UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JAN 7 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA #239-2452. Review of Acute Inhalation Studies and Dermal Sensitization Study Required to Complete Review of Labeling for Reregistration of Methamidophos (Monitor)

TO: William Miller, Product Manager (16) Tox. Chem. No. 378A
Insecticide-Rodenticide Branch
Registration Division (TS-767)

From: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THROUGH: Edwin Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 12/17/85

1/5/85

Record No. 160720

Action Requested:

The Toxicology Branch has been requested to review/rereview two acute inhalation studies and one dermal sensitization study in order to complete the review of the labeling requirements for reregistration of Methamidophos (Monitor). One of the acute inhalation studies has been reviewed previously by the Toxicology Branch.

Response:

The Toxicology Branch has determined that the submitted labeling statement adequately reflects the toxicity studies conducted on the chemical. No changes in the toxicity section of the label are necessary.

Discussion:

The dermal sensitization study indicated that Methamidophos Technical, the same formulation specified in the label, is not a sensitizer under the conditions of the study (Chevron Chemical Co., Accession No. 257935, 11/13/84). Of the two acute inhalation

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studies reviewed, only one was acceptable as a usable study (Mobay Chemical Corp., Accession No. 257935, 9/11/84). The other study was classified as Core Supplementary because it did not meet the basic requirements of the EPA testing guidelines (Mobay Chemical Corp., Accession No. 250925, 6/28/83). The exposure period was only for one hour (the guidelines suggest at least four hours) and there were obvious problems with the aerosol generating system. It appears that the sample was too viscous to generate sufficient respirable and/or inhalable particles. As a result, the nominal concentrations did not correlate well with the analytical concentrations and the particle distribution was not uniform between dose levels.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization 81-6 TOX. CHEM. NO.: 378A

ACCESSION NUMBER: 257935

TEST MATERIAL: Methamidophos Technical (SX-1490 and SX-1456)

SYNONYMS: Monitor

STUDY NUMBER(S): Not available

REPORT NUMBER: SOCAL 2135

SPONSOR: Chevron Chemical Company, Ortho Division, Richmond, California and Mobay Chemical Corporation, Agricultural Chemicals Division, Kansas City, Missouri

TESTING FACILITY: Chevron Environmental Health Center, Richmond, California

TITLE OF REPORT: Modified Buehler Test for the Skin Sensitization Potential of Methamidophos Technical (SX-1490)

AUTHOR(S): Korenaga GL, Cushman JR, Wong ZA

REPORT ISSUED: 11/13/84

IDENTIFYING VOLUME: Volume 1, Reference 12

CONCLUSION: Methamidophos was not a sensitizer under the conditions of this test. DNCB, the positive control gave a sensitization response.

Toxicity Category: N/A

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

The test chemical was methamidophos technical, a brown liquid (SX-1456 for preliminary screens and SX-1490 for the actual study). SX-1456 had a purity of 71.3% and SX-1490 had a purity of 73.8%.

Animals:

Male Hartley albino guinea pigs, supplied by the Charles River Breeding Laboratory (Wilmington Massachusetts) were used for the study. The animals were 31 days old on the first day of the induction period. They weighed between 251-326 grams at the time of randomization.

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Protocol:

A modification of the procedure described by Buehler was used for the test. Prior to the main study, a pretest screening was done to determine the maximum nontoxic concentration after 10 repeated doses. This concentration was determined to be 25% (wt./wt. in distilled water). The following table summarizes the study design of the main study:

Group	Test Material (No. of Animals)		
	Induction	First Challenge	Second Challenge
Methamidophos Technical	25% Methamidophos Technical (14)	25% Methamidophos Technical (14)	25% Methamidophos Technical (14)
Methamidophos Technical Irritation Control	Distilled Water (10)	25% Methamidophos Technical (10)	Distilled Water (10)
Methamidophos Technical Vehicle Control	Distilled Water (10)	Distilled Water (10)	25% Methamidophos Technical (10)
DNCB 1-chloro-2,4-dinitrobenzene	0.1% DNCB (in 80% Ethanol) (10)	0.1% DNCB (in Acetone) (10)	0.1% DNCB (in Acetone) (10)
DNCB Irritation Control	80% Ethanol (10)	0.1% DNCB (in Acetone) (10)	Acetone (10)

The induction phase of the study consisted of 10 topical applications scheduled on alternate days over a 22-day period. The right flank of each animal was clipped free of fur on day 1 of the study and weekly thereafter. The first induction application was administered using a Hill Top Chamber^{R}. Three tenths of a ml of the appropriate dosing solution was applied and the chamber was held in place for six hours with a cohesive wrap. After removal of the wrap, the application sites treated with 1-chloro-2,4-dinitrobenzene (DNCB, positive control) or the DNCB vehicle were wiped with dry gauze pads. All other application sites were wiped with gauze pads moistened with distilled water. The nine remaining induction applications were made by administering 0.4 ml of the dosing solution to the skin of the right flank and covering the site with gauze and a polyethylene square. The animals were wrapped for six hours as before. The technical control animals were inadvertently not dosed until day 7 of the study; they received 10 induction applications with distilled water using the procedures described above.

Skin reactions were read 24 and 48 hours after the initial application. To assess the effects of repeated application, a 24-hour reading was also performed after the fifth and tenth applications. Evaluation was based on the scoring system of Draize et al.

The animals were challenged on day 35 of the study, 7 days after the tenth induction application for the vehicle control group and 14 days after the tenth induction application for all other groups. The Hill Top Chamber^{R} was used to apply 0.3 ml of the appropriate test material to the upper left flank. The Methamidophos Technical and Methamidophos Technical irritation controls groups were challenged with 25% Methamidophos Technical, the vehicle control group was challenged with distilled water and the DNCB and DNCB irritation control groups were challenged with 0.1% DNCB (w/w in acetone). Twenty-four hours after dosing the test sites were were depilated with Neet Cream Hair Remover^{R}. Two hours later, the sites were scored according to the Draize system. Scoring was also conducted at 48 and 72 hours.

Seven days following the first challenge, the animals were challenged again using the lower left flank as the test site. The Methamidophos Technical and the vehicle control groups received 25% Methamidophos Technical, the Methamidophos Technical irritation control group received distilled water, the DNCB group received 0.1% DNCB (w/w in acetone) and the DNCB irritation control group received acetone. The animals were depilated as described before and skin irritation was evaluated at approximately 24, 48 and 72 hours following the challenge.

The authors stated that "an irritation reaction was considered to be a sensitization reaction when two conditions were met: 1) the skin irritation scores observed following the challenge of a Methamidophos- or DNCB-induced animal were greater than the scores observed in those animals following the first application of Methamidophos or DNCB; 2) the challenge scores of a Methamidophos- or DNCB-induced animal were greater than any scores observed in the corresponding vehicle and/or irritation control group(s) following either first induction dose or challenge".

All the animals were weighed once per week during both the acclimation and test periods. No tissues were taken from animals sacrificed at the end of the study. Samples of liver and small intestine were retained from animal No. B6, but not examined histopathologically.

RESULTS:

Skin Irritation During Induction Period:

Two of the 15 animals dosed with 25% Methamidophos Technical showed slight eythema following the initial application. Repeated topical application, as evaluated 24 hours after the fifth application, resulted in very slight erythema in five animals and very slight to slight erythema with no edema to well-defined edema 24 hours after the tenth application. One animal died on day six from intussusception of the anterior jejunum due to the wrapping. None of the ten animals showed any irritation at any time following application of distilled water. None of the ten animals treated with 0.1% DNCB showed any skin irritation at 24 and 48 hours after the first induction application. All ten animals showed very slight to severe erythema and very slight to moderate edema after the fifth application, and moderate to severe erythema and very slight to moderate edema 24 hours after the tenth application.

Sensitization:

Following the first challenge, 10/14 animals in the Methamidophos Technical group gave reactions of very slight to well-defined erythema and 3/10 animals in each of the vehicle control group and the irritation control group showed very slight erythema. Following the second challenge, 8/14 animals in the Methamidophos Technical group and 3/10 of the irritation control group showed very slight to well-defined erythema. Two of ten animals in the vehicle control group showed very slight irritation following first exposure to Methamidophos Technical. None of the Methamidophos Technical-induced animals having combined erythema and edema scores of more than one showed these scores after both challenges. The authors stated that "due to the presence of well-defined erythema in the irritation control group following the second challenge, the irritation observed in the Methamidophos Technical group was not interpreted to be sensitization. In both first and second challenges, the incidence of background skin irritation was slightly greater in the Methamidophos Technical group than in either the irritation or vehicle control group." As a result, the authors concluded that Methamidophos did not prove to be a sensitizer in this test.

Following the first challenge, all 10 animals in the DNCB group exhibited well-defined to severe erythema and very slight to slight edema, and 9/10 animals in the DNCB irritation control group gave responses of very slight erythema and no edema to slight edema. After the second challenge, all ten DNCB-induced animals exhibited very slight to severe erythema and no edema to slight edema. None of the DNCB irritation control animals showed any irritation. Only one DNCB animal was interpreted to exhibit a sensitization reaction following the second challenge. However, seven of ten DNCB-induced animals showed combined irritation scores of two or greater at 24, 48, and 72 hours after the second challenge (indicative of a sensitization response). None of the DNCB irritation control animals showed an acute irritation response with the same persistence.

No significant differences were noted in the body weights of any of the animals during the study.

DISCUSSION:

This was an adequate sensitization study. The only item of concern is that the controls were started later than the treated animals.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation 81-3 TOX. CHEM. NO.: 378A

ACCESSION NUMBER: 257935

TEST MATERIAL: Technical Methamidophos

SYNONYMS: Monitor; O,S-Dimethyl phosphoramidothioate

STUDY NUMBER(S): 84-041-02

REPORT NUMBER: 519

SPONSOR: Mobay Chemical Corporation, Agricultural Chemicals Division, Kansas City, Missouri

TESTING FACILITY: Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Dept., Stilwell, Kansas

TITLE OF REPORT: Acute Inhalation Toxicity Study with Technical Methamidophos (Monitor^{R}) in Rats

AUTHOR(S): Sangha GK

REPORT ISSUED: September 11, 1984

IDENTIFYING VOLUME: Volume 1, Reference 4

CONCLUSION: The four-hour LC_{50} of technical methamidophos in male Sprague-Dawley rats was 63.2 (52-78.7 95% Conf. Int.) mg/m^3 air and in females was 76.5 (61.5-128.4) mg/m^3 air.

Toxicity Category: I

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

The substance tested was O,S-Dimethyl phosphoramidothioate (Technical methamidophos or Monitor^{R}). It was a clear liquid with 70.5% active ingredient. The batch number was 9030005 and the formula number was 605500. The chemical was supplied by Mobay Chemical Corporation, Agricultural Chemicals Division.

Animals:

Young adult male and female Sprague-Dawley rats were obtained from Sasco, Inc., Omaha, Nebraska. Their weights ranged from 172-272g for males and 176-238g for females.

Protocol:

Groups of ten male and ten female rats were exposed for four hours to the following concentrations of technical methamidophos aerosol in mg/m^3 air (Nominal=N, Analytical=A): 195(N), 19.0(A); 382(N), 33.1(A); 420(N), 57.2(A); 466(N), 56.0(A); and 509(N), 82.5(A). In addition, females were also exposed to 560(N), 62.5(A) and 622(N), 172.5(A). Only the heads of the animals were exposed to the test material. Concurrent controls were exposed under identical conditions, but to room air only. The following three groups of controls were used: Group 1 for exposure concentration of 57.2 mg/m^3, Group 2 for exposure concentrations of 19.0, 33.1, 56.0, 62.5 and 82.5 mg/m^3 and Group 3 for exposure concentration of 172.5 mg/m^3 air. These groups corresponded to the different batches of animals used during the study.

The aerosol was generated as a liquid aerosol using an apparatus that consisted of two concentric nozzles. The test material was conducted into the inner nozzle at a constant rate. Filtered and dried air was compressed into the outer nozzle. When released from pressure, the air finely atomized the test substance. A constant airflow was maintained through the chamber and was continuously monitored. Prior to loading the animals into the chamber, the test atmosphere was generated from about 20 minutes so that an equilibrium in the chamber atmosphere could be reached and wall losses were minimized during the actual exposure. During the exposure period, temperature and humidity levels were continuously monitored.

Particle size distributions for each dose level were determined twice during the exposure period. Samples were drawn from the chamber near the animals' breathing zone. Nominal and analytical concentrations were both determined. The animals were observed for mortality and signs of toxicity during exposure, approximately 0.5-0.66, 1-1.5 and 1.5-4 hours post-exposure and then twice daily up to 14 days. Body weights were taken prior to exposure and on days 3, 7 and 14 post exposure. All surviving animals were sacrificed by CO_2 asphyxiation on the 14th day after exposure. A complete gross pathological exam was performed on each rat that died during the study and on the animals sacrificed at termination. Tissue samples of lungs, liver and kidneys were preserved in 10% buffered formalin for possible future histopathological examination. Statistical analyisis was performed on body weights with the Waller-Duncan test.

RESULTS:

The temperature range throughout the study remained within the normal limits. The relative humidity levels were lower than the stipulated range of 40-60% because of the use of dry air in generating the aerosol. These levels did not appear to show any adverse effects on the study. The actual concentrations of the aerosol were generally 8.7 to 16% of the nominal value except the 172.5 mg/m^3 air concentration which was 27.7% of the nominal value. The mean particle size distributions (MMD) ranged from 0.32 to 0.88 micrometers except for one sample with MMD of 0.13 micrometers and another with MMD of 1.0 micrometers. The average MMD was 0.53 micrometers. Almost all the particle mass was withing the respirable range of the animals.

All male and female rats showed cholinergic signs of toxicity. These signs included salivation, lacrimation, muscle fasciculations, tremors, decreased activity, piloerection, and hypothermia. Ocular and nasal irritation and occasional corneal opacity were also observed. The signs lasted from one

to ten days in males and one to fourteen days in females. The mean body weights of male animals were significantly lower than the corresponding control animals on days 3 and 7 at all concentrations, and on day 14 at exposure concentrations of 19 and 56 mg/m^3 air. The mean body weights of female animals were significantly lower than the corresponding controls on day 3 at all concentrations, on days 7 and 14 at concentrations 56.0 and 62.5 mg/m^3 air and on day 7 at concentration 57.2 mg/m^3 air. In some cases, the responses at similar concentrations were slightly different. When this was the case, the mortality data and the concentration data was averaged in calculating the LC_{50} value.

The four-hour LC_{50} of technical methamidophos for male rats was 63.2 mg/m^3 with 95% confidence intervals of 52-78.7 mg/m^3 air and the four-hour LC_{50} value for female rats was 76.5 mg/m^3 air with 95% confidence intervals from 61.5-128.4 mg/m^3 air. No gross lesions were observed in control animals. In the compound treated animals, the signs and lesions observed were lacrimation, salivation, nasal discharge and dark or red lungs. Two females showed eye opacity.

DISCUSSION:

This was an adequate acute inhalation study. The only areas of concern relate to the low humidity in the test chambers due to the use of dry air in generating the aerosol, and the wide variation in the starting weights of the control male animals (172-272 grams).

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation 81-3 TOX. CHEM. NO.: 378A

ACCESSION NUMBER: 250925

TEST MATERIAL: Technical Methamidophos

SYNONYMS: Monitor, O,S-Dimethyl phosphoramidothioate

STUDY NUMBER(S): 80-041-12

REPORT NUMBER: 394

SPONSOR: Mobay Chemical Corporation, Agricultural Chemicals Division, Kansas City, Mo.

TESTING FACILITY: Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Dept., Stilwell, Kansas

TITLE OF REPORT: Acute Inhalation Toxicity Study with Technical Methamidophos (Monitor) in Rats

AUTHOR(S): Sangha GK

REPORT ISSUED: June 28, 1983

IDENTIFYING VOLUME: Single volume, reference 3

CONCLUSION: Under conditions of the study, the LC_{50} for one hour was 377 (301-502) mg/m^3 for males and 241 (205-280) mg/m^3 for females.

Toxicity Category: II

Classification: Core supplementary. Too short exposure period, poor particle size distribution, insufficient particles of respirable size.

MATERIALS AND METHODS:

Chemical:

The substance tested was Technical Methamidophos (Monitor) or O,S-Dimethyl phosphoramidothioate. The batch number was 9030005 and the purity was 75.1%. The physical form was a thick, clear liquid and the source was Mobay Chemical Corporation, Agricultural Chemicals Division.

Animals:

Young adult male and female Sprague-Dawley rats were obtained from Sasco, Inc., Omaha, Nebraska. The body weights ranged from 198 to 270 grams for males and 166 to 212 grams for females.

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Protocol:

Groups of ten male and ten female rats were exposed for one hour to the following concentrations of technical methamidophos aerosol (mg/m^3 air) N=Nominal, A=Analytical
Females: 550(N) 60(A), 615(N) 168(A), 650(N) 259(A), 672(N) 196(A), 745(N) 160(A), and 1000(N) 319(A).
Males: 672(N) 163(A), 745(N) 160(A), 1000(N) 319(A), 1390(N) 253(A).
The following control groups were used during the study:
Control group #1: with exposure concentration 60 mg/m^3 air
Control group #2: with exposure concentrations 168, 160, 319 and 253 mg/m^3 air
Control group #3: with exposure concentration 259 mg/m^3 air
Control group #4: with exposure concentrations 163 and 196 mg/m^3 air

The chemical was generated as a liquid aerosol using an apparatus that consisted of two concentric nozzles. The test material was conducted into a fine inner nozzle by an infusion pump. The outer nozzle had compressed, filtered and dried air, which when released, finely atomized the test substance. The aerosol was blown into the chamber from the top. A constant airflow through the chamber was maintained and continuously monitored with the aid of a flowmeter. The animals were placed such that only their heads were exposed. Temperature and humidity were recorded continuously in the exposure chambers. The humidity levels for the 60 mg/m^3 dose level could not be monitored because of a malfunction in the probe. Particle size distributions were measured for all the dose levels except the lowest level. Sampling at this level was considered to be unnecessary because enough data under similar conditions was already available. Nominal and analytical concentrations were also determined.

All animals were observed for mortality and signs of toxicity during exposure, approximately 1/2, 3/4 to 1 hour, one to five hours post exposure and then twice daily for 14 days. Individual body weights were recorded prior to exposure and on days 2,3,7 and 14 of the post-exposure period. All surviving animals were sacrificed with CO_2 on day 14 after exposure. Complete necropsies were performed on all rats (including those that died during the course of the study). Tissues of liver, lungs and kidneys were excised and fixed in 10% buffered formalin for possible histopathological examination. Statistical analyses were conducted on the body weight data using the Waller-Duncan test. The LC_{50} values were calculated on the basis of nominal concentrations and on the basis of impactor samples (when available).

RESULTS:

The temperature ranges in the exposure chamber were within normal limits. The relative humidity ranges were lower than the expected range because of the use of dry air in generating the aerosol. The authors stated that the one-hour exposure at this range of relative humidity did not seem to affect the study. The actual concentrations based on filter sampling was much lower than the nominal concentrations. Also, the cascade impactor sampling data did not correlate well with the nominal concentrations, but the values were better than the filter samplings. Therefore, the LC_{50} values were calculated on the basis of the impactor sample concentrations.

The MMD during the study varied from 0.85 to 1.5 micrometers with an average of 1.13 micrometers. The authors state that the data show that 50% of the particle mass was below 1.13 micrometers and thus was respirable.

Actually, this was not true for all the dose levels. In the two lowest dose levels, only 20% was below 1.5 micrometers. About 90% of mass was below 5 micrometers and was inhalable.

All exposed male and female rats showed signs of toxicity during exposure and post-exposure periods. Cholinergic symptoms were observed and included salivation, lacrimation, decreased activity, muscle fasciculation, ataxia, gasping, tremors, runny eyes and runny noses. The duration of symptoms ranged from one to five days. The mean body weights of all treated male and female rats showed a decrease from the initial body weights on days 2,3,4 and 7; whereas the mean body weights of control groups showed an increase from the initial body weights during the observation period. The mean body weights of male rats showed a significant decrease from the control values on days 2,3 and 4 at all exposure levels, on day 7 at exposure concentrations 163, 160, and 253 mg/m^3 air, and on day 14 at exposure concentration 163 mg/m^3 air. The mean body weights of females showed a significant decrease from controls on day 2 at 60 mg/m^3, on days 2 and 3 at 168, 259, 196, 160 and 319 mg/m^3, and on day 4 at 259, 196 and 160 mg/m^3.

The one-hour LC_{50} for male rats was 377 with 95% Confidence Interval of 301-502 mg/m^3, and the one-hour LC_{50} value for female rats was 241 with a 95% Confidence Interval of 205-289 mg/m^3. The LC_{50}'s on the basis of nominal concentrations was 1033 mg/m^3 (854-1311) for males and 690 (596-779) mg/m^3 for females. Gross pathology findings included: males-hemorrhagic and/or congested cervical lymph nodes (8), congestion in lungs and nasal turbinates (1), edema in neck region (2), prolapsed penis with inflammation (2), dark red lungs (3), petechiae on thymus (1), lacrimation and salivation (2), and dark red nasal turbinates (1). No gross lesions were found in male controls. For females, gross lesions included: hydronephrosis of kidney (2), edema in the neck (3), congested lungs (2), salivation (1), congested nasal passages (8), lungs and nasal turbinates red (4), congested cervical lymph nodes (2), lacrimation (1), and caudal edges of liver black (1). One control had a the midsection of the left lung adhering to the thoracic wall. Histopathological findings included pulmonary congestion in treated animals. The remaining lesions were found in both treated and control animals. The study authors considered these to be common for rats of this age.

DISCUSSION:

This study had some serious problems. First of all, the animals were only exposed for one hour. This was not a sufficient amount of time to comply with the EPA Guidelines. Second, the sample being tested was a viscous liquid. As a result, it was difficult to generate a uniform particle distribution for the inhalation study. This was evident from the difficulty the study authors had with comparing the nominal concentrations with the analytical concentrations. They finally used the cascade sample results to calculate the LC_{50}. This is not normally done. The particle size distribution data shows highly inconsistent particle size distributions between dose levels. In addition to this, many of the particles were not respirable. The sample was just too viscous to use in this particular apparatus. It should have been diluted.