007112

Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - Rat (81-1).

TOX. CHEM NO: 663P MRID NO.: 408837-12.

TEST MATERIAL: SD 208304.

SYNONYMS: Fortress; IN 43898; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; Record Number 234,369.

STUDY NUMBER: WTP 352.

SPONSOR: Shell Development Company Westhollow Research Center Houston, TX 77082.

SUBMITTER: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE 19898.

TESTING FACILITY: Shell Development Company, Westhollow Research Center, Houston, Texas 77082.

TITLE OF REPORT: Acute Oral Toxicity of SD 208304 in The Rat.

AUTHORS: W.L. Wilborn and J.S. Klingensmith.

REPORT ISSUED: July, 31, 1986.

CONCLUSIONS:

Toxicity Category: I

Estimated range of LD_{50} (oral, male rat) = 2.0 - 4.0 mg/kg).
Estimated range of LD_{50} (oral, female rat) = 0.5 - 2.0 mg/kg).

The estimated LD_{50} value of SD 208304 in rats is 2.0 mg/kg male and female rats combined. Clinical signs for male and female rats included hypoactivity, hunched posture, dyspnea, generalized tremors, watery salivation, unsteady stance, chewing movements, splayed hind limbs, ataxia, depressed myotactic placing reflex, incoordination, and death. These signs were not observed in the 0.5 mg/kg test group.

The onset of clinical signs of toxicity was within 1 hour after dosing. Recovery from these symptoms in all surviving animals occurred within 1 day after dosing.

Core Classification: **Minimum**

A. **MATERIALS:**

1. Test compound: SD 208304.

Description: liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient (reported in MRID No. 408837-15).
Stability: The test material was found to be stable and the concentrations remained constant during the period of the study as the result of analytical determinations.

2. Test animals:

Species: Rats
Strain: Fisher 344
Age: 10 weeks old.
Weight: 138-245 g.
Source: Harlan Sprague-Dawley, Houston, Texas.
Food: Purina Formulab #5008, animals were given free access to food and water.

B. **METHODS:**

Groups of 5 males and 5 females were assigned to treatment group given orally by gavage an emulsion of SD 208304 in corn oil. Rats were quarantined for 7 days before testing. Rats were fasted overnight before dosing. Animals were observed for a total of 14 days after dosing. Body weight was measured on days 0, 7, and 14 after dosing. Gross necropsy was performed on all survivors and on the rats that died during the testing period. Doses and lethality are presented in the table under results.

C. **RESULTS AND DISCUSSION:**

The number of rats that died during the 14 day test period are listed in the table below. Because the onset of death was so rapid, differences in body weight values between groups were not evaluated.

Dose (mg/kg)	Male rats deaths/dosed	Female rats deaths/dosed
0.5	0/5	0/5
2.0	0/5	5/5
4.0	5/5	5/5
8.0	5/5	5/5
16.0	5/5	5/5

estimated range of LD_{50} (oral, male rat) = 2.0 - 4.0 mg/kg).
estimated range of LD_{50} (oral, female rat) = 0.5 - 2.0 mg/kg).

Clinical Signs

The rats exhibited hypoactivity, hunched posture, dyspnea, generalized tremors, watery salivation, unsteady stance, chewing movements, splayed hind limbs, ataxia, depressed myotactic placing reflex, incoordination, and death. These signs were not observed in the 0.5 mg/kg test group.

The onset of clinical signs of toxicity occurred within 1 hour after dosing. Recovery from these symptoms in all surviving animals occurred within 1 day after dosing.

Gross pathology

Excess salivation in the mouth and stomach were noted.

Signed quality assurance and GLP statements were present.

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Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - Mouse (81-1).

TOX. CHEM NO: 663P MRID NO.: 408837-13.

TEST MATERIAL: SD 208304.

SYNONYMS: Fortress; IN 43898; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; Record Number 234,369.

STUDY NUMBER: WTP 356.

SUBMITTER: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE 19898.

TESTING FACILITY: Shell Development Company, Biological Sciences Research Center, Modesto, CA

TITLE OF REPORT: Acute Oral Toxicity of SD 208304 Technical in The Mouse.

AUTHORS: C.J. Yankovitch, L.A. Malley, D. Stevens, and R.G. Helman.

REPORT ISSUED: June, 30, 1986.

CONCLUSIONS:

Toxicity Category: I

Estimated LD_{50} (oral, male mouse) = 41 mg/kg).
Estimated LD_{50} (oral, female mouse) = 26 mg/kg).

Clinical signs of toxicity included: hypoactivity, hunched posture, lacrimation, diarrhea, ataxia, splayed limbs, paresis, pus-like eye discharge, no stool, unsteady stance, dyspnea, generalized tremors, salivation, ataxia, and incoordination.

Gross pathology findings in the mice that died during the observation period were: brown material in the stomach were noted, perioral saliva accumulation, diarrhea, and wet matted hair coat on the ventral surface. No treatment-related effects were reported in the survivors.

Core Classification: Not applicable.

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A. **MATERIALS:**

1. Test compound: SD 208304.

Description: yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient (purity is listed in MRID No. 408837-16).
Stability: not provided.

2. Test animals:

Species: Mice.
Strain: $B6C3F_1$.
Age: 6-8 weeks old.
Weight: 18-23 g.
Source: Harlan Sprague-Dawley, Inc., Houston, Texas.
Food: animals were given free access to food and water.

B. **METHODS:**

Groups of 5 males and 5 females were assigned to treatment group given orally by gavage an emulsion of SD 208304 in corn oil. Mice were quarantined for 7 days before testing. Mice were fasted overnight before dosing. Animals were observed twice daily for a total of 14 days. Body weight was measured on days 0, 7, and 14 after dosing. Gross necropsy was performed on all survivors. Doses and lethality are presented in the table under results.

C. **RESULTS AND DISCUSSION:**

The number of mice that died during the 14 day test period are listed in the table below. Female mice in the 35 mg/kg group had lower body weight values compared to controls. No other decreases in body weight were reported.

Dose (mg/kg)	Male mice deaths/dosed	Female mice deaths/dosed
0	0/5	0/5
20	0/5	2/5
35	1/5	3/5
50	4/5	5/5
65	5/5	5/5

estimated LD_{50} (oral, male mice) = 41 mg/kg).

Clinical Signs

The mice exhibited hypoactivity, wet urogenital area, hunched posture, lacrimation, small amount of feces, diarrhea, ataxia, splayed limbs, paresis, pus-like eye discharge, not eating, no stool, unsteady stance, dyspnea, generalized tremors, salivation, unsteady stance, splayed hind limbs, ataxia, incoordination, and death.

The onset of clinical signs of toxicity was not reported. Recovery from these symptoms in most of the surviving animals occurred within 3 days after dosing.

Gross pathology

Findings in the animals that died during the observation period were: brown material in the stomach were noted, perioral saliva accumulation, diarrhea, and wet matted hair coat on the ventral surface. No treatment-related effects were reported in the survivors.

A signed quality assurance and GLP statement were present.

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Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - Rabbit (81-1).

TOX. CHEM NO: 663P MRID NO.: 408837-14.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; Record Number 234,369.

STUDY NUMBER: HLR 186-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, E.I. DuPont de Nemours & Company, Inc. 19714.

TITLE OF REPORT: Approximate Lethal Dose (ALD) of IN 43898 in Female Rabbits.

AUTHORS: J.W. Sarver.

REPORT ISSUED: July 1, 1987.

CONCLUSIONS:

Toxicity Category: I

Estimated approximate lethal dose (oral, female rabbit) = 6.7 mg/kg.

Core Classification: Not applicable.

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A. **MATERIALS:**

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient.
Stability: not provided.

2. Test animals:

Species: Rabbits (female).
Strain: New Zealand White.
Age: not provided.
Weight: 1809 - 2590 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. **METHODS:**

Groups containing 1 female rabbit were randomly assigned and given orally by gavage a suspension of IN 43898 in 0.5% methylcellulose. The rabbits were quarantined for about 14 days before testing. The rabbits were fasted overnight before dosing. Animals were observed twice daily for a total of 14 days after dosing. Body weight was measured on days 1 (day of treatment) and at least three times weekly after dosing.

C. **RESULTS AND DISCUSSION:**

The number of rabbits that died during the 14 day test period are listed in the table below. The rabbits were reported to exhibit slight weight loss (1-5% of initial body weight) at 1 day after dosing, and sporidically throughout the study

Dose (mg/kg)	Female mice deaths/dosed
1.5	0/1
2.1	0/1
3.0	0/1
4.5	0/1
6.7	1/1
10.0	1/1

Estimated approximate lethal dose (oral, female rabbit) = 6.7 mg/kg.

Clinical Signs

No common clinical signs of toxicity were reported. All deaths occurred within 2 hours after dosing. The rabbit given 10 mg/kg IN 43898 died before exhibiting any clinical signs of toxicity. The rabbit exposed to 6.7 mg/kg of IN 43898 exhibited lethargy, salivation, cyanosis and constriction of the pupils before death.

Gross pathology

No gross pathology was performed in this study.

Signed quality assurance and GLP statements were present.

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Secondary Reviewer: Marion Copley, D.V.M. 2/15/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - Rabbit (81-4).

TOX. CHEM NO: 663P MRID NO.: 408837-17.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 204-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, E.I. DuPont de Nemours & Company, Inc. 19714.

TITLE OF REPORT: Eye Irritation Test in Rabbits of IN 43898.

AUTHORS: Rudolph Valentino.

REPORT ISSUED: April 22, 1987.

CONCLUSIONS:

Toxicity Category: I

Under the experimental conditions, because of the acute toxicity of 0.1 ml of IN 43898, it is not feasible to study the potential eye irritancy properties of IN 43898 in rabbits.

Groups of 2 rabbits were exposed to 0.01 or 0.05 ml of IN 43898. Both rabbits died within 4 hours after exposure to 0.05 ml of undiluted IN 43898. In both rabbits exposed to 0.01 ml of IN 43898, at one hour after exposure, generalized, slight corneal opacity at 1 and 4 hours was observed as well as moderate redness of the conjunctiva and moderate iritis. Except for moderate iritis, total recovery was observed within 24 hours after exposure. Except for constriction of the pupils, no other clinical signs of toxicity were observed at this dose.

Core Grade: **Minimum**

Although the number of animals per dose is insufficient (six animals per dose should be used), this study is core graded minimum since a new eye irritation study would not be expected to alter the Toxicity Category of I for this chemical.

A. **MATERIALS:**

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rabbits (female and male).
Strain: New Zealand White.
Age: not provided.
Weight: 2181 - 2252 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. **METHODS:**

The rabbits were quarantined for about 2 weeks before testing began. Two rabbits were incapacitated by the neck and 0.05 ml (or in another experiment, 0.01 ml) of the undiluted solution of the test compound was dropped into the conjunctival sac of the right eye. The eyelid was closed for about 20 seconds to limit the amount of test compound from escaping. Both eyes of one of the two rabbits were washed with lukewarm water. The left eye of the rabbit received distilled water and served as the control. The same protocol was performed for the two groups of 2 rabbits exposed to 0.01 or 0.05 ml of the test agent.

The test was scored by method of Draize (1959). A maximum possible score was 110.0. Changes were observed and scored in the cornea, iris and conjunctiva at 1, 4, 24, 48, and 72 hours or until the rabbits died. Body weight was not measured whereas clinical signs were recorded.

C. **RESULTS:**

Both rabbits died within 4 hours after exposure to 0.05 ml of undiluted IN 43898. Clinical signs included diarrhea, severe salivation and/or nasal discharge, and constriction of the

pupils.

In both rabbits exposed to 0.01 ml of IN 43898, at one hour after exposure, generalized, slight corneal opacity at 1 and 4 hours was observed as well as moderate redness of the conjunctiva and moderate iritis. Except for moderate iritis, total recovery was observed within 24 hours after exposure. Moderate iritis was resolved by 48 hours after exposure. Except for constriction of the pupils, no other clinical signs of toxicity were observed at this dose.

Signed GLP and quality assurance statements were present.

007112

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Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Delayed Hypersensitivity - Guinea Pig (81-6).

TOX. CHEM NO: 663P MRID NO.: 408837-19.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 430-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, E.I. DuPont de Nemours & Company, Inc. 19714.

TITLE OF REPORT: Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with IN 43898 in Guinea Pigs.

AUTHORS: W.J. Brock.

REPORT ISSUED: September 9, 1987, revised: October 26, 1987.

CONCLUSIONS:

IN 43898 is not a skin sensitizer under the conditions and the dose (0.4 ml of 1% IN 43898) used in this study.

Core Classification: **Minimum**

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A. **MATERIALS:**

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient.
Stability: "The test material was assumed to be stable under the conditions of administration."

Positive control material:

1-Chloro-2,4-dinitro-benzene (DNCB).
97% purity, Lot No. A11G, Eastman Kodak Co., CAS No: 97-00-7, stability was assumed by the authors under conditions of this test.

2. Test animals:

Species: Guinea pigs (female and male).
Strain: Duncan Hartley albino.
Age: not provided.
Weight: 433 - 551 g.
Source: Charles River Breeding Laboratories, Stone Ridge, NY.
Food: animals were given free access to food (Purina Certified Guinea Pig Chow #5026) and water.

B. **METHODS:**

Overall, guinea pigs were exposed for 6 hours to IN 43898, DNCB (as a positive control), and 80% ethanol in water as the vehicle (and a negative control as well) once per week for 3 weeks (the induction phase) and then once 2 weeks later (the challenge phase).

The guinea pigs were quarantined for 1 week prior to exposure to the test agent. The test substance was applied to the shaved area on the backs of 10 male and 10 female guinea pigs and patched with an occlusive bandage. The same method was used for 5 male and 5 female guinea pigs who received the vehicle control as well as 2 male and 3 female guinea pigs who received the positive control agent, DCNB. At each exposure period, the skin was evaluated for skin reaction at 2 and 48 hours after exposure by method of Draize (1959). Body weight was measured weekly.

C. RESULTS AND DISCUSSION:

A range finding study was performed initially with the use of 0.4 ml of 50%, 25%, 10%, 5%, 1% and 0.5% (v/v) of IN 43898 in 80% ethanol. Based on the acute toxicity of IN 43898, the highest dose tested in this study was a 1% suspension of IN 43898 in 80% ethanol. The type of toxic response found in the range-finding study was not reported.

During the induction phase, no dermal irritation was found in the vehicle or test group animals. Positive control animals exhibited erythema, edema and necrosis during the second or third treatments in the induction phase.

During the challenge phase, no dermal irritation was seen in animals in the negative control group. As shown in the table below, slight patchy erythema was seen in the test and the other control groups. Severe erythema with necrosis, edema or blanching were seen in the positive control group.

Summary of Skin Responses

Challenge Phase

	Test		Negative Control		Vehicle Control		Positive Control	
Response	24hr	48hr	24hr	48hr	24hr	48hr	24hr	48hr
No reaction	20/20	19/20	4/4	4/4	9/10	10/10	0/5	0/5
Slight patchy erythema	0/20	1/20	0/4	0/4	1/10	0/10	1/5	1/5
Severe erythema	0/20	0/20	0/4	0/4	0/10	0/10	4/5	4/5

IN 43898 is not a skin sensitizer under the conditions and the dose (0.4 ml of 1% IN 43898) used in this dermal sensitization study.

Signed quality assurance and GLP statements were present.

Reviewed by: Sanford W. Bigelow, Ph.D. 2/16/89
Section II, Toxicology Branch I (IRS) (TS-769C).
Secondary Reviewer: Marion Copley, D.V.M. 2/23/89
Section II, Toxicology Branch I (IRS) (TS-769C).

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DATA EVALUATION REPORT

STUDY TYPE: Acute Delayed Neurotoxicity in the Adult Hen (81-7).

TOX. CHEM NO: 663P MRID NO.: 408987-02.

TEST MATERIAL: Fortress Technical.

SYNONYMS: Fortress; SD 208304; IN 43898; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. 54593-83-8; Record Number 234,369.

STUDY NUMBER: 3545-84.

SUBMITTER: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

SPONSOR: Shell Development Company, P.O. Box 1380, Houston, TX 77001.

TESTING FACILITY: Stillmeadow, Inc. 9525 Town Park Drive, Houston, TX 77036.

TITLE OF REPORT: Acute Delayed Neurotoxicity Study in Hens with SD-208304.

AUTHORS: J.L. Maedgen.

REPORT ISSUED: September 8, 1986.

CONCLUSIONS:

SD 208304 did not cause delayed neurotoxicity in adult hens even at single doses (14.5 or 19 mg/kg) above the LD_50. The only signs of toxicity reported in the animals exposed to SD 208304 were squatting and a decrease in activity within hours following treatment with SD 208304. Following SD 208304 exposure, ataxia was seen at about 7 days in the first treatment period and at 1 hour in the second treatment period.

Core Classification: Minimum

A. **MATERIALS:**

1. Test compound: SD 208304, two levels of purity.

Description: 736B, clear yellow liquid.
736C, clear amber liquid.
Batch #, purity: Lot No. 2-1-0-0, 97% TGAI, designated 736B.
Lot No. 2-4-0-0, 80% TGAI, designated 736C.
Stability: not provided.

2. Control Materials:

Negative: corn oil (1 group of 12 chickens).

Positive/Final dose(s): (1 group of chickens).

Tri-ortho-cresol-phosphate (TOCP), 500 mg/kg (1 ml/kg of a 500 mg/ml test solution).

Protection agents/Final dosage:
(the test groups were pretreated with these agents)

2-Pyridine aldoxime methiodide (2-PAM)/50 mg/kg (0.5 ml/kg of a 100 mg/kg solution).

plus

Atropine/10 mg/kg (0.67 ml/kg of a 15 mg/kg solution).

3. Test compound: SD 208304.

Dose levels used on 2 test groups of 12 chickens:

first group - 736B test solution (97% TGAI): 19 mg/kg.

second group - 736C test solution (80% TGAI): 14.5 mg/kg.

4. Test animals:

a. Species: Hen Strain Production Red Age 13-14 months
Weight: 1.75 - 2.7 kg
Source: Texas Animal Specialties (Humble, TX).
Food: Purina Layena Poultry Feed, the birds were given free access to both feed and tap water except during the fasting stage prior to dosing. The hens were quarantined for 1 week before testing began.

5. GLP/QA:

Signed GLP and quality assurance statements were present.

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B. TEST PERFORMANCE

1. Preliminary lethality test.

A preliminary dose range-finding study was performed to reconfirm the range of acute lethality of SD 208304. After fasting for 16 hours, groups of 4 hens were treated by oral intubation with 16.5, 18, or 20 mg/kg 736B. In another test, groups of 4 hens were treated by oral intubation with 10, 15, 20, or 25 mg/kg 736C. Animals were examined twice daily for mortality.

The onset of mortality was not reported. No clinical signs of toxicity were reported.

One of four hens treated with 18 mg/kg 736B and all of the hens treated with 20 mg/kg 736B died. An LD_{50} value of 18.36 mg/kg for 736B was calculated by method of Litchfield and Wilcoxon (1949. J. Pharmacol. Exper. Therap. 96:99-115).

Of those hens treated with 736C, 1 of 4 treated with 10 mg/kg died, 2 of 4 treated with 15 mg/kg died, 3 of 4 treated with 20 mg/kg died, and all of the hens treated with 25 mg/kg died. An LD_{50} value of 13.98 mg/kg for 736C was calculated by method of Litchfield and Wilcoxon (1949. J. Pharmacol. Exper. Therap. 96:99-115).

2. Delayed neurotoxicity test

All hens were pretreated intramuscularly with 50 mg/kg of 2-PAM plus 10 mg/kg atropine and were pretreated again 4.5 hours later and again 24 hours after treatment with 19 mg/kg of 736B or with 14.5 mg/kg 736C. The negative control group received corn oil (1 ml/kg) and the positive control group received TOCP (500 mg/kg in corn oil). All hens received another injection of atropine plus 2-PAM on day 21 for a repeated acute delayed neurotoxicity test. On day 21, animals were treated with atropine and 2-PAM as well as the test agent as on day 0 of this test. On day 22, the animals were injected with an additional dose of atropine and 2-PAM.

Also, 2 hens in the 736B test group were injected with atropine and 2-PAM 13 hours after treatment on day 0. On day 2, one animal in the 736B test group and two animals in the 736C test group received injections of atropine and 2-PAM. No reason was provided for this added dosing with the protecting agents.

Body weight was measured on day 0 and weekly thereafter. At 102 hours after dosing with 736B or 736C, animals were examined twice daily for clinical signs of

toxicity and three times weekly for signs of delayed neurotoxicity by two different observers who scored their results independently. The groups were scored blind. Observations were not made during the four days immediately after exposure so that acute cholinergic reactions would not be confused with delayed neurotoxic responses. Because delayed neurotoxicity is manifested as aberrant behavioral changes involving the gait and locomotor activity of the chicken, a scoring system was used based on the method employed by Chambers and Casida (1967. Toxicol. Appl. Pharmacol. 10:105-118).

At the time of evaluation, each animal was gently prodded to stimulate motor activity so that subtle changes in gait could be detected.

At the end of the second 21-day observation period, histological examination was performed on animals in the negative control and test groups by in situ fixation of the following tissues:

- spinal cord (upper cervical bulb, mid-thoracic and lumbosacral regions),
- peripheral nerves (sciatic nerve - distal 2 cm above the branching of the sciatic nerve into the peroneal and the tibial nerve), the left tibial nerve (distal 1.5 cm leading to the lateral calf muscle), and
- brain (medulla oblongata, cerebellum, attached brain stem).

The positive test group animals were sacrificed on day 21 and evaluated histologically in the same manner as those animals in the test group.

RESULTS:

1. Body weight

No differences of absolute body weight or in body weight gain were reported in the test groups when compared to the negative control group. The positive control group exhibited a body weight loss (-0.193 kg) compared to control (+0.015 kg) of between days 0 and 21.

2. Clinical signs of toxicity:

Observations were made on days 4, 6, 8, 11, 13, 15, 18, and 20 after the first treatment. Observations were made on days 25,

27, 29, 32, 34, 36, 39, and 41 after the second treatment. Table 4 attached below taken from the report shows the onset, frequency of the clinical signs of toxicity in the negative control and 2 test groups of birds during the first and second treatments and in the positive control group in the first treatment.

During the first and second treatment periods, in the 736B and 736C test groups, clinical signs included squatting and a decrease in activity within 24 hours following dosing (Table 4). During the first treatment period, ataxia was observed at about 7 days in the 736B test group and at 2 hours in the 736C test group. During the second treatment period, ataxia was seen within 24 hours after exposure to 736B or 736C.

In the positive control group, the first signs of delayed neurotoxicity were observed in one animal on day 4 after treatment and was manifested as an unsteadiness in walking that continued until day 11. By day 13, all 10 birds were eliciting delayed neurotoxicity ranging in response from slight unsteadiness to extreme difficulty in walking often falling. In one animal, paralysis of one leg was observed. By day 20, all animals exhibited some degree of delayed neurotoxicity.

Compared to the positive control group during the first treatment period, the severity, frequency and duration of ataxia was lower than that in the 736B and 736C test groups. The decrease in activity in the 736B and 736C test groups lasted longer, occurred more frequently, and was more severe than in the positive control group. Squatting in the 736B and 736C test groups was observed with similar severity, occurred more frequently but did not last as long as in the positive control group.

No signs of delayed neurotoxicity were elicited in the two test groups (treated with 736B or 736C) and the negative control group.

3. Gross necropsy and histopathology:

During gross necropsy, one animal in the 736C test group had a well-vascularized mass posterior to the ovary. No findings were made in the 736C test and the positive control group. One animal in the negative control group had a few follicles and a normal-shaped egg within the terminal oviduct.

During histopathological examination, no increase in the number of lesions were found in the brain, spinal cord or peripheral nerves in the 2 test groups when compared to the negative control group. The incidence of minimal lymphocytic foci of the sciatic nerve were similar in the negative control and the 2 test groups. No evidence of axonal degeneration was observed in the two test groups.

In the positive control group, lesions were found in the peripheral nerves, spinal cord and cerebellum. Axonal degeneration was observed in the cerebellum, medulla, and in the spinal cord; a common response during organophosphate poisoning.

DISCUSSION:

SD 208304 did not cause delayed neurotoxicity in adult hens even at single doses (14.5 or 19 mg/kg) above the LD_50.

The only signs of toxicity reported in the 736B and 736C test groups were squatting, ataxia and a decrease in activity.

The decrease in activity observed in the 736B and 736C test groups lasted longer, occurred more frequently, and was slightly more severe than in the positive control group. Squatting observed in the 736B and 736C test groups occurred with similar severity and happened more frequently but did not last as long as in the positive control group.

Lesions in the cerebellum and/or the cerebellum are not characteristic of organophosphate poisoning. Axonal degeneration in the central and/or peripheral nervous systems is the hallmark of organophosphate poisoning.

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Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

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_____ 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.

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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.

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Skin Irritation - Rabbit (81-5).

TOX. CHEM NO: 663P MRID NO.: 408837-24.

TEST MATERIAL: IN 43898-16.

SYNONYMS: Fortress 10G; Fortress 10% Granule; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. (for TGAI) 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 324-88.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Primary Dermal Irritation Study with IN 43898-16 in Rabbits.

AUTHORS: William J. Brock.

REPORT ISSUED: May 25, 1988.

CONCLUSIONS:

Toxicity Category: IV

The test substance caused no dermal irritation in 5 of the 6 rabbits. Slight erythema was observed at 4 hours in the sixth rabbit and developed into mild erythema by 24, 48, and 72 hours. The mild erythema had resolved by 6 days after the application of IN 43898-16. Dermal edema was not observed in any rabbits. No clinical signs of toxicity were reported.

Core Classification: Minimum

A. MATERIALS:

1. Test compound: IN 43898-16 (a formulation containing 10% TGAI IN 43898).

Description: brown solid granule.
Batch #: not provided.
Purity: 10% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rabbits (6 females).
Strain: New Zealand White.
Age: not provided.
Weight: 4092 - 4351 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. METHODS:

Six female rabbits were used for testing the potential for dermal irritation on unabraded skin. At least 24 hours prior to application of the test compound, the hair on the backs was clipped from the scapula to the lumber region. A gauze patch was applied containing 0.5 g of IN 43898-16 (moistened with distilled water and held there by rubber sheeting. The patch was removed 4 hours later and washed with warm water. The treatment area was evaluated for signs of edema and erythema at 4, 24, 48, and 72 hours and 6 days after application of the test compound by the method of Draize (1959). The adjacent areas of skin were used for comparison.

C. RESULTS:

The test substance caused no dermal irritation in 5 of the 6 rabbits. Slight erythema was observed at 4 hours in the sixth rabbit and developed into mild erythema by 24, 48, and 72 hours. The mild erythema had resolved by 6 days after the application of IN 43898-16. Dermal edema was not observed in any rabbits. No clinical signs of toxicity were reported.

Signed quality assurance and GLP statements were present.

PC2/fortress/fortskin.083

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Delayed Hypersensitivity - Guinea Pig (81-6).

TOX. CHEM NO: 663P MRID NO.: 408837-25.

TEST MATERIAL: IN 43898-16.

SYNONYMS: Fortress 10G; Fortress 10% Granule; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. (for TGAI) 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 474-88.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with IN 43898-16 in Guinea Pigs.

AUTHORS: William J. Brock.

REPORT ISSUED: August 8, 1988.

CONCLUSIONS:

IN 43898-16 is not a skin sensitizer.

In the main study, during the induction phase, no dermal irritation was found in the test or vehicle groups. Positive control animals exhibited severe erythema with necrosis in the second and third treatments during the induction phase.

During the challenge phase, no dermal irritation was seen in the test group or the negative control group. As shown in the table below, moderate to severe erythema was seen in the positive control group. Body weight increased in all groups.

Core Classification: **Minimum**

25

A. **MATERIALS:**

1. Test compound: IN 43898-16 (a formulation containing 10% TGAI IN 43898).

Description: brown solid granule.
Batch #: not provided.
Purity: 10% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

Positive control material:

1-Chloro-2,4-dinitro-benzene (DNCB).
97% purity, Lot No. A11G, Eastman Kodak Co., CAS No. 97-00-7, stability was assumed by the authors under conditions of this test.

2. Test animals:

Species: Guinea pigs (female and male).
Strain: Duncan Hartley albino.
Age: not provided.
Weight: 469 - 552 g.
Source: Charles River Breeding Laboratories, Stone Ridge, NY.
Food: animals were given free access to food (Purina Certified Guinea Pig Chow #5026) and water.

B. **METHODS:**

Overall, guinea pigs were exposed for 6 hours to IN 43898-16, DNCB (as a positive control), and 80% ethanol in water as the vehicle (and a negative control as well) once per week for 3 weeks (the induction phase) and then once 2 weeks later (the challenge phase).

The guinea pigs had an quarantine period of 1 week prior to exposure to the test agent. The test substance was applied to the shaved area on the backs of 10 male and 10 female guinea pigs and patched with an occlusive bandage. The same method was used for 5 male and 5 female guinea pigs who received the vehicle control as well as 2 male and 3 female guinea pigs who received the positive control agent, DNCB. At each exposure period, the skin was evaluated for skin reaction at 2 and 48 hours after exposure by method of Draize (1959). Body weight was measured weekly.

C. **RESULTS AND DISCUSSION:**

A range finding study was performed in 2 male and 2 female guinea pigs with the use of 0.4 ml (0.3113 g) of undiluted IN 43898-16. No dermal irritation was found so the undiluted test material was used in the main study.

In the main study, during the induction phase, no dermal irritation was found in the vehicle or test group animals. Positive control animals exhibited severe erythema with necrosis in the second and third treatments during the induction phase.

During the challenge phase, no dermal irritation was seen in the test group or the negative control group. As shown in the table below, moderate to severe erythema was seen in the positive control group. Body weight increased in all groups.

Summary of Skin Responses

Challenge Phase

	Test		Negative Control		Positive Control	
Response	24hr	48hr	24hr	48hr	24hr	48hr
No reaction	10/10	10/10	5/5	5/5	0/5	0/5
Mild erythema	0/10	0/10	0/5	0/5	1/5	3/5
Moderate erythema	0/10	0/10	0/5	0/5	2/5	1/5
Severe erythema	0/10	0/10	0/5	0/5	2/5	1/5

IN 43898-16 is not a skin sensitizer.

Signed quality assurance and GLP statements were present.

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 12/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - Rabbit (81-2).

TOX. CHEM NO: 663P MRID NO.: 408837-21.

TEST MATERIAL: IN 43898-16.

SYNONYMS: Fortress 10G; Fortress 10 Granule; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. (for TGAI) 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 291-88.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Acute Dermal Toxicity Study with IN 43898-16 in Rabbits.

AUTHORS: William J. Brock.

REPORT ISSUED: July 25, 1988.

CONCLUSIONS:

Toxicity Category: III

Clinical signs observed in rabbits were diarrhea, lethargy, exophthalmos, and pupillary constriction. Dermal effects were slight erythema as seen in 3 rabbits the day after dosing which resolved by day 4 after dosing. No dermal edema was seen throughout the study. Gross necropsy in the female rabbit that died showed moderate hemorrhage in the cranial (anterior) lobe of the lung. No gross effects were reported in the remaining, surviving rabbits.

LD_{50} (dermal, male rabbit) = >2000 mg/kg.
LD_{50} (dermal, female rabbit) = >2000 mg/kg.

Core Classification: **Minimum**

28

A. MATERIALS:

1. Test compound: IN 43898-16 (a formulation containing 10% TGAI IN 43898).

Description: brown solid granule.
Batch #: not provided.
Purity: 10% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rabbits (female and male).
Strain: New Zealand White.
Age: not provided.
Weight: males: 2179 - 2431 g.
females: 1879 - 2202 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified High Fiber Rabbit Chow #5325) and water.

B. METHODS:

Groups containing 5 male and 5 female rabbits were randomly assigned and exposed dermally to 2000 mg/kg of the test agent. The rabbits were quarantined for about 14 days before testing. The hair, from the scapula to the lumbar region were clipped about 24 hours prior to application of the test agent. The test agent was evenly dispersed on the clipped area (about 190 sq.cm.) and covered with an occlusive dressing for 24 hours. Once the dressing was removed, the application area was washed with water and the reaction of the skin to the test compound was evaluated.

Animals were observed for a total of 14 days after dosing (except for weekend days). Body weight was measured on the day of treatment and on post-treatment days 1, 7 and 14. Gross necropsy was performed on all animals. Doses and lethality are presented in the table under results.

C. RESULTS AND DISCUSSION:

On female rabbit was found dead at 1 day after treatment. Body weights decreased up to 11% of the initial body weight at 1 day following exposure.

Dose mg/kg	Male rabbits deaths/dosed	Female rabbits deaths/dosed
2000	0/5	1/5

LD_{50} (dermal, male rabbit) = >2000 mg/kg.
LD_{50} (dermal, female rabbit) = >2000 mg/kg.

Clinical Signs of Toxicity

Clinical signs observed in rabbits were diarrhea, lethargy, exophthalmos, and pupillary constriction.

Dermal effects included slight erythema seen in 3 rabbits the day after dosing which resolved by day 4 after dosing. No dermal edema was seen throughout the study.

Gross Necropsy

Gross necropsy in the female rabbit found dead showed moderate hemorrhage in the cranial (anterior) lobe of the lung. This response was not reported to be attributed to the exposure to the compound. No gross effects were reported in the remaining, surviving rabbits.

Signed quality assurance and GLP statements were present.

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - Rabbit (81-2).

TOX. CHEM NO: 663P MRID NO.: 408837-15.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 506-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, E.I. DuPont de Nemours & Company, Inc. 19714.

TITLE OF REPORT: Acute Dermal Toxicity Study of IN 43898 in Rabbits.

AUTHORS: W.J. Brock.

REPORT ISSUED: September 25, 1987.

CONCLUSIONS:

Toxicity Category: I

LD_{50} (oral, male rabbit) = 18.5 mg/kg
LD_{50} (oral, female rabbit) = 12.5 mg/kg

Clinical signs observed in rabbits at all dose levels were salivation, diarrhea, and rapid or labored breathing. In dose groups greater than 5 mg/kg, weakness and incoordination were observed. Tremors, clear nasal discharges, constricted pupils, and wet perineum were observed in all dose groups except for the 20 mg/kg dose group (HDT).

Body weights decreased up to 14% of the initial body weight at 1 day following exposure 12, 17 or 20 mg/kg IN 43898.

Core Classification: **Minimum**

A. **MATERIALS:**

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: technical grade, 86% active ingredient.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rabbits (female and male).
Strain: New Zealand White.
Age: not provided.
Weight: males: 2127 - 2710 g.
females: 2022 - 2634 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. **METHODS:**

Groups containing 5 male and 5 female rabbits were randomly assigned and exposed dermally with the test agent. The rabbits were quarantined for several days before testing. The hair, from the scapula to the lumbar region were clipped about 24 hours prior to application of the test agent. The test agent was evenly dispersed on the shaved area and covered with an occlusive dressing for 24 hours. Once the dressing was removed, the application area was washed with water and the reaction of the skin to the test compound was evaluated. The rats were allowed free access to water and food during the testing period.

Animals were observed for a total of 14 days after dosing (except for days 10 and 11 for some dose groups). Body weight was measured on the day of treatment and on post-treatment days 7 and 14. Gross necropsy was performed on all animals that were found dead during the study. Doses and lethality are presented in the table under results.

C. **RESULTS AND DISCUSSION:**

Body weights decreased up to 14% of the initial body weight at 1 day following exposure 12, 17 or 20 mg/kg IN 43898. In surviving rabbits, body weight values were greater than initial body weight values at the end of the study.

Dose mg/kg	Male rabbits deaths/dosed	Female rabbits deaths/dosed
5	0/0*	0/5
12	0/5	2/5
17	2/5	5/5
20	3/5	4/5

* - Male rabbits were not exposed to 5 mg/kg IN 43898.
LD_{50} (dermal, male rabbit) = 18.5 mg/kg (90% C.I. 15-42 mg/kg)
LD_{50} (dermal, female rabbit) = 12.5 mg/kg (95% C.I. 0.9-16 mg/kg)

Clinical Signs of Toxicity

Clinical signs observed in rabbits at all dose levels were salivation, diarrhea, and rapid or labored breathing. These signs were "less apparent" in the 5 mg/kg dose group. In dose groups greater than 5 mg/kg, weakness and incoordination were observed. Tremors, clear nasal discharges, constricted pupils, and wet perineum were observed in all dose groups except for the 20 mg/kg dose group. Lethargy, low or prostrate posture, loss of righting reflex, pallor, brown stained perineum and red oral discharge were seen infrequently in rabbits exposed to 20 mg/kg IN 43898. Corneal opacities were observed in 3 male rabbits exposed to 12 mg/kg IN 43898.

Most of the clinical signs occurred within 1 day of treatment and lasted through day 6-8 post treatment. For most of the rabbits, clinical signs disappeared by day after exposure. By day 14 after exposure, no signs were observed.

Gross Necropsy

Gross necropsy showed clear discharges in the oral cavity and brown stained perineum in male and female rabbits.

Note: A range finding study was performed. Groups containing 1 male rabbit were exposed to 28, 30, or 50 mg/kg IN 43898 whereas groups of 1 female rabbit were exposed to 5, 20, or 200 mg/kg IN 43898. All animals died within 24 hours except for the female rabbit exposed to 5 mg/kg IN 43898 who survived. Clinical signs observed in these rabbits included: tremors, incoordination, rapid, or labored breathing, pallor, hunched posture, paralysis, salivation, and clear ocular and nasal discharges. No clinical signs were exhibited by the female rabbits exposed to 5 or 20 mg/kg IN 43898.

Signed quality assurance and GLP statements were present.

PC2/fortress/fortderm.074

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 3/24/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 3/28/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity - Rat (81-3).

TOX. CHEM NO: 663P MRID NO.: 408837-16.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 679-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, E.I. DuPont de Nemours & Company, Inc. 19714.

TITLE OF REPORT: Acute Inhalation Toxicity Study of IN 43898 in Rats.

AUTHORS: Rudolph Valentino.

REPORT ISSUED: December 3, 1987.

CONCLUSIONS:

Toxicity Category: I

actual LC_{50} (inhalation, male and female rat) = 0.58 ppm (95% C.I. 0.51-0.67 ppm) taken from impinger, not the breathing zone.

Clinical signs observed in rats at all dose levels (except 0.3 ppm) were gasping, salivation, red nasal and ocular discharges, tremors and lethargy during and after exposure. All clinical signs occurred within 3 days of exposure.

Gross necropsy showed no evidence of toxicity specifically associated with any organ.

Core Classification: Minimum.

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This study has the following deficiencies:

1) the actual doses to which rats were exposed were derived from impinger samples taken from the sample lines. Instead, actual IN 43898 concentration should be obtained from the breathing zone of the rats, and

2) the aerodynamic particle size at each test concentration was not reported.

Although the actual doses received by the animals and the aerodynamic particle size of the test agent were not measured, this study is core graded minimum since a new inhalation study would not be expected to alter the Toxicity Category of I for this chemical.

A. MATERIALS:

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: Lot 4-3-0-0, RIR-25-018-86.
Purity: 86% technical grade of active ingredient.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rats (female and male).
Strain: Crl:CD BR.
Age: 8-week old.
Weight: males: 234 - 265 g.
females: 189 - 211 g.
Source: Charles River Breeding Laboratories, Kingston, NY.
Food: animals were given free access to food (Purina Certified Rodent Chow #5002) and water.

B. METHODS:

Groups containing 5 male and 5 female rabbits were randomly assigned, placed in a cylindrical restrainer, fitted with a conical nose piece, and exposed to the test agent for 4 hours. The rats were quarantined for seven days before testing. The temperature and oxygen concentration were measured. The atmospheric concentration of IN 43898 was measured at about 30-minute intervals during the 4-hour exposure period.

The rats were exposed to two equilibration periods of 30 minutes each: the first, the time needed to reach the desired IN 43898 concentration in the chamber and the second, for a decline in the IN 43898 concentration in the chamber.

The relative humidity inside the chamber was reported to not have been measured because of concerns of IN 43898 exposure to the technician conducting the study.

Animals were observed for clinical signs during exposure. Clinical observations and body weight were measured daily for 14 days after exposure. Gross necropsy was performed on all animals that were found dead during the study and on all survivors. Doses and lethality are presented in the table under results.

C. RESULTS AND DISCUSSION:

The oxygen concentration and temperature inside the chamber were 21% and 26-29°C, respectively.

Body weight

Body weight losses up to an average of 5.1% to 16% of the initial body weight at 1 day were observed in the surviving male rats exposed to 0.3, 0.42, 0.43, 0.61 or 0.71 ppm IN 43898. At 1 day after IN 43898 exposure, body weight losses averaged 4.4% to 16% in surviving female rats exposed to 0.3, 0.42, 0.43, and 0.61 ppm IN 43898.

Actual Mean Dose ppm[a]	Nominal Concentration ppm[b]	Male rabbits deaths/dosed	Female rabbits deaths/dosed
0.30	1.6	0/5	0/5
0.42	1.8	0/5	2/5
0.43	2.0	0/5	2/5
0.61	2.1	0/5	5/5
0.71	2.3	2/5	5/5
1.0	2.6	5/5	5/5
1.7	87[c]	5/5	5/5

a - The actual atmospheric concentration was based on the chromatographic analysis of impinger samples taken from the sample lines (not from the breathing zones of the rats).

b - The nominal atmospheric concentration was based on the syringe drive rate and chamber airflow rate.

c - This value was reported as artificially high because the incomplete vaporization of the test material in the mixing flask.

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Clinical Signs of Toxicity

Clinical signs observed in rats at all dose levels (except 0.3 ppm) were gasping, salivation, red nasal and ocular discharges, tremors and lethargy during and after exposure. Other clinical signs observed in the 0.61 and 0.71 ppm dose groups were wet, urine-stained perineum, diarrhea, exophthalmos, compound-stained fur, prostration, spasms, convulsions, and limpness. No clinical signs were seen in the 0.3 ppm dose group. All clinical signs occurred within 3 days of exposure. Information regarding the recovery from these clinical signs in surviving rats was not provided.

Gross Necropsy

Gross necropsy showed no evidence of toxicity specifically associated with any organ.

Signed quality assurance and GLP statements were present.

007112

Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - Rabbit (81-2).

TOX. CHEM NO: 663P MRID NO.: 408837-22.

TEST MATERIAL: IN 43898-4.

SYNONYMS: Fortress 10G; DPX-43898-4; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. (for TGAI) 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 507-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Approximate Lethal Dose (ALD) by Skin Absorption of IN 43898-4 in Rabbits.

AUTHORS: William J. Brock.

REPORT ISSUED: September 23, 1987.

CONCLUSIONS:

Toxicity Category: N/A.

ALD (dermal, male rabbit) = >2250 mg/kg.

No rabbits died in this study. One rabbit exposed to 2250 mg/kg IN 43898-4 had an initial body weight loss of 20% on day 7, most of which was regained by day 14 after dosing. Diarrhea was observed in 2 rabbits at days 2 and 3 following exposure. Mild edema and erythema were seen in all rabbits at 24 hours following treatment.

Core Classification: **Supplementary.** This core grade is based on the insufficient number of animals required to determine the potential dermal toxicity of a test agent. Subdivision F testing guidelines §81-2 state that a minimum of 6 animals per dose should be used.

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A. MATERIALS:

1. Test compound: IN 43898-4.

Description: brown solid.
Batch #: not provided.
Purity: 10.7% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rabbits (male).
Strain: New Zealand White.
Age: not provided.
Weight: 2067 - 2258 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. METHODS:

Three male rabbits were randomly assigned and exposed dermally to the test agent. The rabbits were quarantined for about 14 days before testing. The hair, from the scapula to the lumbar region were clipped about 24 hours prior to application of the test agent. The test agent was moistened with dimethyl phthalate to form a paste ans evenly dispersed on the clipped area and covered with an occlusive dressing for 24 hours. Once the dressing was removed, the application area was washed with water and the reaction of the skin to the test compound was evaluated.

Animals were observed for a total of 14 days after dosing (except for weekend days). Body weight was measured on the day of treatment and on post-treatment days 1, 7 and 14. Gross necropsy was not performed. Doses and lethality are presented in the table under results.

C. RESULTS AND DISCUSSION:

No rabbits died in this study. One rabbit exposed to 2250 mg/kg IN 43898-4 had an initial body weight loss of 20% on day 7, most of which was regained by day 14 after dosing. Diarrhea was observed in 2 rabbits (the particular rabbits were not specified) at days 2 and 3 following exposure. Mild edema and erythema were seen in all rabbits at 24 hours following treatment.

Dose mg/kg	Male rabbits deaths/dosed
2250	0/1
2250	0/1
670	0/1

ALD (dermal, male rabbit) = <2250 mg/kg.

Signed quality assurance and GLP statements were present.

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Reviewed by: Sanford W. Bigelow, Ph.D. 2/13/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - Rat (81-1).

TOX. CHEM NO: 663P MRID NO.: 408837-20.

TEST MATERIAL: IN 43898-16.

SYNONYMS: Fortress 10G; Fortress 10 Granule; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; Record Number 234,369.

STUDY NUMBER: HLR 289-88.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Acute Oral Toxicity Study with IN 43898-16 in Male and Female Rats.

AUTHORS: John W. Sarver

REPORT ISSUED: August 8, 1988.

CONCLUSIONS:

Toxicity Category: I

LD_{50} (oral, male rat) = 53 mg/kg (95% C.I. 38 - 117 mg/kg).
LD_{50} (oral, female rat) = 9 mg/kg (95% C.I. 4 - 13 mg/kg).

The clinical signs of toxicity most often observed in male and female rats were: lethargy, tremors, hunched posture, labored and rapid breathing, clear and red ocular discharges, salivation, red or brown oral discharges, diarrhea, and wet and yellow-stained perineum. The onset, frequency and/or recovery from these clinical signs across dose groups were not reported.

No specific organ toxicity was associated with acute exposure to IN 43898-16 after gross examination.

Core Classification: **Minimum**

A. **MATERIALS:**

1. Test compound: IN 43898-16 (a formulation containing 10% TGAI IN 43898).

Description: brown solid granule.
Batch #: not provided.
Purity: 10% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rats
Strain: Crl:CD BR
Age: 8 weeks old.
Weight: 25 mg/kg group: males: 214 g
females: 168 g
Source: Charles River Breeding Laboratories, Kingston, NY.
Food: Purina Certified Rodent Chow #5002, animals were given free access to food and water.

B. **METHODS:**

Groups of 10 males and 10 females were assigned to treatment groups and given, by gavage, a suspension of IN 43898 in Mazola corn oil. Rats were quarantined for 7 days before testing. Rats were fasted for about 24 hours before dosing. Animals were observed for a total of 14 days after dosing. Body weight was measured daily but not on weekends. From each group, 3 survivors and 3 rats that died during the testing period were arbitrarily selected for gross necropsy. Doses and lethality are presented in the table under results.

C. **RESULTS AND DISCUSSION:**

The number of rats that died during the 14 day test period are listed in the table below. Deaths occurred up to 3 days after dosing. Body weight loss was defined as slight to severe in male and female rats (up to 17%) at 2 days after dosing.

Dose (mg/kg)	Male rats deaths/dosed	Dose (mg/kg)	Female rats deaths/dosed
25	0/10	6	3/10
35	5/10	12	7/10
50	5/10	25	9/10
75	6/10	50	10/10

LD_{50} (oral, male rat) = 53 mg/kg (95% C.I. 38 - 117 mg/kg).
LD_{50} (oral, female rat) = 9 mg/kg (95% C.I. 4 - 13 mg/kg).

Clinical Signs

The clinical signs of toxicity most often observed in male and female rats were: lethargy, tremors, hunched posture, labored and rapid breathing, clear and red ocular discharges, salivation, red or brown oral discharges, diarrhea, and wet and yellow-stained perineum. Less frequently observed clinical signs included prostrate posture, tenseness, hyperactive or aggressive behavior, convulsions and lung noise, gasping or rapid breathing, loss of the righting reflex, dark eyes, exophthalmos, and yellow- or brown-stained fur. The right eye was missing in one male rat in the 25 mg/kg dose group about 1 hour after dosing.

The onset, frequency and/or recovery from these clinical signs across dose groups were not reported.

Gross pathology

No specific organ toxicity was associated with acute exposure to IN 43898-16 after gross examination.

Signed GLP and quality assurance statements were present.

A3

Reviewed by: Sanford W. Bigelow, Ph.D.
Section II, Toxicology Branch I (IRS) (TS-769C) 2/13/89
Secondary Reviewer: Marion Copley, D.V.M.
Section II, Toxicology Branch I (IRS) (TS-769C) 2/14/89

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity - Rat (81-1).

TOX. CHEM NO: 663P MRID NO.: 408837-11.

TEST MATERIAL: IN 43898.

SYNONYMS: Fortress; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; Record Number 234,369.

STUDY NUMBER: HLR 282-87.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE.

TITLE OF REPORT: Acute Oral Toxicity Study with IN 43898 in Male and Female Rats.

AUTHORS: John W. Sarver

REPORT ISSUED: August 25, 1987.

CONCLUSIONS:

Toxicity Category: I

LD_{50} (oral, male rat) = 4.8 mg/kg (95% C.I. 4.4-5.3 mg/kg).
LD_{50} (oral, female rat) = 1.8 mg/kg (95% C.I. 1.7-2.0 mg/kg).

Rats exposed to IN 43898 exhibited slight to sporadic body weight loss. Clinical signs for male and female rats included fasciculations and yellow-stained perineum.

Core Classification: **Minimum**

A. **MATERIALS:**

1. Test compound: IN 43898.

Description: pale yellow liquid.
Batch #: 4-3-0-0, produced 3/7/86.
Purity: technical grade, 86% active ingredient.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:

Species: Rats
Strain: Crl:CD BR
Age: 8 weeks old.
Weight: 2.3 mg/kg group: males: 241-267 g
females: 235-253 g
Source: Charles River Breeding Laboratories, Kingston, NY.
Food: Purina Certified Rodent Chow #5002, animals were given free access to food and water.

B. **METHODS:**

Groups of 10 males and 10 females were assigned to treatment group given by gavage an emulsion of IN 43898 in Mazola corn oil. Rats were quarantined for 7 days before testing. Rats were fasted overnight before dosing. Animals were observed for a total of 14 days after dosing. Body weight was measured daily but not on weekends except when warranted by the condition of the rats. From each group, gross necropsy was performed on 3 survivors and on 3 rats that died during the testing period. Doses and lethality are presented in the table under results.

C. RESULTS AND DISCUSSION:

The number of rats that died during the 14 day test period are listed in the table below. Body weights loss was defined as slight to sporadic in males (up to 22%) and in females (up to 14%).

Dose (mg/kg)	Male rats deaths/dosed	Dose (mg/kg)	Female rats deaths/dosed
2.3	0/10	1.0	0/10
4.0	1/10	1.5	0/10
4.5	2/10	1.9	8/10
5.0	9/10	2.3	9/10
6.0	8/10		

LD_{50} (oral, male rat) = 4.8 mg/kg (95% C.I. 4.4 - 5.3 mg/kg).
LD_{50} (oral, female rat) = 1.8 mg/kg (95% C.I. 1.7 - 2.0 mg/kg).

Clinical Signs

Male rats reportedly exhibited lethargy, tremors, spasms, fasciculations, and wet and yellow-stained perineum. Less frequent signs of toxicity included prostate and hunched posture, lung noise, labored and rapid breathing, loss of righting reflex as well as clear and dry red ocular, nasal, oral discharges.

Females rats exhibited fasciculations, and yellow-stained perineum. Female rats exposed to 1.0 mg/kg exhibited no clinical signs of toxicity.

The onset and/or recovery from these symptoms were not reported. Except for the 1.0 mg/kg group of females, the dose group in which these clinical signs occurred was not specified. Individual animal or summary tables are also missing from the report.

Gross pathology

No specific organ toxicity was associated with acute exposure to IN 43898.

Signed GLP and quality assurance statements were present.

Reviewed by: Sanford W. Bigelow, Ph.D. 2/14/89
Section II, Toxicology Branch I (IRS) (TS-769C)
Secondary Reviewer: Marion Copley, D.V.M. 2/15/89
Section II, Toxicology Branch I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - Rabbit (81-4).

TOX. CHEM NO: 663P MRID NO.: 408837-23.

TEST MATERIAL: IN 43898-16.

SYNONYMS: Fortress 10G; Fortress 10 Granule; SD 208304; O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) phosphorothioic acid; phosphorothioic acid, O,O-diethyl, O-(1,2,2,2-tetrachloroethyl) ester; CAS No. (for TGAI) 54593-83-8; Record Number 234,369.

STUDY NUMBER: HLR 239-88.

SPONSOR: Agricultural Products Department, E.I. du Pont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: E.I. du Pont de Nemours and Company, Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, P.O. Box 50, Wilmington, DE 19714.

TITLE OF REPORT: Acute Dermal Toxicity Study with IN 43898-16 in Rabbits.

AUTHORS: William J. Brock.

REPORT ISSUED: April 19, 1988.

CONCLUSIONS:

Toxicity Category: II

At 1 and 24 hours, moderate iritis and minimal to copious blood-tinged discharge were observed in all rabbits; conjunctival redness and slight to mild chemosis were observed in 5 rabbits; slight corneal opacity was seen in 4 rabbits; and mild corneal opacity was seen in 2 rabbits. At 48 hours after treatment, all ocular irritation had resolved in 2 rabbits, and by 72 hours in 3 rabbits, and by 7 days in the remaining rabbit.

Core Classification: Supplementary. This core grade is due to the fact that the gender was not specified in which the positive findings were reported. Since this compound is more toxic in female rabbits, the findings in this study on the female rabbit is crucial.

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A. **MATERIALS:**

1. Test compound: IN 43898-16 (a formulation containing 10% TGAI IN 43898).
Description: brown solid granule.
Batch #: not provided.
Purity: 10% active ingredient, 90% inert ingredients.
Stability: "The test material was assumed to be stable under the conditions of administration."

2. Test animals:
Species: Rabbits (1 female and 5 males).
Strain: New Zealand White.
Age: not provided.
Weight: 2683 - 3458 g.
Source: Hare Marland, Hewitt, NJ.
Food: animals were given free access to food (Purina Certified Rabbit Chow #5322) and water.

B. **METHODS:**

The rabbits were quarantined for about 2 weeks before testing began. Five males and 1 female were examined for eye injury before testing had begun. The rabbits were incapacitated by the neck and 0.1 ml (80 mg aliquots) of the undiluted solution of the test compound was dropped into the conjunctival sac of the left eye. The right eye of the rabbit received distilled water and served as the control.

The test protocol was performed by method of Draize (1959). A maximum possible score was 110.0. Changes were observed and scored in the cornea, iris and conjunctiva at 1, 24, 48, and 72 hours. One rabbit (the particular rabbit was not specified) was examined 7 days after treatment. Body weight and clinical signs (except for those of the eye) were not recorded.

C. **RESULTS:**

The gender or the individual rabbit was not specified relating to the clinical signs observed. At 1 and 24 hours, moderate iritis and minimal to copious blood-tinged discharge were observed in all rabbits; conjunctival redness and slight to mild chemosis were observed in 5 rabbits; slight corneal opacity was seen in 4 rabbits; and mild corneal opacity was seen in 2 rabbits. At 48 hours after treatment, all ocular irritation had resolved in 2 rabbits, and by 72 hours in 3 rabbits, and by 7 days in the remaining rabbit.

Signed GLP and quality assurance statements were present.

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