EPA Reviewer: Anna Lowit, Ph.D.
Reregistration Branch 2, Health Effects Division (7509C)
EPA Secondary Reviewer: Judy Facey, Ph.D.
Reregistration Branch 2, Health Effects Division (7509C)

Signature: [signature] **Date** 4/7/04
Signature: [signature] **Date** 4/7/04

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TXR#: 0051394

DATA EVALUATION RECORD

Updated Executive Summary to Previous TXR # 005415

STUDY TYPE: Carcinogenicity - mice, [drinking water] OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 068103

DP BARCODE: D284267
SUBMISSION NO.: S618557

TEST MATERIAL (PURITY): MITC (93.14%)

SYNONYMS: Methyl isothiocyanate

CITATION: Satoh, R. (1980) Two-year Chronic Oral Toxicity and Oncogenicity Study with Methyl Isothiocyanate in Albino Mice (106 Week Final Report). Unpublished study prepared by Nippon Experimental Medical Research Institute Co. December 1980. MRID no. 00150075 Unpublished

Kashimo, M.; Sato, H. (1985) Two-Year Chronic Oral Toxicity and Oncogenicity Study in Albino Mice (106-Week Final Report): Methyl Isothiocyanate: Addendum to Final Report: T 52. Unpublished report prepared by Nippon Experimental Medical Research Institute Co., Ltd. April 1985. MRID no. 151942 Unpublished.

SPONSOR: Nor-Am Agricultural Products

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 00150075) MITC (93.14% ai., Lot no. MS25206) was administered to 70 ICR:JCL albino mice/sex/dose in drinking water at dose levels of 0, 5, 20, 80, and 200 ppm (approximately equivalent to 0, 0.82, 3.30, 11.83, and 25.71 mg/kg bw/day in males and 0, 0.91, 3.66, 13.03, 29.03 mg/kg/day in females) for 106 weeks. Drinking water solutions were prepared daily. Six mice/sex/group were sacrificed at 26 and 52 weeks for determination of clinical and histopathological parameters.

Survival after 106 weeks among the control, 5, 20, 80, and 200 ppm levels were comparable for

male and female mice (35%, 25%, 29%, 28%, and 37 % alive for males; 37%, 38%, 37%, 39%, and 37%, for females).

Body weight gain was decreased significantly at the 80 and 200 ppm level in male mice and at the 200 ppm level in female mice periodically throughout the study up to week 98. From week 98-termination, the mean body weights were comparable for all treatment groups. Approximately 15% and 30% less water was consumed at the 80 and 200 ppm levels, respectively, by male and female mice.

Changes in hematological and clinical chemistry parameters were sporadic and inconsistent. RBC count decreased for males at the 80 and 200 ppm was accompanied by an increase in reticulocytes for males at the 200 ppm level during week 52, but not at week 106. Total blood protein decreased for males and females at the 80 and 200 ppm levels during week 26 accompanied by decreased blood urea nitrogen values for males at the 80 and 200 ppm levels. Cholesterol values were decreased for females at the 200 ppm level also during week 26. By week 106, female aspartate aminotransferase values were increased at the 200 ppm level.

Relative and absolute pituitary weights for the 200 ppm level were increased for females at the interim sacrifices at weeks 26 (relative only), 52 and 106 and for males during week 52. Relative and absolute thyroid weights increased at the 80 and 200 ppm levels in males and females at week 52 and females only at termination.

There were treatment related gross pathological effects observed by the authors. A dose-dependant increase in the incidence of cystic ovaries was observed. An increase in tumors was not observed in treated animals. The DER lists several tissues (most notably the female mammary gland, colon, and rectum) which were not examined pathologically. Also, the mice in the study exhibit minimal toxicity which is indicative that a maximum tolerated dose was not achieved. It is difficult to determine MITC's carcinogenic potential based on the results of this study.

The LOAEL is 80 ppm (3.30 and 3.66 mg/kg/day for males and females, respectively), based on decreased body weight gain throughout the majority of the study and reduced water consumption. The NOAEL is 20 ppm (0.82 and 0.91 mg/kg/day for males and females, respectively).

This carcinogenicity study in the mice is **unacceptable/guideline** and does **not** satisfy guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice. Although the study provides well-conducted stability studies of MITC in water, the study does not provide actual analytical results of the concentration of MITC actually provided to the mice or concentration of MITC in the drinking water at the time of removal from the cages.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were not provided.

DATA FOR ENTRY INTO ISIS

Carcinogenicity Study - mice (870.4200b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
068103	00150075	carcinogenicity	mice	106 weeks	oral	drinking water	0.82-29.03	0, 0.82, 3.30, 11.83, 25.71 M 0, 0.91, 3.66, 13.03, 29.03 F	0.82	3	decrease in body weight and water consumption	Toxicity

Methyl isothiocyanate (MITC) P.C. Code 068103
83-2 Carcinogenicity Study - Mice, MRID 460075-037
Addendum to DER 005415

Executive Summary: Five groups of 70 ICR:JCL albino mice/sex/group received MITC in their drinking water at levels of 0, 5, 20, 80 and 200 ppm (equivalent to 0.75, 3.0, 12 and 30 mg/kg/day, respectively) for 106 weeks. Six mice/sex/group were sacrificed at 26 and 52 weeks for determination of clinical and histo-pathology paramters (MRID 460075-037).

Survival after 106 weeks among the control, 5, 20, 80 and 200 ppm levels was comparable, with percent alive for males being 35, 25, 29, 28 and 37, respectively and for females 37, 38, 37, 39 and 37, respectively.

Body weight gain decreased significantly at the 80 and 200 ppm levels during weeks 13 and 52, being comparable to the controls by the termination of the study. Reduced water intake was observed at the 80 and 200 ppm levels. Platelet count increased for females at the 80 and 200 ppm levels during week 26, but not at the 52 or 106 intervals. RBC count decreased for males at the 80 and 200 ppm levels accompanied by an increase in reticulocytes for males at the 200 ppm level during week 52, but not at week 106. Total blood protein decreased for males and females at the 80 and 200 ppm levels during week 26 accompanied by decreased blood urea nitrogen values for males at the 80 and 200 ppm levels. Cholesterol values were decreased for females at the 200 ppm level also during week 26. By week 106, female aspartate aminotransferase values were increased at the 200 ppm level. Relative pituitary weights for the 200 ppm level were increased for females during weeks 26, 52 and 106 and for males during week 52. Relative thyroid weights increased at the 80 and 200 ppm levels in males and females by week 52 and for males at the 200 ppm level by week 106. The additional histopathological information requested in DER 005415 preclude further evaluation of the carcinogenic potential of MITC.

This study is not acceptable and does not satisfy the Guideline Data Requirement for a carcinogenicity study (83-2) in mice. It is deficient for the 6 items listed on pages 43 and 44 of DER 005415. Analytical data on the stability and actual concentrations of MITC in the drinking water are requested. This study is Core Classified-Supplementary.

Methyl isothiocyanate (MITC) P.C. Code 068103
83-2 Carcinogenicity Study - Mice, MRID 460075-037
Addendum to DER 005415

The following table summarizes body weight gain (g) and percent change as compared to the controls during weeks 0-13, 0-52 and 0-106.

Week	Control		5 ppm		20 ppm		80 ppm		200 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0-13	22.1	14.7	22.2	15.1	21.6	14.9	20.9	14.9	19.3	14.0
			0	+3	-2	+1	-5	+1	-13	-5
0-52	24.9	18.3	24.8	19.1	24.5	18.7	23.1	18.3	23.0	16.4
			0	+4	-2	+2	-7	0	-8	-10
0-106	22.9	18.7	22.8	18.8	21.7	18.9	22.1	18.1	23.1	17.8
			0	0	-5	+1	-3	-3	0	-5

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