9-26-94

C11275

Primary Review by Ray Landolt 9/21/94
Review Section I, TB II/HED (7509C)
Secondary Review by Mike Ioannou 9/26/94
Review Section I, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: 90-Day Inhalation Study - Rat (82-4)

Test Material: Methyl isothiocyanate

Synonym: MITC, Methyl mustard oil

MRID 412214-07
P.C. No. 068103
Barcode D194652
Submission S447097

Classification: Wood (Timber) Treatment

Study No. 374/77

Date of Study: September 26, 1978

Title of Report: T22 Methyl Isothiocyanate: ZK 3.318
A 12-13 Week Inhalation Study in the Rat

Authors: G. Rosskamp, G. Schobel, A.S. Bhargava,
P. Staben and G. Schuppler

Testing Facility: Schering AG, Pharmaceutical Research, Germany

Sponsor: Nor-Am Chemical Company

Registrant: Degussa Corporation

Executive Summary: In a subchronic inhalation study (MRID 412214-07) 3 groups of 10 rats/sex/dose received a nose-only inhalation exposure to MITC at 3.16, 30.67 and 137.13 ug/L 4 hours/day, 5 days/week over a 12 to 13 week period. There were two control groups of 10 rats/sex/dose, one maintained in the laboratory without inhalation exposure and the other in the chamber without exposure to MITC.

By extrapolation from a four to six hour exposure (82-4 Guideline Data Recommendation for 6 hour exposure) the NOEL and LOEL levels are 2.1 (low dose) and 20.6 ug/L (mid dose), respectively. Effects reported at the mid dose were decreased body weight, food efficiency and blood protein values accompanied by increased water intake. At the high dose (91.9 ug/L) the animals exhibited apathy, salivation, nasal discharge and stimulated vocalization. These animals exhibited a decrease in body weight, food intake and food efficiency accompanied by an increase in water intake. Alterations in clinical chemistry values at this dose include decreased total protein with increased alkaline phosphatase and alanine aminotransferase values.

This study is classified Core Mininum and satisfies the 82-4 Guideline Data Requirement 82-4 for a 90-day inhalation study.

1

A. Materials:

1. Test Compound: Methyl isothiocyanate (ZK 3.318) with a purity of 95.69% was used in this study. Contaminants are [redacted] in trace amounts

2. Test Animals: Male and female Wistar rats weighing between 142 and 239 g were used in this study.

B. Study Design - Allocation of animals

1. Ten rats/sex were maintained in the laboratory as untreated controls.

Test Group	Analytical Concentration ppm	Analytical Concentration ug/L	Male	Female
Chamber Control	-	-	10	10
Low Dose	1.04	3.16	10	10
Mid Dose	10.09	30.69	10	10
High Dose	45.11	137.13	10	10

The doses selected for this study were based on a range finding study in which two groups of 5 rats/sex/group were exposed to 100 ppm MITC. One group that received a 1-hour daily exposure for 4-days exhibited "moist noses and mouths" with an apathetic appearance. The other group received a 4-hour daily exposure for 4-days exhibited "bloody noses and mouths" with death of 2/10 animals within 4-days.

When not exposed to the test material all animals were housed individually in air conditioned rooms (20-23°C and relative humidity of 50-56%) with a 12 hour light/dark cycle provided for a uniform environment. Food and water were available ad libitum.

2. Exposure: The animals received a nose-only exposure to a gas-air mixture generated in a dynamic air flow chamber for 4-hours/day, 5-days/week over a 12 to 13 week period. The 82-4 Guideline Data Recommendation for a 90-day inhalation study is 6-hour exposure. To correct for the four exposure in this study one may use Haber's rule which states that the animal response is constant when the product of the concentration (C) of a substance, multiplied by time (t), during which the exposure experienced is a constant (C x t = K). By extrapolation, the inhalation exposure of the low, mid and high dose in this study would be 2.1, 20.6 and 91.9 ug/L, respectively for a 6-hour exposure.

2

Relative humidity and temperature within the chamber ranged between 46-53% and 21-22°C, respectively. Chamber concentrations of the air-gas mixture of MITC were monitored from samples drawn for 10 minutes during the first and third hour exposure for infra-red analysis. Chamber design and generation of the air-gas mixture of MITC on pages 7 and 8 of this report are attached.

C. Methods and Results:

1. Observations:

a. Gross signs of toxicity were generally limited to the high dose with all animals apathetic in appearance during days 27 to 85 accompanied by salivation and nasal discharge during days 1 to 85 of the study. Stimulated vocalization was reported for 6/20 animals during days 58 to 78. Additional signs observed at the high dose include dyspnea, stiff-legged gait and enlarged abdomem.

b. One animal died during week 4 at the high dose due to experimental error (blood sampling).

c. Body weight was recorded weekly. A significant ($p<0.01$) decrease in body weight gain was reported for males (63%) and females (47%) at the high dose as compared to the chamber control group. At the mid dose body weight gain was decreased (not significant) for males (11%) and females (15%) as compared to the chamber controls.

d. Food consumption was recorded weekly. A significant ($p<0.05$) decrease in food consumption was reported for males (6%) and females (8%) at the high dose as compared to the chamber controls. Food intake for the low and mid dose animals were comparable to the chamber control group.

e. Food efficiency calculated from the mean values reported in the table on the following page show that food efficiency was affected to a great extent at the high dose males and females and to a lesser degree in the mid dose males and females with a decrease of 15 and 12%, respectively.

Food Efficiency (%)

	Chamber Control	Exposure (ug/L) 3.16	30.69	137.1
Males	7.5	7.6	6.4	2.9
Females	5.7	5.5	5.0	3.0

The following table from the text of this study summarizes the tables, in German, submitted of the mean values and standard deviations for changes in body weight gain, food consumption and water intake.

Group	Food consumption (kg)		Water consumption (kg)		Bodyweight gain (g)	
	M	F	M	F	M	F
I (untreated control)	1.44/0.08	1.12/0.06	2.58/0.26	2.34/0.20	158/18	77/17
II (sham dose)	1.24/0.08	1.07/0.05	2.45/0.16	2.31/0.24	93/16	62/ 7
III ZK 3.318 (≈ 1 ppm)	1.22/0.04	1.03/0.05	2.37/0.31	2.35/0.26	93/21	57/13
IV ZK 3.318 (≈ 10 ppm)	1.29/0.05	1.05/0.06	2.79/0.23*	2.8 /0.5*	83/19	53/11
V ZK 3.318 (≈ 45 ppm)	1.17/0.05*	0.98/0.05**	2.71/0.28	2.69/0.27*	34/26**	33/13**

--- $p < 0.05$; ___ $p < 0.01$ (comparisons with group I)

* $p < 0.05$; ** $p < 0.01$ (comparisons with group II)

f. Water intake (recorded twice weekly) increased at the mid dose significantly ($p<0.05$) for males (14%) and females (21%) and at the high dose for males (16%) as compared to the chamber controls. An increase (not significant) in water intake was reported for the high dose females (11%).

g. Ophthamoscopic examination of all animals during weeks -2, -1 and 12 of the study were negative.

2. Clinical Findings:

a. Hematology - Blood was withdrawn during weeks -2, 4 and 12 from 5 animals/sex/group for determination of the following parameters (the checked (*) parameters are recommended by Subdivision F Testing Guidelines of November 1989).

* Erythrocyte count
* Leukocyte count
  Reticulocyte count
* Differential count
* Thrombocyte count
* Hemoglobin concentration
* Hematocrit
  Mean corpuscular hemoglobin
  Mean cell volume

4

A significant ($p<0.05$) increase in leucocyte and lymphocyte count during week 4 accompanied by a significant ($p<0.01$) increase in neutrophil count during weeks 4 and 12 were reported for the high dose females. Hematocrit and erythrocyte values were significantly ($p<0.05$) increased for the high dose males by week 4. Bone marrow analysis revealed a significant ($p<0.05$) reduction of eosinophilic granulopoiesis in the high dose females by week 12. These changes are considered spurious events and not dose related.

Thromboplastin time, partial thromoplastin time, thrombin time and fibrinogen determined during weeks -1, 4 and 12 from 5 animals/sex/dose were without an effect on the parameters determined.

b. Blood Chemistry - Blood was withdrawn during weeks -1, 4 and 12 from 5 animals/sex/dose for determination of the following parameters (the checked (*) parameters are recommended by Subdivision F Testing Guidelines of November 1989). The check (**) parameters were omitted.

* Alkaline phosphatase	* Total Protein
* Aspartate aminotransferase	* Albumin
* Cholesterol	* Urea
* Lactic acid dehydrogenase **	* Phosphate **
* Glucose (fasting)	* Calcium **
Alanine aminotransferase	* Sodium **
Protein electrophoresis	* Bilirubin **

A significant ($p<0.05$) decrease in total protein was reported for the mid and high dose males and for the high dose females by week 12 of the study. Fasting glucose values were significantly ($p<0.05$) reduced by week 12 for the high dose females. At the high dose a significant ($p<0.05$) increase in alkaline phosphatase values were reported for males and females accompanied by significantly ($p<0.01$) increased alanine aminotransferase values in males by week 12.

c. Urinalysis parameters were examined during weeks 4 and 12 from 5 animals/sex/dose for examination of the following parameters (checked (*) parameters are recommended by Subdivision F Testing Guidelines of November 1989).

* Blood	* Appearance	* Sediment
* Protein	* Glucose	* Specific Gravity
* Ketone bodies	* Urobilinogen	pH
* Total bilirubin	(omitted)	

No changes were recorded related to the test material.

3. Terminal Findings:

Histopathological examination of the following tissues are recommeneded by Subdivision F Guidelines of November 1989. The checked (*) tissues were examined from all animals of the control and high dose. In addition lungs, liver and kidneys of all low and mid dose animals are to be examined. The checked (X) organs were weighed from 10 rats/sex/dose.

*	aorta	* X	pituitary	*	mammary gland
	eyes	*	ileum	* X	spleen
	caecum	*	trachea	*	muscle
*	colon		jejunum	* X	adrenals
*	duodenum	*	bone marrow	*	uterus
* X	brain	* X	liver	*	ovaries
*	skin	*	lung		oviduct
* X	heart	* X	lymph node	*	pancreas
*	testes	*	stomach	*	spinal cord
	epididymis	* X	kidneys	*	peripheral nerve
	esophagus		rectum	*	thyroid/parathyroid
*	thymus		salivary glands	*	urinary bladder

Bronchi and prostate were examined in addition to the recommended tissues.

a. Macroscopic findings - No gross pathological findings were reported relative to the test material.

b. Organ Weights - Absolute and relative organ weight changes correlate with the decrease in body weight for the high dose males and females.

c. Histopathological examination of the untreated controls and the high dose animals were without effect on the tissues examined. Tissues of the low and mid animals were not examined.

D. Discussion: This study was conducted with 10 rats/sex/dose of 3.16, 30.67 and 137.13 ug/L. The animals received a nose-only inhalation exposure of MITC 4-hours/day, 5-days/week over a 12 to 13 week period. To correct for the four hour exposure the doses for a six hour exposure for the low, mid and high dose would be 2.1, 20.6 and 91.9 ug/L, respectively

Clinical determinations of hematology, chemistry and urinalysis parameters were conducted on 5 rather than the 10 animals/sex/dose. No definitive data were provided from the terminal observations to support the clinical findings reported. Adequate information was provided from the hematology, urinalysis and blood chemistry values to determine the NOEL and LOEL for this study.

The low and mid dose animals were not subjected to histopathologic evaluation of lungs, liver and kidenys. However, the high dose animals were without an effect on histopathological examination and preclude the need to examine the low and mid dose tissues.

E. Conclusions: NOEL = 2.1 ug/L

LOEL = 20.6 ug/L with decreased body weight, food efficiency and blood protein values accompanied by increased water intake.

Classification of Data - Minimum

This study was conducted prior to the November 1989 Guidelines for testing and was not classified as a Guideline study because of the deficiencies cited in the discussion. This study does contain useful information and is acceptable for a 90-day inhalation study.

Page_____ is not included in this copy.

Pages 8 through 9 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.