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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

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JUN 19 1989

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 239-2471 - Acephate: Acute Dermal Toxicity Study with Methylthioacetate, a Contaminant of Technical Grade Acephate

TOX Chem No.: 2A (Acephate)
584D (Methyl-thioacetate)
TOX Project No.: 9-0304
Record No.: 231845

FROM: John Doherty 5/23/89
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: William H. Miller, PM 16
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THROUGH: Edwin R. Budd, Section 5/15/89 E.B. 5/30/89
Section I, Toxicology Branch I (IRS) Support
Health Effects Division (H7505C)

The Ortho Division of the Chevron Chemical Company has submitted an acute dermal toxicity study in rabbits with the chemical methylthioacetate (MTA). MTA is a contaminant of technical grade acephate. Previous studies (refer to J. Whalan review dated September 5, 1985 for EPA Registration No. 239-2471) indicated that MTA causes effects in the eye and optic nerve of rabbits following exposure. Mr. Whalan requested a series of studies to help clarify the potential of MTA to affect the eye, visual system, optic nerve and tract. Several studies submitted in response to Mr. Whalan's request were previously reviewed (J.D. Doherty memorandum, date pending). This current submission consists of a rabbit

dermal toxicity study to clarify the LD_{50} of MTA and attempts to establish a threshold level for MTA to affect the eye and ocular system. The study was reviewed and the following comments apply.

Toxicology Branch Comments

1. The study was reviewed and determined to be SUPPLEMENTARY. The following LD_{50} for acute dermal toxicity was determined.

   LD_{50} = 531 (438 to 644) mg/kg for both sexes combined.

2. The male rabbits dosed with 200 mg/kg and above had some evidence of optic tract lesions described as "histiocytic infiltration, granulomatous inflammation, necrosis, or vascular change" which were reported as resulting in previous studies following dosing with MTA. The number of rabbits affected with these lesions was 2/14, 1/13, and 1/3 for the groups dosed with 200, 400, and 800 mg/kg. Females were not reported as being affected with these lesions.

3. The issues related to MTA as a possible hazard to humans are being addressed in a separate memorandum (J.D. Doherty memorandum, date pending.

Reviewed by: John Doherty 5/13/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin R. Budd 5/15/89
Section I, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: 81-2 - Acute Dermal Toxicity - Rabbits

TOX Chem No.: 2A
584D

Accession No.: 401459-02

Test Material: Methylthioacetate (CAS 1534-08-03), Lot No. SX-1760

Synonyms: MTA

Study No(s).: IRDC 415-049; CEHC 2885; and S-3049

Sponsor: Chevron Environmental Health Center

Testing Facility: International Research and Development Company

Title of Report: The Acute Dermal Toxicity of Methylthioacetate (MTA) in Adult Male and Female Rabbits.

Author(s): J.R. Rittenhouse

Report Issued: April 6, 1988

Conclusions:

LD_{50} = 531 (438 to 644) mg/kg for combined males and females (cumulative LD_{50}).

Male rabbits had evidence of optic tract lesions at 200 mg/kg and above but the incidences were only 2/14, 1/13, and 1/3 for the groups dosed with 200, 400, and 800 mg/kg. Females were not reported as being affected.

Classification: CORE - SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A statement provided by Margery T. Wirth, Director of Quality Assurance (but signed by some other individual) attested that the report was reviewed by the Quality Assurance Department and that inspection of the protocol and random samples for conduct of the study were made.

Review

In this study six groups of male and female rabbits (New Zealand White, approximately 3 months of age) were dosed with methylthioacetate according to the following protocol:

Number of Rabbits		Dosage Level
Males	Females	(mg/kg)
15	15	0
5	5	50
15	15	100
15	15	200
15	15	400
10	10	800

The test article was applied undiluted and as received to the prepared (hair removed from the treatment area with clippers) using a gas tight Hamilton syringe. Following application the test sites were covered with plastic film and gauze bandaging and secured with Dermiform tape. Collars were attached to the rabbits to prevent ingestion of the test material. The test material was kept in contact with the rabbits for 24 hours. The rabbits were sacrificed at days 4, 7, and 14 (5 rabbits at each sacrifice time, except for the rabbits dosed with 50 and 800 mg/kg/day).

Since this study was designed to assess for specific pathological changes in the rabbit optic nerve and chiasma, special pathological procedures were included in the protocol. These included the skull with brain, eye, optic nerve, and pituitary being preserved in situ and the skull be sent in toto to the sponsor for further processing for microscopic evaluation.

Results:

The cumulative LD_{50}s were determined for both sexes at day 4 and at days 7 to 15 as follows:

	Day 4	Day 7 to 15
	(Data are Reported in mg/kg)	
Male Rabbits	648 (448 to 935)	612 (428 to 875)
Female Rabbits	468 (377 to 580)	468 (377 to 580)
Combined Sexes	544 (448 to 661)	531 (438 to 644)

The symptoms reported included "decreased activity" which was evident after 6 hours. Most of the rabbits died within 1 to 6 hours. The rabbits were reported as being healthy by day 2. Body weight changes were not dose related.

The study report states that "Pupillary response to direct light was normal in all rabbits during the study." The test method used to assess for pupillary response was not described.

Dermal irritation reactions were evident in some rabbits which included erythema and edema (slight to moderate). There was also some evidence of desquamation and fissuring and one rabbit exhibited dark discoloration.

The pathology report was prepared as a separate Appendix B and was signed by Ward R. Richter. Dr. Richter reported that the compound-related lesions of the optic nerve and optic chiasma consisted of "histiocytic infiltration, granulomatous inflammation, necrosis or vacuolar change." The following table illustrates the incidence of these observations as reported in Dr. Richter's summary table.

Lesion		0	50	100	200	400	800
Histiocytic Infiltration	M	0	0	0	1	0	0
	F	0	0	0	0	0	0
Granulomatous Inflammation	M	0	0	0	1	0	0
	F	0	0	0	0	0	0
Necrosis	M	0	0	0	1	0	1
	F	0	0	0	0	0	0
Vacuolar Change	M	0	0	0	1	1	0
	F	0	0	0	0	0	0

[Note: There were 15 of each sex reported examined for the controls and group receiving 100 mg/kg. There were 14 and 13 of each sex reportedly examined for the groups dosed with 200 and 400 mg/kg. There were three males and no females reported

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examined for the group dosed with 800 mg/kg and 5 of each sex for the group dosed with 50 mg/kg.]

The above table does not show definite evidence of a dose-related effect of MTA on the optic nerve. Inspection of the data table presented by Dr. Richter for optic chiasma also does not show any evidence of an effect of MTA in this structure.

The original pathology report for the rabbits on this study was retabulated for incidence of "histiocytic infiltration, granulomatous inflammation, necrosis and vacuolar change." This retabulation indicated that there were 0/15, 0/5, 0/15, 2/14, 1/13, and 1/3 male rabbits affected with at least one of these lesion types for the control, 50, 100, 200, 400, and 800 mg/kg dosed groups. One male rabbit in the group dosed with 200 mg/kg had more than one type of lesion. No females were affected with these lesions.

Conclusions:

This study is SUPPLEMENTARY. A dermal toxicity study is not required for MTA because it is not a pesticide (it is a contaminant of a pesticide). The study, however, is considered to have demonstrated an LD_{50} following dermal application of MTA.

Toxicology Branch 1 (TB-1) does not consider this study to be helpful in assessing the potential of MTA to affect the eye, optic tract, and visual system. The study report maintains that the pupillary response to direct light was normal but did not describe the method or frequency of assay for evaluating pupillary response. Previous reports indicate that MTA caused delayed or absent pupillary response. The histopathological evaluation of the optic nerve and optic chiasma did, however, indicate that some of the male rabbits dosed at 200 mg/kg and above had lesions in these structures similar to lesions previously reported as resulting from MTA treatment. The conclusion of the study report as provided by the pathologist was that these lesions are compound-related. TB-1 considers that the relationship between MTA dosing and the development of these lesions as demonstrated in this study to be indefinite.