(11-10-87)

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DATA EVALUATION REPORT

Primary Reviewer: Sidney Stolzenberg, Ph.D.
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Acute Toxicity

Species: Rat

Guideline: 81-1 and 81-2

Study Title: Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats.

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-03
EPA Record No. 197763/197764
Caswell No: 427 M

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Hatano Research Institute, FDSC
Hatano, Kanagawa, 257, JAPAN

Study Number(s): Contract No. 56-271-1
Project No. A-82-2734

Final Report Date: 10-21-82

Study Author(s): K. Hashimoto, and T. Ohtaki

Animal Used: Sprague - Dawley rat from Charles River, Japan, 5-7 weeks old

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Test Compound: MTI-500 (Ethofenprox, Lot Nos. ST-101 (96%) and ST-102 (96%), specitic gravity = 1.072 (40/4°C)

Methods:

The study consisted of 4 dosage routes with 2 groups of 10 males and 10 females for each route of administration tested. The compound was administered by melting (m.p. = 35.4-36.8°C) without dilution. The doses administered were considered to be the highest technically feasible.

A. Oral Dose: 20 and 40 ml/kg (21.44 and 42.88 g/kg by gastric intubation. Lot No. ST-101

B. Subcutaneous Dose: 15 and 30 ml/kg (16.58 and 31.16 g/kg), back of neck. Lot No. ST-101

C. Intraperitoneal Dose: 20 and 40 ml/kg (21.44 and 42.88 g/kg). Lot No. ST-101

D. Percutaneous: Dorsal hair along the spine, 4x5 cm area, was trimmed the day prior to compound application. The compound was applied in even thickness to trimmed area and removed 24 hours later. LOT # ST-102 was used.

Results:

A. Oral: No mortality. Clinical signs immediately observed were piloerection and crouching, reduced spontaneous activity and frequency of respiration in all of both doses. Within 2-4 hours, muddy diarrhea in all but 1 low dose male. At 6 hours, 6 to 10 males, 3 to 10 females on high dose had "blood like substance" around eyelids and nose and seen in all animals of both doses by 24 hours. Also, soiled hair in all and majority had "greyish white soft stools." By 3 days, clinical signs in all had subsided. No significant body weight gain difference between the high or low dose groups although female high dose was slightly lower than low dose. (n.s.).

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At necropsy, day 14, hemorrhagic points over lungs in all treated, also congestion at liver and discoloration of renal cortex. Histopathology revealed "mesh-like hemorrhage" in lungs but no findings in liver or renal cortex.

B. Subcutaneous: No deaths. Clinical signs were piloerection, transient fluctuations in respiration frequency, crouching in many at both doses and sexes, persisting in some to 6 hours. In high dose both sexes, injection site markedly swelled with injected compound, with developing mild edema, compound leakage from injection site. At 24 hours, bloody encrustation around eyelids and nostrils and soft feces in all; soiled fur. Dorsal neck injection site swelling reduced in size but edema from dorsal neck to forelegs in all treated rats; some showing "minor" scar and depilation at injection site. On day 2, soft feces was no longer evident but on day 3, edema in dorsal neck to forelegs was still evident in high dose. By day 14, most clinical signs reversed but thickening of skin and slight edema at injection site still evident. Pathology, day 14, revealed retention of pale yellow viscous liquid and granulation tissue around fluid at injection area down to forelegs. Congestion of liver but no histopathological liver abnormalities.

C. Intraperitoneal: No deaths. Immediate clinical signs were piloerection in all, crouching and "hollowed belly", dose related. At 1 day, brownish muddy diarrhea in both doses, persisting in some to day 2. Clinical signs were not evident by day 14. Body weight showed small decrease on day 1 but normal resumption of increase, similar with both doses although slightly lower (n.s.) for high dose females. Necropsy on day 14 revealed whitish yellow granules at surface of organs, especially fat tissue, abdominal wall, omentum, mesenterium and testes. Hemorrhagic points in lungs, congestion of liver also was seen. Histopathology revealed minor granuloma on serous membrane of liver, spleen and parietal peritoneum but no compound related change is claimed.

D. Percutaneous: No deaths: The only clinical signs were crouching and reduced spontaneous movement up to 12 hours post-dosing. Body weight gains were similar for both doses in both sexes. At necropsy, no changes noted for gross or microscopic pathology.

Conclusion

Acute oral LD50 > 42.88 g/kg	Tox Category = IV
Acute Subcutaneous LD50 > 31.16 g/kg	Tox Category = N/A
Acute IP LD50 > 42.88 g/kg	Tox Category = N/A
Acute percutaneous LD50 > 2.14 g/kg	Tox Category = N/A

Core Classification = Minimum Data

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Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Acute Toxicity

Species: Mouse

Guideline: 81-1 and 81-2

Study Title: Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice.

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-04
EPA Record No. 197763/197764
Caswell No: 427 M

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Hatano Research Institute, FDSC
Hatano, Kanagawa, 257, JAPAN

Study Number(s): Contract No. 56-271-1
Project No. A-82-35-42

Final Report Date: 10-21-82

Study Author(s): K. Hashimoto, and Y. Nishijima

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Test Compound: MTI-500 (Ethofenprox), Lot No. ST-101 and ST-102, both 96% purity, sp. g. of 1.072 (40/4°C), melting pt. 35.4-36.8.

Vehicles: None. Compound was administered without dilution in melted form.

Methods: ICI mice, 5 weeks old, from Japan Charles River were dosed by 4 different routes. Compound was administered full strength, without dilution by melting. All high doses administered were considered maximum feasible doses by the respective routes.

A. Oral Dose: Ten of each sex per group received 50 and 100 ml/kg (53.6 and 107.2 g/kg) of Lot No. SF-101 by gastric intubation.

B. Subcutaneous Dose: Ten of each sex per group received 25 and 50 ml/kg (26.8 and 53.6 g/kg), Lot No. ST-101 in the interscapular region.

C. Intraperitoneal Dose: Ten of each sex per group received 6.25, 12.5, 25.0 and 50.0 ml/kg (6.7, 13.4, 26.8 and 53.6 g/kg)

D. Percutaneous: Ten of each sex per group were first shaved along the spine within an area of 1 cm^2. The test sample was applied 24 hours later to the shaven area and removed 24 hours later. Doses were 1 and 2 ml/kg (1.07 and 2.14 g/kg).

Observation period in all above tests was 14 days except the i.p. test which was extended to 21 days because of failure to recover at 14 days. Necropsies were performed on all that died as soon as possible and on the last day of the observation period. Histopathology was performed "on representative cases".

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Results:

A. Oral

Mortality: one male in low dose on day 5, 1 female low dose on day 1, 1 female high dose day 3.

Clinical Observation: All on both doses had severe watery diarrhea within 15-20 minutes of dosing, more severe in high dose, therefore markedly soiled fur and animals walked with "tails lifted up." Body temperature "tended to be elevated temporarily," increased respiration and more food seeking movement. At 24 hours, soft yellow feces and in some animals anal prolapse occurred; also abdominal swelling piloerection, facial edema. Diarrhea ceased by 48 hours, then gradual recovery from clinical signs to almost normal by 5 days post-treatment.

Body Weight: Increased weight gain slightly lower in high dose treated groups of both sexes, vs the low dose group.

Pathology: No change ascribable to test compound, including histopathology, in those that died or survived.

B. Subcutaneous:

Mortality: None

Clinical Signs: Swelling "like a lump" at injection site at intrascapular back region. At high dose, leakage of sample resulted in fur soiling. Swelling at injection site continued to day 14.

Body Weight Gain: No differences between the 2 doses in either sex.

Pathology: No effects on gross or histopathology except at injection site where granulomas formed in subcutaneous connective tissue.

C. Intraperitoneal

Mortality: In males, 2 at low dose both dying on day 7; 3 at 12.5 ml/kg dose between days 5-7; 4 at 25 ml/kg on days 1, 5, 7 and 14; 3 at highest dose on days 5-7. In females, 1 at 12.5 ml/kg on day 6, 7 at 25 ml/kg dose between days 5-12, 7 at highest dose between days 5-14.

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Clinical Signs: Reduced spontaneous movement beginning 15 minutes post dosing. At 24 hours, facial edema, mild swelling of abdomen, soft feces. After 2 days, spontaneous motion further reduced, reduced food intake, soft feces, piloerection and facial edema became more marked, especially in animals that died.

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Body Weight Gain: Dose related decrease especially in males. However, in females, weights between the 4 groups became similar between days 14-21 post-dosing.

Pathology: Faintly yellow milk white substance adhering to abdominal organs, assumed to be injected compound, especially adhering to liver and kidney, and mild inflammation on these organs. Histopathology revealed no compound related changes except for small granulation on serous membrane and on parietal side of peritoneum of liver, spleen and digestive tracts.

D. Percutaneous

Mortality: None

Clinical Signs: None observed

Body Weight Gain: No differences between the groups.

Pathology: No compound related effects

Conclusions

Acute oral LD50 > 107.2 g/kg	Tox Category: IV
Acute subcutaneous LD50 > 53.6 g/kg	Tox Category: N/A
I.P. LD50 = about 25 mg/kg	Tox Category: N/A
Percutaneous LD50 > 2.14 g/kg	Tox Category: N/A

Comment: "Tails lifted up" seen with the oral route may indicate "straub tail" and a CNS effect.

Core Classification = Minimum data

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Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Acute Inhalation

Species: Rat

Guideline: 81-3

Study Title: MTI-500 Acute Inhalation Toxicity in Rats, 4-Hour Exposure

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-05
EPA Record No. 197763/197764
Caswell No: 427 M
Tox Branch Project No. 7-0971

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Huntington Research Centre
Huntington, Cambridgeshire, England.

Study Number: MTC 60/821079

Study Author(s): G. C. Jackson, C. J. Hardy, G. C. Clark, R. L. Gregson, D. L. Lewis, C. Gopinath

Date: April 19, 1983

Test Compound: MTI-500 (Ethofenprox), Lot No. ST-101 96% purity.

Vehicles: Acetone

Doses: Vehicle control: Acetone
Dose: 5.9 mg/l/4 hours
Route: Inhalation

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Methods: Wistar COBS rats from Charles River UK, 5 males, 5 females per group, 6-8 weeks old, 142-183 g, were exposed for 4 hours in an inhalation chamber to an MTI-500 concentration of 5.9 g/m^3 (actual concentration) of air. The test compound was in a solution containing 10% acetone. One control group was exposed to acetone, a second control group was untreated. Particle size of 95% of the test compound was < 5.5 um. Observation period was 14 days.

Results:

Mortality: None

Clinical Observations: During exposure, treated rats showed eye closing, "abnormal respiratory movements", acetone exposed rats were hypoactive. After exposure, lethargy was seen in all MTI-500 treated rats for about 1 hour after removal from chamber, but 2 females in treated group were hyperactive for 2 days after exposure, 1 remained hyperactive for 4 days; loss of hair was seen in 3 treated females within the 14 day observation period.

Body Weight Gain: Lower body weight gain for MTI-500 exposed females during 14 day observation period was considered not compound related because there was a divergence from controls (lower weight gain) even before exposure.

Food and Water Intake: Both food and water intake were slightly reduced for the first day following compound exposure.

Pathology:

Lung Weight: Based on absolute and relative mean weights, no effect was seen.

Gross and Microscopic Pathology: No effects on gross pathology of any organ; no effect on microscopic pathology of lung, liver or kidneys.

Conclusions:

Inhalation LC50 > 5.9 mg/L/4 hours Tox. Category III

Core Classification: Minimum data

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DATA EVALUATION REPORT

Primary Reviewer: Sidney Stolzenberg, Ph.D.
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Primary eye irritation

Species: Rabbits

Guideline: 81-4

Study Title: MTI-500 Primary Ophthalmic Stimulation Test in Rabbits

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-06
EPA Record No. 197763/197764
Caswell No: 427 M
Tox Branch Project No. 7-097i

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Nippon Experimental Medical Research Institute, Ltd., Tokyo, Japan

Laboratory Identification No.: NEMRS-H-85-55

Study Date: Oct. 24, 1985

Study Author(s): M. Kashima

Test Compound: MTI-500 (Ethofenprox), Lot No. St-103 96.3 purity.

Vehicle: None

Dose: 0.1 ml, melted and without dilution, equivalent to about 100 mg

Route: In conjunctival sac of right eye

Methods: Six male "Japanese white rabbits", 2.24 to 3.01 kg, received 0.1 ml melted test compound, undiluted, to the right conjunctival sac. The left eye was used for untreated control. Each treated rabbit was graded on a scale of 0-4 for corneal opacity, 0-2 for condition of iris, 0-3 for conjunctival rubor and 0-4 for conjunctival edema. Grading intervals were 1, 24, 48 and 72 hours post-dosing.

Results: The following are the actual mean results summarized by the investigators, exactly as it appeared in the applicant's data.

Table 1

Results of Changes in Primary Ophthalmic Stimulant Property

Observation items	After Administration			
	1h.	24h.	48h.	72h.
Corneal Opacity	0	0	0	0
Anomalies in iris	0	0	0	0
Conjunctival redness	1.0	0.8	0.5	0
Conjunctival edema	0.2	0	0	0

Note) Each figure indicates mean value of the grading obtained in 6 rabbits.

Conclusion by the investigators is that these results "indicate a negative effect" and the compound had no "stimulant property" in the eye.

Comments: The Method and Procedure for this study appears acceptable, in accordance with Guideline 81-4. However, grading of the results does not conform to guideline 81-4. Areas of cornea examined are not indicted. Conjunctival examination should include redness, chemosis and discharge

In view of the fact that the procedure was correct and all observed effects were completely reversible by 72 hours, we find it reasonable to accept this study.

Conclusion: P.I.S. at 1 hour = 1 for conjunctival redness or edema, P.I.S. at 24 hours is $\leq$ 0.8 for conjunctival redness or edema, P.I.S. at 72 hours = 0; completely reversible.

Tox. Category: IV

Core Classification: Minimum acceptable.

DATA EVALUATION REPORT

Primary Reviewer: Sidney Stolzenberg, Ph.D.
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Primary Dermal Irritation

Species: Rabbits

Guideline: 81-5

Study Title: MTI-500 Primary Skin Stimulation Test in Rabbits

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-07
EPA Record No. 197763/197764
Caswell No: 427 M
Tox Branch Project No. 7-0971

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Nippon Experimental Medical Research Institute, Tokyo 104 Japan

Laboratory Identification No.: NEMRI-H-85-55

Study Date: Aug. 23, 1985

Study Author(s): M. Kashima

Test Compound: MTI-500 (Ethofenprox), Lot No. ST-103, 96.3% purity, sp. g. = 1.067 at 40.1°C.

Vehicle: None used. Compound was applied in melted form.

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Doses: Vehicle control: None
Test compound: Ethofenprox, 5 ml
Route: Direct application to skin

Method: "Japanese white rabbits," 2.0 - 2.5 kg, 6 males, supplied by Ichikawaya Co. in Tokyo, received 5 ml of compound applied to a 2.5 cm^2 previously shaved area along the midline of the back. Exposure time was 4 hours when residual substance was removed. Skin reaction evaluation with aid of photographs, was at 30 minutes, 24, 48 and 72 hours. If a positive reaction occurred, further observation was continued on days 5, 7 and 14 mainly for reversibility. A grading system of 0-4 for 1) erythema and scab formation and 2) edema was used. The animals were also observed for clinical signs and skin pathology, including histopathology of ~~Of~~ skin exposed to compound.

Results:

One of the 6 rabbits had a grade 1 erythema reaction (slight) from 48 hours to 7 days. There were no skin effects in the 5 other rabbits. No remarkable clinical signs or pathology of skin was observed. Conclusion by the investigators was, "the compound was judged to have no essential stimulation."

Conclusions:

P.I.S. Rating: 0.1 to 0.5. Minimally irritating Tox. Category IV

Core Classification. Minimum data.

DATA EVALUATION REPORT

Primary Reviewer: Sidney Stolzenberg, Ph.D.
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D
Review Section V, Tox. Branch (TS-769C)

I. Study Type: Skin Sensitization

Species: Guinea Pig

Guideline: 81-6

Study Title: MTI-500 Skin Sensitization Test in Guinea Pigs

EPA Identification Numbers: EPA ID No. 2724-EUP-UI/2724-EUP-UO
EPA Accession No. 402377-08
EPA Record No. 197763/197764
Caswell No: 427 M

Sponsor: Zoecon Industries
Dallas, Texas 75234

Testing Laboratory: Nippon Experimental Medical Research Institute, Ltd.
Tokyo 104 Japan

Study Number(s) : None given

Final Report Date: Oct. 31, 1985

Study Author(s): S. Satoh, D.V.M. and K. Kobyashi, D.V.M.

Animals Used: English Hartley guinea pigs, male, from Japan Charles River; 348-510 g

Test Substance MTI-500 (Ethofenprox Lot No. St-103, sp. g. 1.067/40.1°C, supplied by Mitsui Toatsu Chemicals, Tokyo, Japan.

Vehicle: Corn Oil

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Method

Each of 3 groups had 20 guinea pigs that received the following treatments in accordance with a maximum sensitazation test.

Group	Test Substance
1 Control	Corn oil
2 (Treatment group)	20% MTI - 500 in corn oil
3 (Positive control)	DNCB (2,4,-dinitrochlorobenzene) in corn oil

For the first sensitization, guinea pigs in all 3 groups received 6 intradermal (i.d.) injections of 0.05 ml per injection at 6 separate sites within a 4x5 cm shaven area of the scapular region. The first 2 i.d. injections in every guinea pig in all 3 groups were a 1:1 mixture of water: Freund's Complete Adjuvant (FCA). The second 2 i.d. injections consisted of test substance; i.e. corn oil for group 1, MTI-500 for group 2 and 0.125% DNCB for group 3. The third 2 i.d. injections were a 1:1 mixture of FCA: test substance.

For the second sensitization a week later, the fur was again shaved in the same region and 500 mg petrolatum containing 10% lauryl sulfate was applied to the shaved area on each guinea pig. Twenty-four hours later, 0.5 ml test substance listed above in the table (2.5% DNCB for group 3) was absorbed on a 2x2 cm piece of lint and applied to the shaved area in the scapular region of each guinea pig, which was kept in place for 48 hours before removal.

For provocation, 2 weeks later, a piece of lint measuring 2x2 cm containing 0.5 ml test substance was applied on a newly shaven area in the abdominal region and kept in place for 24 hours before removing.

Evaluation of response by a 0-3 scoring system for erythema and edema at 24 ,48 and 72 hours following removal of the patch in the abdominal area was performed using photography as an aid. Animals were also monitored for clinical observations, body weight and pathology especially at the subcutaneous and muscular provocation sites.

Results

No sensitization reaction was seen in any control or MTI 500-treated animals. Positive responses were seen for all 20 guinea pigs in the DNCB-treated group. No effects on weight gain, clinical observations or pathology in the MTI-500 treated group were seen.

Conclusion

No skin sensitization due to MTI-500 was seen.

Core Classification: Minimum data