tested under activated conditions.

The Committee considered the sister chromatid exchange assay in V79 cells (84-2b, MRID #41221412) to be unacceptable and the data evaluation record (HED Doc. No. 011275) to be adequate. The test was negative up to 3.5 μg/ml without metabolic activation and 5 μg/ml with metabolic activation, the highest concentrations used; but higher concentrations could have been used since it did not attain appropriate toxicity levels.

The Committee recommended an in vivo cytogenetics assay, as a follow-up to the positive in vitro results. Also a repeat of the unscheduled DNA synthesis assay is necessary to satisfy the data gap in other genotoxic effects category.

F. Reference Dose (RfD):

Because of insufficiency of the data base and because of the uncertainty arising from deficiencies of the existing studies, the Committee did not recommend establishing an RfD for this chemical.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee on pesticide residues (JMPR).

E. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB, RfD/Peer Review Committee Chairman), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Dave Anderson, Kerry Dearfield, Susan Makris, Henry Spencer, William Sette, and Rick Whiting. In attendance also was Clark Swentzel substituting for Marcia Van Gemert (Chief, TB II).

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

Tim McMahon _____

Mike Ioannou _____

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Marcia Van Gemert _____

CC: Stephanie Irene
Marcia Van Gemert
Mike Ioannou
Tim McMahon
Debra Edwards
Albin Kocialski
Beth Doyle
Kerry Dearfield
RfD File
Caswell File

F. Material Reviewed:

1. Brown, D. (1984). Methyl Isothiocyanate: A chronic oral (drinking water) toxicity and carcinogenicity study in the rat. MRID No. 00150078, HED Doc. No. 005415. Classification: Core-supplementary data. This study does not satisfy data requirements 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Satoh, R. (1980). Two-year chronic oral toxicity and oncogenicity study with Methyl Isothiocyanate in albino mice. MRID No. 00150075, 00151942, HED Doc. No. 005415. Classification: Core-supplementary data. This study does not satisfy data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Herling, R. (1988). T104 Methyl Isothiocyanate: 1-Year oral toxicity in beagle dogs. MRID No. 41240701, 92114014, HED Doc. No. 000000. 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.

4. Barker, L. (1987). T98 Technical Methyl Isothiocyanate: 2-Generation oral (drinking water) reproduction study in the rat. MRID No. 40974601, 40974602, HED Doc. No. 007145. Classification: Core-supplementary data. This study, as presented, does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Irvine, L. (1984). Methyl Isothiocyanate (MITC) oral (gavage) teratology study in the rat. MRID No. 00150077, HED Doc. No. 005414. Classification: Core-supplementary data. This study, as presented, does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Irvine, L. (1984). Methyl Isothiocyanate (MITC) oral (gavage) teratology study in the New Zealand whit rabbit. MRID No. 00150076, HED Doc. No. 005414. Classification: Core-supplementary data. This study, as presented, does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

7. Rosskamp, G. et al. (1978). T22 Methyl Isothiocyanate: ZK 3.318; A 12-13 week inhalation study in the rat. MRID No. 41221407, HED Doc. No. 011275. Classification: Core-minimum data. This study satisfies data requirement 82-4 of Subpart F of the Pesticide Assessment Guideline for subchronic inhalation toxicity in rats.

8. Scobel, C. and Schweinfurth, H. (1986). T20/2-Methyl Isothiocyanate: Subacute (28-30) dermal toxicity study in the

rat. MRID No. 41221406, HED Doc. No. 0112214. Classification: Core-minimum data. This study satisfies data requirement 82-2a of Subpart F of the Pesticide Assessment Guideline for subacute dermal toxicity in rats.

9. Tsubura, Y. et al. (19..) . One-month toxicological study with MITC in rats by dermal application. MRID No. 00132815, HED Doc. No. 003991. Classification: Core-supplementary data. This study does not satisfy data requirement 82-2 of Subpart F of the Pesticide Assessment Guideline for one-month dermal toxicity study in rats.

10. Shirasu, Y. (1978). T25 Methyl Isothiocyanate: Microbial mutagenicity testing on methyl Isothiocyanate. MRID No. 41221410, HED Doc. No. 011275. Classification: Acceptable. This study satisfies data requirement 84-2b of Subpart F of the Pesticide Assessment Guideline for structural chromosomal aberrations.

11. Heidemann, A. (1988). T102 Methyl Isothiocyanate: Sister chromatid exchange assay in chinese hamster V79 cells with Methyl Isothiocyanate technical (MITC). MRID No. 41221412, 92114019, HED Doc. No. 011275. Classification: unacceptable. This study does not satisfy data requirement 84-4 of Subpart F of the Pesticide Assessment Guideline for testing for other genotoxic effects.

12. Cifone, M. (1985). Evaluation of Methyl Isothiocyanate in the rat primary hepatocyte unscheduled DNA synthesis assay. MRID No. 00150072, HED Doc. No. 005368. Classification: unacceptable. This study does not satisfy data requirement 84-4 of Subpart F of the Pesticide Assessment Guideline for testing for other genotoxic effects.

13. Miltenburger, H. (1984). Evaluation of the results from testing the substance ZK 3.318, Methyl Isothiocyanate for mutagenic potential in the HGPRT test. MRID No. 00150073, 92114016, HED Doc. No. 009826. Classification: Unacceptable. This study does not satisfy data requirement 84-2a of Subpart F of the Pesticide Assessment Guideline for gene mutation testing.

14. Miltenburger, H. (1984). Evaluation of the results on testing the substance ZK 3.318, Methyl Isothiocyanate for mutagenic potential in the in vitro chromosome aberration test. MRID No. 00150074, HED Doc. No. 005368. Classification: Acceptable, as upgraded by the RfD Committee. This study satisfies data requirement 84-2b of Subpart F of the Pesticide Assessment Guideline for structuraL chromosomal aberrations.