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

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OCT 30 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

TO: Portia Jenkins, PM # 12
Fungicides/Herbicides Branch
Registration Division TS-767C

FROM: D. Ritter, Toxicologist DLR 10-6-87
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

THRU: R. Bruce Jaeger, Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C RBJ 10/21/87

THRU: Dr. T. M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: EPA Reg. # 11678-4: Cotnion-M; Azinphos-Methyl Technical 85D. Submission of toxicity data.

The following studies were submitted and reviewed in support of this action (Product Specific data requirements for MUPs):

	Study	Results	TOX Cat.	CORE
1.	Acute oral, Rat	LD_{50} = 7.8 mg/kg	I	Guideline
2.	Acute Dermal, Rabbits	LD_{50} > 2000 mg/kg	III	Guideline
3.	4 Hr. Inhal. Rat	LC_{50} > 0.21 mg/L	II	Suppl.*

* Only one dose level used; no venicle control (acetone) used.

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4.	Eye Irrit., Rabbit	Mild $ transitory eye irritant	III	Supplementary
5.	Prim. Derm. Irr., Rabbit	Not a dermal irritant	III	Supplementary
6.	Derm. Sens. Guinea Pig	Not a strong Dermal Sens.		Supplementary*

A mutagenic assay in Histidine auxotrophs of Salmonella Typh. is undergoing review by Dr. Chen of this Branch. His review will follow.

Recommendation:

1. The Inhalation Study must be repeated using more than one dose level and using a vehicle control group.

2. The Rabbit Eye Irritation study and the Rabbit Primary Skin Irritation study require submission of background and historical data on this unknown strain test animal.

3. The Guinea Pig dermal sensitization study is rated Supplementary, but need not be repeated due to its systemic toxicity upon repeated dermal application.

4. The Confidential Statement of Formulation should be submitted for this product.

*A new study is not required due to the systemic toxicity of the dermally applied material.

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Reviewed by: D. Ritter, Toxicologist DGR 10-6-87
Section I , Tox. Branch (TS-769C)
Secondary Reviewer: R. Bruce Jaeger, Section Head
Section I , Tox. Branch (TS-769C) RBJ 10/13/87 006416

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral, Rat TOX. CHEM. NO. 374

ACCESSION NUMBER: 402801-01 '82 FIFRA Guideline #: 81-1

MRID NO.: NA

TEST MATERIAL: Cotnion - M

SYNONYMS: Azinphos Methyl; Guthion.

STUDY NUMBER(S): MAK/116/AZM

SPONSOR: Makhteshim-Agan (America) Inc.

TESTING FACILITY: Life Science Research Israel LTD., Ness Ziona, Israel

TITLE OF REPORT: Acute Oral Toxicity in the Rats.

AUTHOR(S): S. Crown.

REPORT ISSUED: 5/19/87.

CONCLUSIONS: Rat Oral LD_{50} = 7.8 (6.3 - 9.5) mg/kg combined males and females.

Classification: CORE - Guideline.

TOX Category: I.

Special Review Criteria (40 CFR 154.7): None exceeded.

A. MATERIALS:

1. Test compound: Cotnion - M. Description: Brown granular pdr. Batch #: 52087. Purity: Not stated.

2. Test animals: Species: Rat. Strain:Sprague-Dawley. Age: 5-6 wks. Weight: 175 - 205 gm. Source: Charles River UK.

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B. STUDY DESIGN:

1. Husbandry: Standard GLP.

2. Feed and Water: Fasted overnight prior to dosing, then ad libitum.

3. Animal assignment:

Animals were assigned 5 M & 5 F to the following test groups:

Low Dose	6.0 mg/kg
Mid Dose	8.0 mg/kg
High Dose	10.0 mg/kg

4. Compound Administration:

Test Material was mixed with polyethylene Glycol 400 and administered by gavage in a single dose on day one of the test in a constant volume of 5 ml.

5. Quality assurance procedures were not performed.

6. Animals were weighed the day before, on day one, then weekly, and at termination on day 15 of the test.

7. Animals received feed and water ad libitum.

8. Animals were inspected four times on the day of dosing, then daily thereafter for signs of toxicity and mortality.

9. Gross necropsy was performed as soon as possible on all animals dying during the study and on all animals surviving till termination.

10. LD_{50} values were calculated from Litchfield and Wilcoxon.

C. RESULTS:

The Authors reported that deaths in all groups occured within 80 minutes. Signs of toxicity included tremors, excessive salivation and dyspnea. Rats expiring early also showed tonic convulsions and involuntary urination. Rats surviving the initial period were free of symptoms after 4 hours.

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MORTALITY

Dose, mg/kg	Males	Females	Combined
6.0	0/5	1/5	1/10
8.0	2/5	5/5	7/10
10.0	3/5	5/5	8/10

LD_{50}, mg/kg, Males = 9.0 (7.2 - 11.4)*

Females = 6.7 (5.6 - 7.9)

Combined = 7.8 (6.3 - 9.5)

* 95% confidence limits.

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Reviewed by: D. Ritter, Toxicologist DR 10-6-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head
Section I , Tox. Branch (TS-769C) RBJ 10/13/87

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity, Rabbits. TOX. CHEM. NO: 374.

ACCESSION NUMBER: 402801-02 FIFRA SUBPART F #: 81-2.

MRID NO.: NA.

TEST MATERIAL: Cotnion - M.

SYNONYMS: Azinphos-Methyl; Guthion

STUDY NUMBER(S): MAK/117/AZM.

SPONSOR: Makhteshim-Agan (America) Inc., New York, NY.

TESTING FACILITY: Life Science Research Israel. LTD.
Ness Ziona, Israel.

TITLE OF REPORT: Acute Dermal Toxicity in Rabbits.

AUTHOR(S): G. Kenan.

REPORT ISSUED: 5/19/87.

CONCLUSIONS: Dermal LD_{50} > 2000 mg/kg, the highest practicable dose.

Classification: CORE - Guideline.

TOX Category: III.

A. MATERIALS:

1. Test compound: Cotnion - M. Description: Brown granular pdr.
Batch #: 52087. Purity: Not stated.

2. Test animals:

Species: Albino rabbit.

Strain: Local (Israel).

Age: Not given.

Weight: 1.8 - 2.2 Kg.

Source: Lobenstein Laboratory, Yoqneam.

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B. STUDY DESIGN:

1. Husbandry: Adequate; Standard GLP.

2. Feed and Water were available ad libitum.

3. Animals were weighed initially, then weekly, and at termination at 15 days.

4. Animal assignment:

Animals were assigned 5 M & 5 F to the following test groups:

Single Dose - 2000 mg/kg*

5. Compound Administration:

The application site was located on the mid-dorsum and consisted of about 10 % of the total surface area. The Test Material was moistened with water, 1 ml per 1 gm of test material, and was applied using a spatula. The site was then occluded with gauze and adhesive. The dressings and all remaining test material were removed after 24 hours and an Elizabethan collar was attached to prevent access during the first 21 hours post-exposure.

Animals' reactions and mortality were recorded four times during the first and third days post-dosing, then twice daily for 14 days (once daily on weekends).

6. Quality assurance procedures were reported.

7. All animals that died or that were sacrificed on schedule were subject to gross pathological examination.

C. RESULTS:

1. Morality and Signs of Toxicity:

No animals expired during the experiment. Tremors, salivation, decreased motor activity and diarrhea were reported in males. One female had a cut on the throat that was attributed to the collar.

2. Body Weights were not adversely affected by treatment.

3. Post-Mortem examination did not reveal abnormalities.

* This was the highest practicable dose.

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Reviewed by: D. Ritter, Toxicologist DVR 10-6-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head
Section I , Tox. Branch (TS-769C) RBJ 10/13/87

DATA EVALUATION REPORT

STUDY TYPE: 4 Hour Inhalation, Rats. TOX. CHEM. NO: 374.

ACCESSION NUMBER: 402801-03 FIFRA SUBPART F #: 81-3.

TEST MATERIAL: Cotnion - M.

SYNONYMS: Azinphos-Methyl; Guthion

STUDY NUMBER(S): T-6726.

SPONSOR: Makhteshim-Agan (America) Inc., New York, NY.

TESTING FACILITY: Product Safety Labs., East Brunswick, NJ.

TITLE OF REPORT: An Acute 4-Hour Inhalaltion Toxicity Study in Rats.

AUTHOR(S): R. Shapiro

REPORT ISSUED: 6/22/87.

CONCLUSIONS: The LC_{50} in this study is greater than 0.21 mg/L.

Classification: CORE - Supplementary - Only one dose level used and there was no vehicle control.

TOX Category: II.

A. MATERIALS:

1. Test compound: Cotnion - M.

Description: Pale brown granular powder.

Batch #: E70427-2.

Purity: Not stated.

2. Test animals: Species: Rat.

Strain: Sprague-Dawley, Wistar derived.

Age: Young adults.

Weight: 190 - 214 gm.

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Source: Charles River, Wilmington, MA. A.

B. STUDY DESIGN:

1. Husbandry: Standard GLP.

2. Feed and Water were supplied ad libitum except during exposure.

3. Animal assignment:

   5 M & 5 F were selected to be subjected to a single aerosol exposure of four hours duration.

4. Compound Administration:

   Test Material was administered by aerosol inhalation in an inhalation chamber in an initial dose dissolved at 13.4% w/w in acetone (first 80 minutes), then 11.7% w/w in acetone (remainder). Total exposure time was 4 hours.

   Animals were observed initially, then every 15 minutes during the first hour, then each 30 minutes for the remainder of the exposure period. Animals were then examined daily for signs of toxicity and mortality until termination on day 14 following exposure.

   All animals that died or that were sacrificed on schedule were subject to gross pathological examination.

   Gravimetric analyses were conducted on chamber solids content at 10, 32, 62, 87, 124, 152, 184, 218 and 232 minutes.

   Particle size was determined using an Andersen cascade impactor at 107 and 209 minutes, and the mass median diameter and the geometric standard deviation were determined.

   Airflow was maintained at an average rate of 39.9 liters per minute.

5. Quality assurance procedures were reported.

C. RESULTS:

1. The measured mean chamber concentration was 0.21 (± 0.03) mg/L air. The nominal concentration was 0.37 mg/L for the test material and 2.62 mg/L for acetone.

2. The MMD was 1.3 (± 2.46) and 1.51 (± 2.38) microns. (96 % in the respirable range).

3. Signs of toxicity were initial fasciculation and tremors, followed by lacrimation, salivation, nasal discharge and chromodaccryorrhea. One male rat expired after about 93 minutes into the exposure period. No other deaths occured.

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Tremors persisted in the females up to day nine. Males had 006416
recovered by day three.

Males lost weight up to day two and females up to day 4, but increases in body weight were at or above normal thereafter.

4. The animal which expired showed congestion of the lungs, heart, liver and spleen. The major vessels were engorged. No other post-mortem findings were reported that could be related treatment.

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D

Reviewed by: D. Ritter, Toxicologist DLR 10-14-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head
Section I , Tox. Branch (TS-769C) RBJ 10/21/87

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DATA EVALUATION REPORT

STUDY TYPE: Eye Irritation, Rabbits. TOX. CHEM. NO: 374.

ACCESSION NUMBER: 402801-04 FIFRA SUBPART F #: 81-4.

TEST MATERIAL: Cotnion - M.

SYNONYMS: Azinphos-Methyl; Guthion

STUDY NUMBER(S): MAK/118/AZM

SPONSOR: Makhteshim-Agan (America) Inc., New York, NY.

TESTING FACILITY: Life Science Research Israel. LTD.
Ness Ziona, Israel.

AUTHOR(S): G. Kenan.

STUDY TITLE: Acute Eye Irritation/Corrosion Study in Rabbits

REPORT ISSUED: 5/19/87.

CONCLUSIONS:

Cotion - M is a mild and transitory eye irritant.

CORE Classification: Supplementary. Unknown strain. Repairable by submitting detailed information on the irritancy response of this strain.

TOX Category: Not established pending receipt of additional data.

A: MATERIALS:

1. Test Material (TM): Cotnion - M.

Description: Brownish granular powder.

Batch #: 50287.

Purity: Not stated.

2. Test Animals: Albino rabbits.

Strain: Local (Israel).

Age: Not stated.

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Weight: 1.9 - 2.5 kg.

Source: A. Loebenstein Laboratories, Yoqneam.

B. STUDY DESIGN:

1. Husbandry - Acceptable; Standard GLP.

2. Feed and Water - Ad libitum

3. Animal Assignment - ".. Six healthy young rabbits."

4. Compound Administration - 100 mg as supplied.

Test animals were examined under sodium fluorescein prior to instillation of the TM. 100 mg was then applied to the lower right eyelid and lids closed for one second then released. The left eye served as a control.

The animals were checked for reactions at intervals throughout the day (intervals not stated). The treated eyes were washed four hours after treatment to remove any residual material, and an Elizabethan color was attached. Animals were subsequently observed for occular response at 1, 24, 48 and 73 hours after dosing. Occular lesions were scored after the method of Draize, 1959.

C. RESULTS:

Five animals showed diffuse conjunctival redness at one hour (grade 2 - 3) and all showed "small pupil" (miosis). All animals showed conjuntival discharge at one hour. All signs of ocular toxicity had disappeared by the end of the first day (24 hours).

D. DISCUSSION:

This Strain of rabbit is not known to us. Subdivision F #81-4 Guidelines suggest that albino animals of known strain should be used. The Registrant should indicate whether the test animals were albinos (had unpigmented eyes), and should provide some history of their demonstrated response to eye irritants.

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Reviewed by: D. Ritter, Toxicologist DDR 10-14-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head RBJ 10/21/87
Section I , Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Prim.Derm. Irr. Rabbit. TOX. CHEM. NO: 374.

ACCESSION NUMBER: 402801-5 FIFRA SUBPART F #: 81-5

TEST MATERIAL: Cotion - M.

SYNONYMS: Azinphos methyl; Guthion.

STUDY NUMBER(S): MAK/119/AZM

SPONSOR: Makhteshim-Agan (America) Inc., New York, NY.

TESTING FACILITY: Life Science Research Israel. LTD.
Ness Ziona, Israel.

TITLE OF REPORT: Primary Skin Irritation Study in Rabbits.

AUTHOR(S): S. Crown.

REPORT ISSUED: 5/5/87

CONCLUSIONS: Cotion - M is not a dermal irritant under the conditions of this study.

CORE Classification: Supplementary. Unknown strain. Repairable by submitting detailed information on the irritancy response of this strain.

TOX Category: Not established pending receipt of additional data.

A. MATERIALS:

1. Test compound: Cotion - M.

Description: Particulated brown powder.

Batch #: 50287.

Purity: Not stated.

2. Test animals:

Species: Rabbits.

Strain: Local (Israel).

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Age: Not given.

Weight: 1.6 - 2.0 kg.

Source: A. Loebenstein Laboratory, Yoqneam.

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B. STUDY DESIGN:

1. Husbandry: Acceptable; GLP.

2. Feed and Water were available ad libitum.

3. Animal assignment and compound Administration:

Six healthy young adult rabbits were prepared by clipping the mid-dorsum free of hair. Single doses of 0.5 gm test material were moistened with distilled water were applied to the site on 25 mm^2 gauze pads. These were secured with porous strips and adhesive tape. The exposure period was for four hours, after which the dressings were removed and the site cleansed with distilled water.

Sites were evaluated for irritation at 1, 24, 48 and 72 hours using the method of Draize, 1959

C. RESULTS:

No signs of dermal irritation or other effects were reported in his study.

D. DISCUSSION:

This Strain of rabbit is not known to us. Subdivision F #81-4 Guidelines suggest that albino animals of known strain should be used. The Registrant should indicate whether the test animals were albinos, and should provide some history of their demonstrated response to skin irritants.

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Reviewed by: D. Ritter, Toxicologist DR 10-20-87
Section I , Tox. Branch (TS-769C)
Secondary reviewer: R. Bruce Jaeger, Section Head
Section I , Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization, Guinea Pig. (Buehler) TOX. CHEM. NO: 374.

ACCESSION NUMBER: 402801-6 FIFRA SUBPART F #: 81-6

TEST MATERIAL: Cotnion - M (Technical Grade)

SYNONYMS: Azinphos Methyl; Guthion.

STUDY NUMBER(S): T-6701

SPONSOR: Makhteshim-Agan (America) Inc., New York, NY.

TESTING FACILITY: Product Safety Labs., East Brunswick, NJ.

AUTHOR(S): R. Shapiro

REPORT ISSUED: 6/29/87.

TITLE OF REPORT: Azinphos-Methyl Technical (Cotnion) EPA Topical Skin Sensitization Test in Guinea Pigs (Buehler).

CONCLUSIONS: Cotnion - M is not a strong dermal sensitizing agent in male Guinea Pigs.

Classification: CORE - Supplementary data.

TOX Category: Not determined; study is rated CORE Supplementary.

A. MATERIALS:

1. Test compound: Cotnion - M.

Description: Light brown granular solid.

Batch #: E70427-2.

Purity: Not given.

2. Test animals:

Species: Male Guinea Pig.

Strain: Harley.

Age: Not stated.

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Weight: 319 - 432 gm.

Source: Davidson's Mill Farm, E. Brunswick NJ.

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B. STUDY DESIGN (Buehler Method):

1. Husbandry: Standard GLP.

2. Feed and Water were Available ad libitum.

3. Animals were weighed initially, on day 23 and at termination.

4. Animal assignment:

The experiment consisted of an initial test to select the maximum non-irritating dose, an Induction Phase and a Challenge Phase.

The maximum non-irritating dose was determined to be the neat product as received. In the Induction phase 10 males were assigned to the test group and 10 to the positive control group. All animals were clipped free of hair over the dorsal thoracolumber region, and the area was divided into four test sites, two on either side of the spine. Clipping was repeated every time a dose was administered. 0.5 gm test material or 0.5 ml positive control, dose consisting of 0.05 - 0.08 % dinitrochlorobenzene (DNCB) in 95 % ethanol, were applied to each animal on a pre-determined site. The sites were occluded using a 2.5 cm^2 gauze patch secured under hypoallergenic tape. After 6 hours the dressings were removed and the areas cleansed of excess test material. 24 hours and 48 hours later the sites were scored for erythema and edema according to the attached system (Appendix A). This procedure was repeated on alternate days until ten doses had been administered. Fourteen days after the tenth dose had been given, a single challenge dose at the same level as the induction dose, was administered to a new site on the left side of each animal. The dermal reaction to this was scored for erythema and edema at 24 and 48 hours according to the above system. The authors decided that an additional challenge dose was not needed.

C: RESULTS:

1. Average weight gains were comparable for the two groups except as noted below.

2. General Reactions:

Positive Control

The dose of PCNB in the positive control group was increased from 0.05 to 0.08 % for the 3rd to 10th doses in order to insure a response. Health status of these animals remained good. One animal died on day 15 because the dressing was too tight.

Test Animals

The dose volume in the test group was reduced to 0.25 gm from 0.5 gm after the 6th dose because of toxicity.

Four animals receiving the test material died during the induction phase; one after the fourth dose and three after the seventh. Symptoms preceding death included tremors, paleness, lethargy, prostration and hypothermia. Two animals lost weight.

3. Dermal Reactions:

Positive Controls

All surviving control animals exhibited non-confluent to confluent erythema; this became apparent in one animal after the first dose. Four animals exhibited erythema after dose 10. Eight of nine survivors exhibited erythema after challenge, of which six were judged to be due to sensitization response. The over all score was 0.8 for the 24 hour post-challenge evaluation and 0.4 for the 48 hour evaluation. This was considered to be a positive sensitization response, thus confirming the method.

Test Animals

Exposure to 0.5 gm (reduced to 0.25 gm after dose 6) did not result in any detectable dermal reaction in the six surviving animals. Irritancy scores from the 24 and 48 hour post-challenge evaluations were 0.0 and 0.0, respectively. This was considered to be a negative sensitization response.

D. DISCUSSION:

Although there was no dermal response to challenge dosing, indicating that the product is not a strong sensitizer, the study contains insufficient numbers of surviving test animals (6/10) to provide conclusive evidence of lack of weak dermal sensitization. The study is therefore rated CORE Supplementary. However, we do not consider that repeating the study at lower doses will be useful; even though a lower dose of test material would be expected to produce less mortality, it could not be expected to produce more evidence of dermal sensitization.