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Reregistration Branch 2, Health Effects Division (7509C)
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Reregistration Branch 2, Health Effects Division (7509C)

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TXR#: 0051394

DATA EVALUATION RECORD

Updated Executive Summary to Previous TXR # 005415

STUDY TYPE: Carcinogenicity (drinking water)- rat; OPPTS 870.4200a [§83-2a]; OECD 451.

PC CODE: 068103

DP BARCODE: D284267
SUBMISSION NO.: S618557

TEST MATERIAL (PURITY): MITC (95-96%)

SYNONYMS: Methyl isothiocyanate

CITATION: Brown, D. (1984) Methyl Isothiocyanate: A Chronic Oral (Drinking Water) Toxicity and Carcinogenicity Study in the Rat: Report No. 2611-14/1R. Unpublished study prepared by Hazleton Laboratories Europe Ltd. February, 1984 MRID no. 00150078. Unpublished.

SPONSOR: Nor-Am Agricultural Products

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 00150078) [MITC (95-96% a.i., batch #s 28.166 and 29.482) was administered to 60 Sprague Dawley CD rats/sex/dose in drinking water at dose levels of 0, 2, 10, and 50 ppm (equivalent to 0, 0.2, 1.0 and 5 mg/kg bw/day) for 102 weeks. Ten rats/sex of the control and high dose were sacrificed after one year. Of this group 5/sex/group were placed on untreated water for 4 weeks to assess reversibility. Drinking water solutions were prepared every two or three days.

Survival after 102 weeks among the control, 2, 10, and 50 ppm levels was comparable; the percent alive for males was 65, 63, 58, and 64, respectively and the percent alive for females was 42, 33, 53, and 53, respectively. Treatment related clinical signs were not observed.

No dose related effects on body weight gain or food intake as compared to controls were reported. Reduced water intake at the high dose was associated with the 'pungent odor and its known to irritate mucous membranes.' No dose related affects on hematology, clinical chemistry,

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urinalysis, or organ weights were reported as compared to control values.

No compound or dose related effects on the incidence of non-neoplastic or neoplastic lesions were reported from ingestion of MITC at doses up to 50 ppm. A maximum tolerated dose was not demonstrated.

A LOAEL was not established in this study. The NOAEL is the highest dose tested, 50 ppm (5 mg/kg/day).

This carcinogenicity study in the rat is **unacceptable-guideline** and **does *not* satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in rats. This study cannot be upgraded due to inadequate concentration and stability analysis of MITC in drinking water.

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

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DATA FOR ENTRY INTO ISIS

Carcinogenicity Study - rats (870.4200a)

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	00150078	carcinogenicity	rats	102 weeks	oral	drinking water	0.2-5.0	0, 0.2, 1.0, 5.0	5	Not established	No adverse effects identified	Inadequate concentration and stability analysis of MITC in drinking water.

Methyl isothiocyanate (MITC) P.C. Code 068103
83-1 & 2 Chronic/Carcinogenicity Study - Rat, MRID 460075-040
Addendum to DER 005415

Executive Summary: Four groups of 60 Sprague Dawley CD rats/sex/group received MITC in their drinking water at levels of 0, 2, 10 and 50 ppm (equivalent to 0.2, 1.0 and 5 mg/kg/day, respectively) for 102 weeks. Ten rats/sex of the control and high dose were sacrificed after one year. Of this group 5/sex/group were placed on untreated water for 4 weeks to assess reversibility then sacrificed (MRID 460075-040).

Survival after 102 weeks among the control, 2, 10 and 50 ppm levels were comparable with percent alive for males being 65, 63, 58 and 64, respectively and for females 43, 33, 53 and 53, respectively.

No dose related effects on body weight gain or food intake as compared to controls were reported. Reduced water intake at the high dose was associated with the "pungent odor and its known to irritate mucous membranes". No dose related affects on hematology, clinical chemistry, urinalysis or organ weights were reported as compared to the control values. No compound or dose related effects on the incidance of non-neoplastic or neoplastic lesions were reported from ingestion of MITC at doses up to 50 ppm. A maximum tolerated dose was not demonstrated.

This study is not acceptable and does not satisfy the Guideline Data Requirement for a chronic/carcinogenicity study (83-1) in the rat. It is deficient for the 11 items listed on pages 1 and 2 of DER 005415. The instability of MITC in aqueous solutions may account for the wide disparity between the nominal and actual concentratons reported and further question the reliability of this study. This study is Core Classified - Supplementary