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DATA EVALUATION RECORD

Updated Executive Summary to Previous TXR # 007415

STUDY TYPE: Reproduction and Fertility Effects Study - rat OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 068103

DP BARCODE: D284267
SUBMISSION NO.: S618557

TEST MATERIAL (PURITY): MITC (95.8-96.5%)

SYNONYMS: Methyl isothiocyanate

CITATION: Barker, L. (1987) T98 Technical Methylisothiocynate: 2 Generation Oral (Drinking Water) Reproduction Study in the Rat: Proj. ID. 5280-194/8. Prepared by Hazleton UK. December 23, 1987. MRID no. 40974601. Unpublished.

Barker, L. (1988) T98A Technical Methylisothiocyanate (MITC): 2 Generation Oral (Drinking Water) Reproduction Study in the Rat: Determination of Methylisothiocyanate Concentration in Drinking Water Solutions for a Multigeneration Study in the Rat: Proj. ID 5289/194/8. Prepared by Hazleton UK. March 7, 1988. MRID no. 40974602. Unpublished.

Bright, J.; Crofts, M. (1986) T91A Methyl Isothiocyanate: Determination of Methyl Isothiocyanate Concentrations in Drinking Water for a Range-finding Multigeneration Study in the Rat: Proj. ID RESID/85/91. Prepared by FBC Limited, Schering Agrochemicals Ltd. February 28, 1986. MRID no. 40974603. Unpublished.

Barker, L. (1985) T91 Technical Methyl Isothiocyanate (MITC): Oral (Drinking Water) Range-Finding Reproduction Study in the Rat: Project ID: TOX/85/203/3. Prepared by Hazletton Laboratories Europe Ltd. November 21, 1985. MRID no. 41057601. Unpublished.

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Davis, C. (1990) Nor-Am Chemical Company Phase 3 Summary of MRID 40974601 and Related MRIDs 40974602. Technical METHYLISOTHIOCYANATE: 2 Generation Oral (Drinking Water) Reproduction Study in the Rat (T98, T98A); Lab ID. 194/8; TOX 85003. Prepared by HAZLETON UK. April 13, 1990. MRID no. 92114015. Unpublished.

SPONSOR: Nor-Am Agricultural Products

EXECUTIVE SUMMARY:

In a two-generation reproduction study (MRID 40974601) MITC (95.8-96.5% a.i., batch # 340178) was administered to 30 parental and 25 F_1 Sprague-Dawley rats /sex/dose in drinking water at dose levels of 0, 2, 10, and 50 ppm (mean intake of MITC in water: 0, 0.16, 0.76, and 3.58 mg/kg/day for parental males; 0, 0.21, 1.01, and 4.76 mg/kg/day for parental females; 0, 0.15, 0.71, 3.40 mg/kg/day for F1 males; 0, 0.19, 0.87, 4.22 mg/kg bw/day for F1 females). Drinking water was prepared with MITC three times a week; solutions were prepared and given to the rats on the next two or three days (for example, solutions prepared on Monday were used on Tuesday and Wednesday). To compensate for anticipated loss of MITC, solutions were over-formulated by 20%.

One litter per generation was tested in this study. The parental generation was treated for 70 days prior to mating. The F1 generation were reared until weaning at which time 25 F1 males and females were selected for mating. Remaining F1 pups were necropsied. F1 generation was treated for 77 days prior to mating. F2 litters were reared to weaning followed by study termination.

No treatment related mortality, clinical signs, or gross pathology were observed in any generation. Although no reduction in body weight was observed in P generation males, males of the F1 generation in the 50 ppm group, exhibited a 29% decrease in body weight gain ($p < 0.05$) compared to control. During the pre-mating phase, gestation and lactation body weight and body weight gain of females were compared among all groups. (Note to the reader: The pre-existing DER lists significant changes in the low and mid groups in P females–these changes have not been confirmed by the current reviewer. See attached sheets). Although sporadic decreases in food intake were observed, food consumption was similar among treatment groups in the P and F1 generations.

In the P and F1 males of 10 and 50 ppm groups, a dose dependant decrease in water consumption was observed (ranging from -3 to -28%; $p< 0.05$) throughout the treatment period. During the premating and lactation phases, P and F1 females of the 10 and 50 ppm groups also exhibited decreased water consumption (ranging from -7% to -37%, $p< 0.05$). Decreased water consumption was attributed by the study director to poor palatability of MITC.

Although no pathological changes were observed in the pituitary gland and the absolute pituitary weights were not changed compared to control, the relative pituitary weights in P females were increased ($p<0.01$) in the 50 ppm P females.

The parental systemic LOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively), based on decreased body weight gain in F1 males. The parental systemic NOAEL is 10 ppm (0.71 and 0.87 mg/kg bw/day in males and females, respectively).

Number of live pups and number of live pups/female were similar among treatment and control groups in both generations. Pup weight were not effected by treatment with MITC in both generations. Time to pinna unfolding, tooth eruption, and eye opening were similar among all groups. Limited functional observations of tail pinch and surface righting were performed on day 1 offspring; air righting was performed on day 17 offspring; grip strength, papillary reflex, visual placing responses, and auditory startle response were performed on day 21 offspring; no treatment related effects were noted.

The offspring LOAEL > 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively). The offspring NOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively).

No changes in the measured reproductive parameters of mating performance, fertility, reproductive performance and the viability and growth of offspring were observed.

The reproductive LOAEL is > 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively). The reproductive NOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively).

This study is **unacceptable-guideline** and does not satisfy the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and No Data Confidentiality statements were provided.

Note to the reader: The pre-existing DER indicates that the relative gonadal weights were 'increased significantly for females of the mid and high level by 64 and 80%, respectively.' As shown on the attached tables extracted from the study report, relative gonadal weights are similar among all treatment and control groups in both generations.

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

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	40974601	reproductive	rats	2-generation	oral	diet	0.15-3.40	0.15, 0.71, 3.40	0.71	3.40	Body weight	Parental/ systemic
068103	40974601	reproductive	rats	2-generation	oral	diet	0.15-3.40	0.15, 0.71, 3.40	3.40	Not established		Offspring
068103	40974601	reproductive	rats	2-generation	oral	diet	0.15-3.40	0.15, 0.71, 3.40	3.40	Not established		Reproductive

Methyl isothiocyanate (MITC) P.C. Code 068103
83-4, Two-Generation Rat Reproduction, MRID 409746-01 & 02,
Addendum to DER 007145

Executive Summary: In a multigeneration reproduction study (MRID 409746-01 & 02) Sprague Dawley CD rats from Charles River received in their drinking water nominal concentrations of MITC (96.5%) at 0, 2, 10 and 50 ppm (equivalent to 0.2, 1.0 and 5 mg/kg/day, respectively) throughout two successive generations.

The Systemic NOEL is 10 ppm. The Systemic LOEL is 50 ppm with a significant ($p<0.05$) decrease in parental body weight gain (29%). Reproductive NOEL is greater than 50 ppm with no adverse effects on reproductive indices or development of the pups at this level.

Minimal parental toxicity was observed in the high dose group, however, the reduced water intake due to the likely unpalatability of the test material limit further testing at higher dose levels.

This study is not acceptable and does not satisfy the Guideline Data Requirement (83-4) for a mulitgeneration reproduction study in the rat. It is Core Classified - Supplementary, but may be upgraded if the deficiencies cited in DER 007145 are satisfied.

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