5-2-95

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

MAY 2 1995

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Sodium Omadine:** Review of 21 Toxicology Studies.

EPA ID# 088004 DP Barcode D190969, D181351, D177620
Case No. 819311 Chem. ID No. 088004

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I
Health Effects Division (7509C)

John E. Whalan 4-21-95

TO: Linda Propst (PM Team # 73)
Special Review and Reregistration Division (7508W)

THRU: Roger L. Gardner, Section Head
Section 1, Toxicology Branch I
Health Effects Division (7509C)

Roger Gardner 4-26-95 KB 4/21/95

Background:

A battery of toxicity studies was submitted to HED to address data gaps identified in the 1985 Sodium Omadine Registration Standard and FIFRA 88 evaluation. An 18-Month Skin Painting Carcinogenicity study in mice was not reviewed because the test article was **Omadine MDS.** The use of bridging data from other omadines has already been discounted on several occasions (meeting with Olin on September 18, 1985 and John E. Whalan memorandum, dated February 7, 1986). Omadine MDS cannot serve as surrogate for sodium omadine because its chemical and toxicologic properties are markedly different. In addition, the following submissions were not reviewed because they are protocols:

90-Day Oral in Rats	TRID No. 470188-022
2-Generation Reproduction in Rats	TRID No. 470188-021
Rat Hepatocyte Primary Culture/DNA Repair	TRID No. 470188-020
Chromosomal Aberration Assay Micronucleus Test	TRID No. 470188-019

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Discussion of Issues:

Test Articles: The submitted studies were performed using 40% and 10% aqueous solutions. This immediately raised an issue since a 90% pure technical product called Sodium Omadine® Powder Industrial Microbiostat was used in many old studies. Diane Petroccione of Olin explained via telephone that during production, [redacted] The 90% powder, [redacted] is no longer produced. The registrant was asked to submit an explanatory letter for the record.

Data Requirements: Since 1985, TB-I has recognized the potential for machinists to receive significant dermal and inhalation exposure to sodium omadine in metalworking fluids. The toxicology data requirements had been based on the High-Exposure Category described in the *Data Call-In Notices for Antimicrobials* policy paper (March 31, 1987).

TB-I has recently learned that the routine exposure of machinists to sodium omadine is under OSHA's purview. Based on telephone conversations with Edward Stein (OSHA), John Whalen (NIOSH), and Andrea Blaschka (EPA), an interagency workgroup, called the O.N.E. Committee, is discussing the roles of each organization in regulating the uses of metalworking fluids, paints, and other products in the industrial setting. The current thinking of the O.N.E. Committee is that OSHA will retain responsibility for machinists. A definitive policy should be available in several years.

The Health Effects Division cannot delay decisions on preservative products used in metalworking fluids, so a workgroup will meet to draft an interim policy. Because of time constraints, Debra Edward (RCAB) has instructed that this document be written under the assumption that OSHA is responsible for all aspects of machine shop uses of metalworking fluids which contain sodium omadine.

Since all other use patterns result in low-exposure, the list of required studies is now limited to the Low-Exposure Category. The net benefit of this decision is that a number of unacceptable studies that would have been needed to support High-Exposure Category uses are no longer needed. Nevertheless, the submitted data do not constitute a complete data base. The data gaps listed in the following table should be resolved as soon as possible:

Guideline	Study	Status
	40% Aqueous Solution	
81-4	Primary Eye Irritation	Missing[1]
81-6	Dermal sensitization	Upgradable
	10% Aqueous Solution	
81-1	Acute Oral Toxicity	Upgradable
81-2	Acute Dermal Toxicity	Upgradable
81-3	Acute Inhalation Toxicity	Missing[2]
81-4	Primary Eye Irritation	Upgradable
81-5	Primary Dermal Irritation	Upgradable
81-6	Dermal sensitization	Missing[2]

[1] Food & Drug Research Laboratory studies no. 88496c and 88496d were screened during FIFRA 88 review and declared unusable for reregistration. HED has no knowledge of a replacement study.
[2] Required in the 1985 Sodium Omadine Registration Standard.

In order to expedite review, the toxicity studies were assigned to Clement International Corporation for review and DER preparation. Since the DER's did not delineate the purity of the test articles, and most did not have executive summmaries, this information was added on secondary boilerplates. In a few cases, the defined doses and Core Classifications were adjusted. Each secondary boilerplate also has a "comments" section which provides clarifications of toxicity issues, and reiterations of penned DER corrections. DER's and secondary boilerplates for each study are appended to this document, along with a Toxicology Profile which presents the status of the database.

Oral v Dermal Testing: Although human exposure to sodium omadine is almost exclusively by the dermal and inhalation routes, the 1985 Sodium Omadine Registration Standard only required a specific route for two of the 83-series guideline studies — the mouse dermal carcinogenicity study, and the rabbit dermal developmental toxicity study. Both of these studies were performed by the dermal route. Dosing was by gavage in the chronic rat and monkey studies.

Chronic Monkey Study: After reviewing a study protocol in 1986, HED recommended that dogs be used instead of monkeys for the chronic study in non-rodents. The registrant chose to use monkeys as the test system, but never provided a justification for this choice. One year is a minuscule portion of a monkey's lifetime. Although Karl Baetcke (TB-I Branch Chief) is willing to consider the requirement for a chronic study satisfied, he believes the study is too short to assess carcinogenicity.

Toxicity Summary - 40% Aqueous Solution:

The acute Toxicity Categories are II for dermal toxicity, III for oral (gavage) and inhalation toxicity, and IV for primary dermal irritation. There was no evidence of dermal sensitization in unacceptable guinea pigs and human studies. A primary eye irritation study was not performed. Clinical signs seen in the acute studies were mostly neurologic, and included lethargy, prostration, ptosis, brown staining on the nose, mouth, and anogenital areas, diarrhea, wetness or alopecia in the anogenital area, ocular discharge, increased salivation, negative righting reflex, hindlimb impairment, ataxia, bloated abdomen, emaciation, decreased temperature, red facial stains, erythema, and edema.

Sodium omadine seems to have a steep dose response curve. This explains the difficulty laboratories had in dose selection. In some studies, the high-dose induced little or no toxicity, while in others, it was overtly toxic and had to be reduced.

Neurologic signs, especially hindlimb impairment and paralysis, were predominant in repeated exposure studies. In a **90-day oral (gavage)/neurotoxicity** study, skeletal muscle atrophy was seen in rats at 2 mg/kg/day (LEL). At 8 mg/kg/day, 95-100% of the rats had minimum to marked hindlimb atrophy, with the females being the most severely affected. The animals at this dose also had decreased body weights (21-22%) and body weight gain, paravertebral muscle atrophy, hypoactivity, piloerection, hindlimb ataxia, slight head searching, emaciation, hindlimb paralysis, and hunched posture. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response. Half of the females were sacrificed *in extremis* because of severe hindlimb motor dysfunction.

Rats dosed in a **90-day dermal** study had atrophy of the hindlimb muscles and subdermal panniculus muscles at 50 mg/kg/day in the males, and at 15 mg/kg/day in the females. Once again, the females were the most sensitive. At 50 mg/kg/day, body weights were decreased 14% in males and 23% in females, and the females had minimal atrophy of the paravertebral muscle, neurotoxic symptoms, and degeneration of some sciatic nerve fiber bundles.

Female rats exposed in a **13-week inhalation** study had hindlimb dysfunction, histopathologic skeletal muscle regeneration, and decreases in body weight and body weight gain at 0.0081 mg/l, the systemic LOEL and highest concentration tested. No toxicity was seen in the males.

The **chronic oral study in a nonrodent** was performed in cynomolgus monkeys. The LEL was defined as 25 mg/kg/day based on emesis in males and females, and decreased female body weight (17%). Neurologic signs were seen in a male and female dosed at 75 mg/kg/day prior to being sacrificed or dying.

In an **80-week dermal carcinogenicity** study in mice, the high-dose of 40 mg/kg/day was both a freestanding systemic NOEL (supported by a range-finding study), and the dermal LEL (based on an increase in epidermal hyperplasia at the skin application site). The dermal NOEL was 15.0 mg/kg/day. Although dermal application of sodium omadine resulted in epidermal hyperplasia at the dosing site, it did not induce any benign or malignant neoplasms. The Health Effects Division RfD Committee considered the high-dose inadequate to assess carcinogenicity.

The NOEL in a **104 week gavage/carcinogenicity** study in rats was 0.5 mg/kg/day. The LOEL was 1.5 mg/kg/day based on significant increases in the incidence of hindlimb skeletal muscle degeneration in both sexes. At the highest dose tested (5.0/3.5 mg/kg/day) there was a significant decrease in mean body weight (as much as 10%) and body weight gain in females throughout the study; a marked increase in nerve fiber degeneration in the sciatic nerve and spinal cord in both sexes; and an increased incidence of retinal atrophy in both sexes. Under the conditions of the study, no increase in neoplasms was observed at any site. Dosing was considered adequate to assess carcinogenicity.

Although no maternal or fetal toxicity was observed in a **developmental toxicity** study in rabbits, 5 mg/kg/day was defined as a free-standing NOEL since a range-finding dose of 7.5 mg/kg/day was frankly toxic.

In a **2-generation reproduction** study in rats, the Parental NOEL was 0.5 mg/kg/day. The Parental LOEL was 1.5 mg/kg/day based on increased incidence of histologic atrophy in the upper hindlimb skeletal muscles (reduction in fiber diameter) in F_1 females (3/25), F_0 males (7/23), and F_1 males (9/25). Additional parental effects seen at 3.5 mg/kg/day included increased histologic atrophy in the upper hindlimb skeletal muscles in F_0 females (19/24), and F_1 females (20/23); and significantly decreased body weight in F_0 and F_1 females. The Reproductive NOEL was 1.5 mg/kg/day. The Reproductive LEL was 3.5 mg/kg/day based on a slightly decreased number of pups per litter born in both generations (possibly a consequence of reduced mating success due to hindlimb atrophy), delayed development in pups from both generations (including open ears and eyes and startle response), and decreased pup body weight and weight gain in both sexes.

Mutagenicity studies, including **Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT), In Vivo Micronucleus Assay in Mice, and Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes**, were negative.

A **Metabolism** study was Core Supplementary because it failed to account for the unrecovered radioactivity, characterize the fecal metabolites, and propose a metabolic pathway. The study demonstrated that sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing levels. Total recovery of administered radioactivity was 85-95% at 4 days postexposure. The urine is the major route of excretion of sodium omadine (73-85% of the dose); the feces are only a minor route of excretion (5-12% of the dose). Most of the administered radioactivity was excreted within the first 12 hours

postdosing. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues. Twelve urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-S-glucuronide (Metabolite K).

Toxicity Summary - 10% Aqueous Solution:

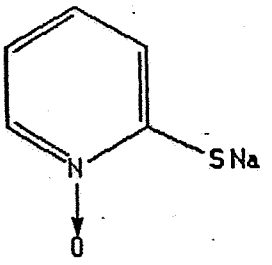
The acute Toxicity Categories are II for dermal toxicity, III for primary eye irritation, and IV for oral toxicity (gavage) and primary dermal irritation. None of these studies is acceptable due to reporting deficiencies, but they are all potentially upgradeable. Neither an inhalation toxicity nor dermal sensitization study was performed. Clinical signs seen in the acute studies included lethargy, prostration, wet anogenital areas, brown staining on body, nasal discharge, emaciation, slight transient ocular irritation, and very slight dermal irritation.

III. Data Requirements (CFR §158.35):

PC CODE: 088004

CASE NO.: 819311

REGISTRANT: Olin Chemicals



REGISTERED USE PATTERNS: Antimicrobial use to inhibit the growth of bacteria and fungi in metal-working fluids (~93% of sales; regulated by OSHA), adhesives, sealants, caulk, patching compounds, pastes, grout, resin/latex/polymer emulsions, synthetic fiber lubricants, laundry detergents and rinse additives, carpet cleaners, jet printer inks, analytical and diagnostic reagents, and specialty industrial products.

Technical and End-Use Product:
Sodium Omadine® 40% Aqueous Solution (40% a.i.)
Sodium 2-pyridinethiol-1-oxide
1-Hydroxy-2-(1H)-pyridinethione, sodium salt
Registration No. 1258-843

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	N	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	N	Dermal sensitization
81-7	N	--	Acute Delayed Neurotoxicity (hen)
82-1a	H,M*	Y	Subchronic Oral (rodent)
82-1b	N	--	Subchronic Oral (nonrodent)
82-2	H*	N	21-Day Dermal
82-3	M,L*	Y	90-Day Dermal
82-4	M,L*	Y	90-Day Inhalation
82-7	N	N	90-Day Neurotoxicity Screening Battery (mammal)

	Required	Satisfied	
83-1a	H*	Y	Chronic Toxicity (rodent)
83-1b	H*	Y	Chronic Toxicity (nonrodent)
83-2	H*	P	Carcinogenicity (two species)
83-3a	H,M,L*	Y	Developmental Toxicity (first species)
83-3b	H*	N	Developmental Toxicity (second species)
83-4	H*	Y	Reproduction
83-5	N	Y	Chronic/Carcinogenicity (see 83-1 & 83-2)
84-2a	H,M,L*	Y	Mutagenicity - Gene Mutation
84-2b	H,M,L*	Y	Mutagenicity - Structural Chrom. Aberr.
84-2c	H,M,L*	Y	Mutagenicity - Other Genotoxic Effects
85-1	H*	N	General Metabolism
85-2	N	--	Dermal Penetration
86-1	N	--	Domestic Animal Safety

Formulation: **Sodium Omadine® 10% Aqueous Solution** (10% a.i.)
Registration No. 1258-1213

	Required	Satisfied	
81-1	Y	N	Acute Oral Toxicity
81-2	Y	N	Acute Dermal Toxicity
81-3	Y	N	Acute Inhalation Toxicity
81-4	Y	N	Primary Eye Irritation
81-5	Y	N	Primary Dermal Irritation
81-6	Y	N	Dermal sensitization
81-7	N	--	Acute Delayed Neurotoxicity (hen)

Y - Yes W - Waived
N - No P - Partially

* **H, M, L** - Required studies for High **(H)**, Medium **(M)** and/or Low **(L)** Exposure Category uses, based on the Bill Burnam Memorandum, *Data Call-In Notices for Antimicrobials* (March 31, 1987).

IV. Toxicology Profile:

Technical and End-Use Product:
Sodium Omadine® 40% Aqueous Solution (40% a.i.)
Sodium 2-pyridinethiol-1-oxide
1-Hydroxy-2-(1H)-pyridinethione, sodium salt
Registration No. 1258-843

	STUDY	RESULTS
81-1	**Acute Oral (Gavage), Rat** Acceptable / Toxicity Category III HED Document No. *???* Study MB 86-8370A; 4-29-87 MRID No. 402478-01	LD_{50} = 2000 mg/kg in males LD_{50} = 1100 mg/kg in females LD_{50} = 1500 mg/kg in combined sexes Clinical signs: lethargy, diarrhea, prostration, ptosis, brown staining on the nose/mouth and anogenital areas, wetness or alopecia at the anogenital area and ocular discharge.
81-2	**Acute Dermal, Rabbit** Acceptable / Toxicity Category II HED Document No. *???* Study MB 86-8370B; 4-29-87 MRID No. 402478-02	LD_{50} = 1900 mg/kg in males LD_{50} = 1800 mg/kg in females LD_{50} = 1800 mg/kg in combined sexes Clinical signs: lethargy, nasal discharge, emaciation, prostration, negative righting reflex, ataxia, ptosis, bloated abdomen, decreased temperature.
81-3	**Acute Inhalation, Rat** Acceptable / Toxicity Category III HED Document No. *???* Study 397-045; 8-28-87 MRID No. 403390-01	4-Hour whole-body, analytical concentrations: LC_{50} = 1.26 mg/l in males LC_{50} = 0.81 mg/l in females LC_{50} = 1.08 mg/l in combined sexes MMAD = 2.3-3.2 μm Clinical signs: increased salivation, hindlimb impairment, prostration, red facial stains, yellow stained abdomen and genital areas.
81-4	**Primary Eye Irritation**	**Data Gap**
81-5	**Primary Dermal Irritation, Rabbit** Acceptable / Toxicity Category IV HED Document No. *???* Study MB 86-8370C; 4-29-87 MRID No. 402478-03	Slight transient erythema and edema.

	STUDY	RESULTS
81-6	**Dermal Sensitization, Guinea Pig** Unacceptable HED Document No. ??? Study MB 86-8370F; 4-29-87 MRID No. 402478-04	**Data Gap** Not a sensitizer in a maximization test (Magnusson-Kligman) up to dose levels which were irritating. **Potentially upgradable. No positive control data were provided.**
81-6	**Dermal Sensitization, Human** Unacceptable HED Document No. ??? Study PI-4750; 8-18-87 MRID No. 403874-01	Not a sensitizer in humans challenged 4 days per week for 3 weeks, then challenged after a 1-week hiatus. **Potentially upgradable. Test article reporting deficiencies.**
82-1a	**3-Month Toxicity/Neurotoxicity Screening Battery (Gavage), Rat** (82-1a) Guideline (82-7) Supplementary HED Document No. ??? Study OLA/2/88; 7-1-88 MRID No. 407569-01 See 82-7	NOEL = 0.5 mg/kg/day LOEL = 2.0 mg/kg/day (neurogenic skeletal muscle atrophy in both sexes) The rats dosed at 8 mg/kg/day had decreased body weight (-21% ♂; -22% ♀) and body weight gain, minimum to marked hindlimb atrophy in 95-100% of males and females (more severe in females), minimal paravertebral muscle atrophy (2/20 ♂; 17/20 ♀), atrophy of the subcutaneous panniculus muscle (20/20 ♂; 17/20 ♀); neurologic signs including slight hypoactivity, piloerection, hindlimb ataxia, slight head searching, emaciation, hindlimb paralysis, and hunched posture; 10/20 females were sacrificed *in extremis* because of severe hindlimb motor dysfunction. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response.
82-3	**90-Day Dermal, Rat** Guideline HED Document No. ??? Study OLA/5/88; 11-3-88 MRID No. 409362-01	NOEL = 15 mg/kg/day in males; 5 mg/kg/day in females LOEL = 50 mg/kg/day in males; 15 mg/kg/day in females (atrophy of the hindlimb muscles and subdermal panniculus muscles) The rats dosed at 50 mg/kg/day had decreased body weight (-14 ♂; -23% ♀) and body weight gain, the females had minimal atrophy of the paravertebral muscle, neurotoxic symptoms and degeneration of some sciatic nerve fiber bundles. There was no dermal irritation.

	STUDY	RESULTS
82-4	**90-Day Inhalation, Rat** Minimum HED Document No. ??? Study 397-042; 5-3-89 MRID No. 411782-01	Systemic NOEL = 0.0081 mg/l in males Systemic NOEL = 0.0011 mg/l in females Systemic LOEL = 0.0081 mg/l in females (hindlimb dysfunction, histopathologic skeletal muscle regeneration, and decreases in female body weight and body weight gain). Tested in Sprague-Dawley strain at analytical concentrations of 0.00046, 0.0011, and 0.0038/0.0081 mg/l in a whole-body chamber, 6 hours/day, 5 days/week, 13 weeks (high concentration was increased after 6 weeks). EAD (GSD) = 1.1-1.4 μm (1.81-2.09).
82-7	**3-Month Toxicity/Neurotoxicity Screening Battery (Gavage), Rat** (82-1) Guideline (82-7) Supplementary HED Document No. ??? Study OLA/2/88; 7-1-88 MRID No. 407569-01 **See 82-1**	**Not required for antimicrobial uses.** NOEL = 0.5 mg/kg/day LOEL = 2.0 mg/kg/day (neurogenic skeletal muscle atrophy in both sexes) The rats dosed at 8 mg/kg/day had decreased body weight (-21% ♂; -22% ♀) and body weight gain, minimum to marked hindlimb atrophy in 95-100% of males and females (more severe in females), minimal paravertebral muscle atrophy (2/20 ♂; 17/20 ♀), atrophy of the subcutaneous panniculus muscle (20/20 ♂; 17/20 ♀); neurologic signs including slight hypoactivity, piloerection, hindlimb ataxia, slight head searching, emaciation, hindlimb paralysis, and hunched posture; 10/20 females were sacrificed *in extremis* because of severe hindlimb motor dysfunction. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response.
83-1a	**Chronic Feeding, Rodent**	See 83-5

	STUDY	RESULTS
83-1b	**1-Year Gavage, Monkey** Minimum HED Document No. ??? Study 397-047; 4-14-89 MRID No. 411781-01	NOAEL = 5 mg/kg/day LEL = 25 mg/kg/day (emesis, decreased female body weight) Mortality occurred at 75 mg/kg/day. Dosing by gavage in *Cynomolgus* species at 0, 5, 25, and 150/75 mg/kg/day (the high-dose was lowered after 6 weeks). No explanation was offered for selecting this species as the test system.
83-2a	**80-Week Dermal Carcinogenicity, Mouse** Supplementary HED Document No. ??? Study OLA/7/90; 2-20-91 MRID No. 421008-01	Systemic NOEL = 40.0 mg/kg/day (HDT) Dermal NOEL = 15.0 mg/kg/day Dermal LEL = 40.0 mg/kg/day (increase in epidermal hyperplasia at the application site.) At 40 mg/kg/day, an increase in the incidence of epidermal hyperplasia at the skin application site was seen in males (20% compared to 0% in controls, $p < 0.01$) and in females (nonsignificant by pairwise comparison but a significant trend, $p < 0.05$). Under the conditions of the study, dermal application of sodium omadine did not induce any benign or malignant neoplasms. The highest dose was considered inadequate to assess carcinogenicity. Tested topically in CD-1 stain at 0, 5, 15, and 40 mg/kg/day.
83-2b	**Carcinogenicity (second species)**	See 83-5
83-3a	**Dermal Developmental Toxicity, Rabbit** Minimum HED Document No. ??? Study 397-044; 12-11-87 MRID No. 404872-01	Developmental NOEL >5 mg/kg/day (free-standing) There was no maternal or fetal toxicity. Tested in New Zealand White strain at 0, 1, 2.5, and 5 mg/kg/day on gestation days 6-19.
83-3b	**Dermal Developmental Toxicity, (second species)**	**Required for High-Exposure Category uses, but not for Low or Medium-Exposure Category uses.**

STUDY		RESULTS
83-4	**2-Generation Reproduction - Rat** Minimum HED Document No. ??? Study OLA/9/88; 1-24-89 MRID No. 410972-01	Parental NOEL = 0.5 mg/kg/day Parental LOEL = 1.5 mg/kg/day in females, and 3.5 mg/kg/day in males based on increased incidence of histologic atrophy in the upper hindlimb skeletal muscles (reduction in fiber diameter) in F_1 females (3/25), F_0 males (7/23), and F_1 males (9/25). Additional parental effects seen at 3.5 mg/kg/day included increased histologic atrophy in the upper hindlimb skeletal muscles in F_0 females (19/24), and F_1 females (20/23); and significantly decreased body weight in F_0 and F_1 females. Reproductive NOEL = 1.5 mg/kg/day Reproductive LEL = 3.5 mg/kg/day based on slightly decreased number of pups per litter born in both generations (possibly a consequence of reduced mating success due to hindlimb atrophy), delayed development in pups from both generations (including open ears and eyes and startle response), and decreased pup body weight and weight gain in both sexes. Dosing by gavage in Crl:CD(SD)BR strain at 0, 0.5, 1.5, and 4.5/3.5 mg/kg/day (the high dose was reduced after 3 weeks).

	STUDY	RESULTS
83-5	**104-Week Toxicity/Carcinogenicity (Gavage), Rat** Guideline HED Document No. ??? Study OLA-3-90; 5-28-91 MRID No. 421009-01	NOEL = 0.5 mg/kg/day LOEL = 1.5 mg/kg/day based on significant increases in the incidence of degeneration of the skeletal muscle of the hindlimbs in both sexes. At the highest dose tested (5.0/3.5 mg/kg/day) there was a significant decrease in mean body weight (as much as 10%) and body weight gain in females throughout the study; a marked increase in nerve fiber degeneration in the sciatic nerve and in the spinal cord in both sexes; and an increased incidence of retinal atrophy in both sexes. Under the conditions of the study, no increase in neoplasms was observed at any site. Dosing was considered adequate to assess carcinogenicity. Dosing by gavage in Crl:CD(SD)BR Sprague-Dawley rats at 0, 0.5, 1.5, or 5.0 mg/kg/day for 2 years. The highest dose was reduced to 3.5 mg/kg/day after 12 weeks.
84-2a	**Gene Mutation:**	
	Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT) Acceptable HED Document No ??? Study PH 314-OL-001-87; 5-20-87 MRID No. 404115-01	Negative for forward mutation in CHO cells exposed up to cytotoxic doses (0.08 μg/ml/-S9; 27 μg/ml/+S9).
84-2b	**Structural Chromosome Aberration:**	
	In Vivo Micronucleus Assay in Mice Acceptable HED Document No ??? Study PH 309-OL-001-87; 3-30-87 MRID No. 403437-01	Negative for micronucleus induction in bone marrow cells of mice tested orally up to toxic doses (575 mg/kg).

	STUDY	RESULTS
84-2c	**Other Genotoxic Effects:**	
	Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes Acceptable HED Document No ??? Study PH 311-OL-001-87; 3-16-87 MRID No. 403875-01	Negative for UDS in rat hepatocytes exposed up to cytotoxic doses (300 ng/ml).
85-1	**Metabolism, Rat** Supplementary HED Document No ??? Study ADL 59798A; 8-25-89 MRID No. 412690-01	**Required for High-Exposure Category uses only.** Sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing levels. Total recovery of administered radioactivity was 85-95% at 4 days postexposure. The urine is the major route of excretion of sodium omadine (73-85% of the dose); the feces are only a minor route of excretion (5-12% of the dose). In the single oral low-dose group and the I.V. dose group, most of the administered radioactivity was excreted within the first 12 hours postdosing. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues. The metabolic profiles in the urine were similar in all dose groups; 12 urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-S-glucuronide (Metabolite K). Groups of Sprague-Dawley rats were administered a single oral dose of 0.5 or 25 mg/kg ^{14}C-sodium omadine, 0.5 mg/kg/day of sodium omadine for 14 days followed by a single oral dose of ^{14}C-sodium omadine (0.5 mg/kg), or a single intravenous dose of 0.5 mg/kg ^{14}C-sodium omadine. **Potentially upgradable.** This study alone does not satisfy the minimum guideline requirements (85-1) for a general metabolism study. The study authors need to account for the unrecovered radioactivity, attempt to characterize the fecal metabolites, and propose a metabolic pathway for sodium omadine.

Formulation: **Sodium Omadine® 10% Aqueous Solution** (10% a.i.)
Registration No. 1258-1213

	STUDY	RESULTS
81-1	**Acute Oral (Gavage), Rat** Unacceptable / Tox. Category IV HED Document No. *???* Study MB 88-9122A; 6-22-88 MRID No. 410275-01	**Data Gap** LD_{50} >5000 mg/kg in combined sexes (gavage). Clinical signs: wet anogenital areas, brown staining on body. **Potentially upgradable (reporting deficiencies)**
81-2	**Acute Dermal, Rabbit** Unacceptable / Tox. Category II HED Document No. *???* Study MB 88-9122B; 6-23-88 MRID No. 410275-02	**Data Gap** At 2000 mg/kg (only dose tested), 4/5 males and 2/5 females died. Clinical signs: lethargy, nasal discharge, emaciation, prostration. **Potentially upgradable (reporting deficiencies)**
81-3	**Acute Inhalation**	**Data Gap**
81-4	**Primary Eye Irritation, Rabbit** Unacceptable / Tox. Category III HED Document No. *???* Study MB 88-9122D; 6-10-88 MRID No. 410275-03	**Data Gap** Slight transient ocular irritation. **Potentially upgradable (reporting deficiencies)**
81-5	**Primary Dermal Irritation, Rabbit** Unacceptable / Tox. Category IV HED Document No. *???* Study MB 88-9122C; 6-10-88 MRID No. 410275-04	**Data Gap** Very slight irritation (<48 hours) **Potentially upgradable (reporting deficiencies)**
81-6	**Dermal Sensitization**	**Data Gap**

TB-I has no knowledge of toxicology data for these registered products:

Triadine™ 10 Industrial Microbiostat (6.4% sodium 2-pyridinethiol-1-oxide; 63.6% hexahydro-1,3,5-tris(2-hydroxyethyl)-S-triazine; 30% inert ingredients; Registration No. 1258-990

Triadine™ 20 Industrial Microbiostat (3.6% sodium 2-pyridinethiol-1-oxide; 71.4% hexahydro-1,3,5-tris(2-hydroxyethyl)-S-triazine; 25% inert ingredients; Registration No. 1258-1205

Cimcool Additive SO Cutting & Grinding Fluid Fungicide (4% a.i.; Registration No. 4808-3

V. Data Gaps: Data requirements that have not been satisfied for Low Exposure Category uses include primary eye irritation and dermal sensitization. All registered uses are in the Low-Exposure Category. Acute studies for the 10% Aqueous Solution are either missing or deficient.

VI. Action Taken to Obtain Additional Information or Clarification: These data base deficiencies were identified by the Registrant and HED in the course of FIFRA 88 review.

VII. Reference Dose (RfD): The RfD is **0.005 mg/kg/day.** This value was derived by dividing the Chronic Rat study NOEL of 0.5 mg/kg/day by an uncertainty factor of 100. A Rat Reproduction study with a Parental NOEL of 0.5 mg/kg/day supports the RfD as a co-critical study. The RfD was verified by HED on March 30, 1995.

VIII. Endpoints for Occupational Risk Assessment: Dermal absorption should be considered to be $\leq$10%. Sodium omadine has no food uses. It is used occupationally as an antimicrobial agent, primarily in metalworking fluids, so exposure is limited to the dermal and inhalation routes. Acute oral exposure can only result from deliberate poisoning.

Short Term Occupational or Residential Exposure (1 to 7 Days):
83-3a — Dermal Developmental Toxicity in Rabbit. NOEL = 5 mg/kg/day (free-standing)

Intermediate Term Occupational or Residential (1 Week to Several Months):
82-3 — 90-day dermal toxicity in rats. NOEL = 5 mg/kg/day
82-4 — 90-day inhalation toxicity in rats. Systemic NOEL = 0.0011 mg/l

Cancer Classification: D Classification

IX. Pending Regulatory Actions: There are at this writing no pending regulatory actions against the Registration of this pesticide.

X. Toxicologic Issues Pertinent to Granting this Request: N/A

Compiled by John E. Whalan
Revised on April 20, 1995

JW 1-20-95

011532

Reviewed by:
Section I, Tox. L... ...09C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-1; Acute Oral Toxicity in Rats

CHEMICAL: Sodium omadine 40% solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Oral LD_{50} in Rats

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370A;

STUDY COMPLETED: April 29, 1987

EXECUTIVE SUMMARY: Wistar Albino rats were given gavage doses of sodium omadine 40% solution ranging from 1000 to 2500 mg/kg. The estimated acute oral LD_{50} for males was 2000 (1700-2300) mg/kg; the LD_{50} for females was 1100 (580-1300) mg/kg; the combined LD_{50} for both sexes was 1500 (1300-1700) mg/kg. Clinical signs included lethargy, diarrhea, prostration, ptosis, brown staining on the nose/mouth and anogenital areas, wetness or alopecia at the anogenital area, and ocular discharge. Necropsy revealed abnormalities of the lungs (hemorrhagic, congested), liver (dark mottled), spleen (dark, pale), heart (dilated), stomach (red areas), intestines (red or yellow areas, distended, containing mucus), brown staining of the nose/mouth and anogenital areas, and red discoloration of the nose in animals with unscheduled deaths; anogenital staining and/or alopecia were observed in treated animals at the scheduled sacrifice.

CORE CLASSIFICATION: **Acceptable.** The test article purity was not reported. This study satisfies guideline data requirements (81-1) for acute oral toxicity in the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: III — Caution

Comments: In keeping with HED procedures, the core classification is changed from "Guideline" to "Acceptable." The DER did not mention that dosing was by gavage. It also lacked an executive summary, so the preceding summary was generated. The penned corrections added by the secondary reviewer read as follows:

"CHEMICAL: Sodium omadine (40% soln.)"

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Acute Oral Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Lisa Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn S. Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 401
Project Officer: Caroline Gordon

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline 81-1; acute oral toxicity in Rats

CHEMICAL: Sodium omadine (40% Soln.)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-01

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Oral LD_{50} in Rats

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370A

STUDY COMPLETED: April 29, 1987

CONCLUSIONS: The estimated acute oral LD_{50} for males was 2.0 (1.7-2.3) g/kg; the LD_{50} for females was 1.1 (0.58-1.3) g/kg; the combined LD_{50} for both sexes was 1.5 (1.3-1.7) g/kg. Clinical signs included lethargy, diarrhea, prostration, ptosis, brown staining on the nose/mouth and anogenital areas, wetness or alopecia at the anogenital area, and ocular discharge. Necropsy revealed abnormalities of the lungs (hemorrhagic, congested), liver (dark, mottled), spleen (dark, pale), heart (dilated), stomach (red areas), intestines (red or yellow areas, distended, containing mucus), brown staining of the nose/mouth and anogenital areas, and red discoloration of the nose in animals with unscheduled deaths; anogenital staining and/or alopecia were observed in treated animals at the scheduled sacrifice.

CORE CLASSIFICATION: Guideline. This study satisfies guideline data requirements (81-1) for acute oral toxicity in the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: III--Caution

A. MATERIALS

011532

1. Test Compound

Test material: Sodium omadine, 40% solution
Identification number: F113D1
Active ingredient: Sodium omadine
Formulation: 40% solution
Purity: Duplicate samples were analyzed and were determined to be 43.70% and 43.76% sodium omadine.
Physical description: Yellow liquid; specific gravity = 1.23
Storage condition: Ambient room temperature and humidity
Stability: Not reported
Dose levels: Seven doses (1.0, 1.1, 1.2, 1.5, 1.9, 2.0, and 2.5 g/kg) were evaluated in males; four doses (1.0, 1.1, 1.2, and 1.5 g/kg) were evaluated in females.
Dosing volume: 0.8-2.0 mL/kg depending on dose (Note: The guidelines recommend limiting variations in dosing volume.)

2. Controls

None

3. Test Animals

Species: Rat
Strain: Wistar Albino
Source: Ace Animals. Animals arrived in seven separate shipments over a 2.5-month period because each dose group was run at a separate time.
Sex: Males and females
Age: ~8 weeks old
Weight: Males, 210-300 g; females, 217-296 g; test day
Number of animals/dose: 10 (5/sex) except at the 3 highest doses when 5 males/dose were used
Housing: Five/sex/cage
Acclimation: 2 days-5 weeks
Identification: Cage cards and indelible body marks
Selection: Random
Feed: Purina Rat Chow #5012 ad libitum except for predose fasting
Water: Ad libitum
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

Animals fasted: 16-20 hours prior to dosing

Dosing: Once __x__; Other _____ (describe)

Observation period: 14 days

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Observation frequency: 1, 2, and 4 hours postdosing and twice daily thereafter

Body weight interval: Pretest, 7 days, and 14 days

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Gross pathology: YES __x__; NO _____

Histopathology: YES _____; NO __x__

C. RESULTS

1. Mortality: Mortality results are presented below:

Dose g/kg	Number of mortalities/number treated	
	Males	Females
1.0	0/5	2/5
1.1	0/5	1/5
1.2	1/5	3/5
1.5	0/5	5/5
1.9	1/5	--
2.0	3/5	--
2.5	5/5	--

-- = Not evaluated

Note: All unscheduled deaths occurred on days 0-2.

2. Clinical Observations: Frequently observed clinical signs included lethargy, diarrhea, ptosis, brown staining on the nose/mouth and anogenital areas, wetness of the anogenital area, and ocular discharge. Staining of the mouth, nose, or anogenital area and alopecia at the anogenital area were observed in some animals up to the scheduled sacrifice time. One female that received the 1.1-g/kg dose was observed with loss of function of the front feet. Animals with unscheduled deaths were observed with signs limited to diarrhea, ataxia, and prostration.

3. Body Weights: With the exception of 1 male receiving 2.0 g/kg sodium omadine, all surviving animals had normal weight gain.

4. Gross Necropsy: Necropsy of animals with unscheduled deaths revealed abnormalities of the lungs (hemorrhagic, congested), liver (dark, mottled), spleen (dark, pale), heart (dilated), stomach (red areas), intestines (red or yellow areas, distended, containing mucus); brown staining of the nose/mouth and anogenital areas; and red discoloration of the nose. Sacrificed animals were normal or were frequently observed with anogenital alopecia and/or staining.

5. LD_{50} Determination: The estimated acute oral LD_{50} for males was 2.0 g/kg (95% confidence limits: 1.7-2.3 g/kg); the LD_{50} for females was 1.1 g/kg (95% confidence limits: 0.58-1.3 g/kg); and the combined LD_{50} for both sexes was 1.5 g/kg (95% confidence limits: 1.3-1.7 g/kg). This values corresponds to Toxicity Category III--Caution.

011532

D. REVIEWERS' COMMENTS

The reviewers are in agreement with the study author's reported findings on the acute oral LD_{50} for sodium omadine in male and female rats. Furthermore, the results of the study indicate a sex-related difference in the toxicity of the test material including the dose at which clinical signs and death occurred.

E. QUALITY ASSURANCE MEASURES

Was the test performed under GLPs? YES _X_; NO ___
A Quality Assurance Statement, signed and dated April 29, 1987, was submitted.

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Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-2; Acute Dermal Toxicity in Rabbits

CHEMICAL: Sodium omadine 40% solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-02

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Acute Dermal Toxicity in Rabbits/LD_{50} in Rabbits

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370B

STUDY COMPLETED: April 29, 1987

EXECUTIVE SUMMARY: New Zealand White rabbits were dermally dosed with sodium omadine 40% solution on the dorsal trunk. The estimated acute dermal LD_{50} for males was 1900 mg/kg (95% confidence limits: 1600-2200 mg/kg); the LD_{50} for females was 1800 mg/kg (95% confidence limits: 1500-2000 mg/kg); and the LD_{50} for both sexes combined was 1800 mg/kg (95% confidence limits: 1600-2100 mg/kg). Clinical signs included few feces, lethargy, yellow nasal discharge, emaciation, prostration, negative righting reflex, ataxia, ptosis, bloated abdomen, unkempt appearance, decreased body temperatures, soiling of the anogenital area, pupillary dilation, wetness of the nose/mouth area, wetness and yellow staining of the forelimbs, loss of hindlimb control, black and yellow staining of the nose/mouth area, mucoid diarrhea, and wetness and brown staining of the anogenital area. Necropsy revealed abnormalities of the treated skin, lungs, liver, spleen, gall bladder, urinary bladder, kidneys, and gastrointestinal tract; redness of the conjunctival area; red coloration of the body wall and body fat; red discharge of the mouth/nose area; excessive fluid in the peritoneal cavity; and brown staining of the anogenital area.

CORE CLASSIFICATION: **Acceptable.** The test article purity was not reported. This

study satisfies guideline data requirements (81-2) for acute dermal toxicity in the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: II — Warning

Comment: In keeping with HED procedures, the core classification is changed from "Guideline" to "Acceptable." The DER lacked an executive summary, so the preceding summary was generated.

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE 40% SOLUTION

Study Type: Acute Dermal Toxicity in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn D Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 397
Project Officer: Caroline Gordon

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV Date: 10/25/91
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-2; acute dermal toxicity in rabbits

CHEMICAL: Sodium omadine

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-02

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Acute Dermal Toxicity in Rabbits/LD_{50} in Rabbits

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370B

STUDY COMPLETED: April 29, 1987

CONCLUSIONS: The estimated acute dermal LD_{50} for males New Zealand albino rabbits was 1.9 g/kg (95% confidence limits: 1.6-2.2 g/kg); the LD_{50} for females was 1.8 g/kg (95% confidence limits: 1.5-2.0 g/kg); and the LD_{50} for both sexes combined was 1.8 g/kg (95% confidence limits: 1.6-2.1 g/kg). Clinical signs included few feces, lethargy, yellow nasal discharge, emaciation, prostration, negative righting reflex, ataxia, ptosis, bloated abdomen, unkempt appearance, decreased body temperatures, soiling of the anogenital area, pupillary dilation, wetness of the nose/mouth area, wetness and yellow staining of the forelimbs, loss of hind limb control, black and yellow staining of the nose/mouth area, mucoid diarrhea, and wetness and brown staining of the anogenital area. Necropsy revealed abnormalities of the treated skin, lungs, liver, spleen, gall bladder, urinary bladder, kidneys, and gastrointestinal tract; redness of the conjunctival area; red coloration of the body wall and body fat; red discharge of the mouth/nose area; excessive fluid in the peritoneal cavity; and brown staining of the anogenital area.

CORE CLASSIFICATION: Guideline. This study satisfies guideline data requirements (81-2) for acute dermal toxicity in the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: II--Warning

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A. MATERIALS

1. Test Compound

Test material: Sodium omadine, 40% solution
Identification number: F113D1
Active ingredient: Sodium omadine
Formulation: 40% solution
Purity: Duplicate samples were analyzed and determined to 43.70% and 43.76% sodium omadine.
Physical description: Yellow liquid; specific gravity = 1.23
Storage condition: Ambient room temperature and humidity
Stability: Not reported

Dose levels: Four doses (1.50, 1.65, 1.80, and 2.0 g/kg) were evaluated

Dosing volume: 1.23, 1.34, 1.46, and 1.62 mL/kg based on the specific gravity (1.23)

2. Controls

None

3. Test Animals

Species: Rabbit
Strain: New Zealand albino
Source: Ace Animals and Clifford Roedel. The animals for each dose group were received separately and were tested at different times during a 4-month period.
Sex: Males and females
Age: ~8 weeks old
Weight: Males, 2.1-3.0 g; females, 2.1-2.8 g; test day
Number of animals/dose: 10 (5/sex)
Identification: Cage notation and ear tags
Housing: Individually
Assignment: Random
Diet: Purina Chow #53-21, ad libitum
Water: Ad libitum
Acclimation period: At least 1 week
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

Animals fasted: Not reported
Dosing: Once __x__; Other _____ (describe)

Skin preparation: ~24 hours prior to application of the test material, the dorsal side of each of the test animal's trunk was clipped free of hair forming an area ~10% of the animal's total body area. The test material was applied to the clipped area with a syringe applicator.

Observation period: 21-28 days (all doses except 1.8 g/kg observed for 21 days)
Observation frequency: 1, 2, and 4 hours postdosing and twice daily thereafter.
Body weight intervals: Pretest, and 7, 14, 21, and 28 days
Gross pathology: YES __x__; NO _____
Histopathology: YES _____; NO __x__

C. RESULTS

1. Mortality: Mortality data are presented below.

Dose (g/kg)	Number of mortalities/number treated	
	Males	Females
1.50	1/5	2/5
1.65	1/5[a]	3/5
1.80	2/5	2/5
2.00	3/5[b]	4/5

[a]A test animal was sacrificed because of moribund conditions.
[b]Two test animals were sacrificed because of moribund conditions.

Note: Most mortalities occurred on days 1 or 2. One male at 2.0 g/kg was sacrificed at day 14; 1 male at 1.56 g/kg sacrificed at day 4; and 1 female at 1.65 g/kg was sacrificed at day 16.

2. Clinical Observations: Frequently observed clinical signs included diarrhea, ataxia, lethargy, emaciation, few feces, lethargy, yellow nasal discharge, unkempt appearance, anogenital soiling, nose/mouth wetness, and yellow staining of the forelimbs.

3. Dermal Irritation: The incidence and severity of dermal reactions compared to the total number of animals are presented in Tables 1 and 2. The test material produced discoloration of the skin (brown, green) lasting <7 days; and up to severe erythema with severe eschar, moderate edema, paleness, dryness, and flaking skin lasting ≤21 days (with the exception of 1 male from the 1.65-g/kg-dose group) that had severe erythema lasting ≥21 days).

4. Body Weights: Most surviving animals showed weight loss during observation; 50-100% of animals with weight loss recovered at least partially by the end of the observation period (Table 3).

5. Gross Necropsy: Necropsy revealed abnormalities of the treated skin (not specified), lungs (congested, hemorrhagic), liver (mottled, yellow, pale), spleen (pale/green), gall bladder (yellow/red), urinary bladder (red fluid filled), kidneys (pitted), gastrointestinal tract (reddened, yellow colored, distended, pale), conjunctival area (reddened), body wall and body fat (reddened), red discharge of the mouth/nose area, excessive fluid in the peritoneal cavity, and brown staining of the anogenital area.

Table 1. Erythema and Edema Scores in Males After Application of Sodium Omadine[a]

Dose (g/kg)	Grade	Erythema: Number of Animals at Study Intervals (day)					Edema: Number of Animals at Study Intervals (day)				
		1	7	14	21	28	1	7	14	21	28
1.5											
	0	0/4	0/4	3/4	3/4	--	0/4	0/4	4/4	4/4	--
	1	0/4	2/4	0/4	1/4	--	0/4	2/4	0/4	0/4	--
	2	4/4	1/4	0/4	0/4	--	1/4	2/4	0/4	0/4	--
	3	0/4	0/4	0/4	0/4	--	3/4	0/4	0/4	0/4	--
	4	0/4	1/4	1/4	0/4	--	0/4	0/4	0/4	0/4	--
1.65											
	0	1/5	2/4	2/4	4/4	--	0/5	0/4	3/4	4/4	--
	1	1/5	0/4	2/4	0/4	--	0/5	1/4	1/4	0/4	--
	2	3/5	2/4	0/4	0/4	--	1/5	3/4	0/4	0/4	--
	3	0/5	0/4	0/4	0/4	--	4/5	0/4	0/4	0/4	--
	4	0/5	0/4	0/4	0/4	--	0/5	0/4	0/4	0/4	--
1.8											
	0	0/3	1/3	1/3	2/3	3/3	0/3	1/3	2/3	3/3	3/3
	1	0/3	0/3	1/3	0/3	0/3	0/3	1/3	1/3	0/3	0/3
	2	3/3	0/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3	0/3
	4	0/3	2/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3
2.0											
	0	0/4	0/3	1/3	2/2	--	0/4	1/3	3/3	2/2	--
	1	1/4	1/3	2/3	0/2	--	0/4	2/3	0/3	0/2	--
	2	3/4	2/3	0/3	0/2	--	0/4	0/3	0/3	0/2	--
	3	0/4	0/3	0/3	0/2	--	4/4	0/3	0/3	0/2	--
	4	0/4	0/3	0/3	0/2	--	0/4	0/3	0/3	0/2	--

[a]The were data extracted from the study report, pp 9-12.
[b]A decrease in the denominator indicate that an animal died or was sacrificed in a moribund state.
[c]-- = Animals were not examined

GUIDELINE SERIES 81-2: Acute dermal toxicity

Table 2. Erythema and Edema Scores in Females After Application of Sodium Omadine[a]

Dose (g/kg)	Scale	Erythema: Number of Animals at Study Intervals (day)					Edema: Number of Animals at Study Interval (day)				
		1	7	14	21	28	1	7	14	21	28
1.5											
	0	0/4	0/3	2/3	3/3	--	0/4	0/3	3/3	3/3	--
	1	0/4	1/3	1/3	0/3	--	0/4	2/3	0/3	0/3	--
	2	3/4	2/3	0/3	0/3	--	3/4	1/3	0/3	0/3	--
	3	1/4	0/3	0/3	0/3	--	1/4	0/3	0/3	0/3	--
	4	0/4	0/3	0/3	0/3	--	0/4	0/3	0/3	0/3	--
1.65											
	0	0/4	0/3	3/3	2/2	--	0/4	0/3	3/3	2/2	--
	1	2/4	1/3	0/3	0/2	--	0/4	0/3	0/3	0/2	--
	2	2/4	1/3	0/3	0/2	--	1/4	3/3	0/3	0/2	--
	3	0/4	0/3	0/3	0/2	--	3/4	0/3	0/3	0/2	--
	4	0/4	1/3	0/3	0/2	--	0/4	0/3	0/3	0/2	--
1.8											
	0	0/3	0/3	1/3	3/3	2/3[d]	0/3	0/3	3/3	3/3	2/3[d]
	1	0/3	0/3	2/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3
	2	3/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	2/3	0/3	0/3	0/3	0/3
	4	0/3	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
2.0											
	0	0/2	0/1	1/1	1/1	--	0/2	0/1	1/1	1/1	--
	1	0/2	1/1	0/1	0/1	--	0/2	1/1	0/1	0/1	--
	2	1/2	0/1	0/1	0/1	--	0/2	0/1	0/1	0/1	--
	3	1/2	0/1	0/1	0/1	--	2/2	0/1	0/1	0/1	--
	4	0/2	0/1	0/1	0/1	--	0/2	0/1	0/1	0/1	--

[a]The were data extracted from the study report, pp 9-12.
[b]A decrease in the denominator indicates that an animal died or was sacrificed in a moribund state.
[c]Data from one animal was "inadvertently not recorded."
[d]-- = Animals were not examined

Table 3. Body Weight Changes in Rabbits After Dermal Exposure to Sodium Omadine[a]

Dose (g/kg)	Mean Pretest Body Weight (kg ± S.D.)	Mean Body Weight (kg ± S.D.) at Study Intervals (day) 7	14	21	28
Males					
1.50	2.5±0.3	2.2±0.3	2.3±0.5	2.4±0.3	--
1.65	2.2±0.1	2.2±0.1	2.0±0.2	2.3±0.3	--
1.80	2.4±0.2	2.3±0.2	2.4±0.2	2.5±0.2	2.5±0.2
2.00	2.2±0.1	2.0±0.1	1.8±0.2	2.1±0.1	--
Females					
1.50	2.5±0.2	2.6±0.2	2.5±0.1	2.8±0.2	--
1.65	2.3±0.3	2.0±0.3	2.0±0.4	2.5±0.3	--
1.80	2.5±0.2	2.3±0.0	2.5±0.2	2.5±0.5	2.5±0.6
2.00	2.5±0.2	2.4[b]	2.3	2.5	--

[a]The were data extracted from the study report, pp. 9-12.
[b]Because of mortality, the weight from only one animal was recorded

6. LD_{50} Determination: The estimated acute oral LD_{50} for males was 1.9 g/kg (95% confidence limits: 1.6-2.2 g/kg); the LD_{50} for females was 1.8 g/kg (95% confidence limits: 1.5-2.0 g/kg); and the LD_{50} for both sexes combined was 1.8 g/kg (95% confidence limits: 1.6-2.1 g/kg). These values corresponds to Toxicity Category II--Warning.

D. REVIEWERS' COMMENTS

The reviewers are in agreement with the study author's reported findings on the acute dermal LD_{50} for sodium omadine in male and female rabbits.

E. QUALITY ASSURANCE MEASURES

Was the test performed under GLPs? YES X; NO ___
A Quality Assurance Statement, signed and dated April 29, 1987, was submitted.

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner
Section I, Tox. Branch I (7509C) Roger Gardner 1/20/95

STUDY TYPE: Guideline 81-3 Acute Inhalation Toxicity in Rats

CHEMICAL: Sodium omadine 40% solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 403390-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Acute Inhalation Toxicity Evaluation on Na Omadine in Rats

AUTHOR: J.G. Drummond

STUDY NUMBER: 397-045

STUDY COMPLETED: August 28, 1987

EXECUTIVE SUMMARY: Sprague Dawley rats were dosed with sodium omadine 40% solution for 4 hours in a whole body chamber. The LC_{50} values, based on analytical concentrations, are as follows:

Males: 1.26 mg/l (95% confidence limits, 0.76-2.10 mg/l)
Females: 0.81 mg/l (95% confidence limits, 0.45-1.45 mg/l)
Combined sexes: 1.08 mg/l (95% confidence limits, 0.71-1.66 mg/l)

The MMAD ranged from 2.3-3.2 μm. Clinical signs included increased salivation, hindlimb impairment, prostration, red facial stains, and yellow stained abdomen and genital areas.

CORE CLASSIFICATION: Acceptable. The test article purity was not reported. This study satisfies Guideline data requirements (81-3) for acute inhalation toxicity for the 40% solution, and is acceptable for regulatory purposes.

TOXICITY CATEGORY: III — Caution

Comments: In keeping with HED procedures, the core classification is changed from "Guideline" to "Acceptable." The DER lacked an executive summary, so the preceding summary was generated.

FINAL

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DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Acute Inhalation Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer E. Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn S. Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 409
Project Officer: Caroline Gordon

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV, Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-3; Acute inhalation toxicity - rats

CHEMICAL: Sodium omadine (40% solutions)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID Number: 403390-01

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Acute Inhalation Toxicity Evaluation on Na Omadine in Rats

AUTHOR: J.G. Drummond

STUDY NUMBER: 397-045

STUDY COMPLETED: August 28, 1987

CONCLUSIONS: Acute inhalation LC_{50} in males: 1.26 mg/L (95% confidence limits, 0.76-2.10 mg/L)
Acute inhalation LC_{50} in females: 0.81 mg/L (95% confidence limits, 0.45-1.45 mg/L)
Acute inhalation LC_{50} in sexes combined: 1.08 mg/L (95% confidence limits, 0.71-1.66 mg/L)

CORE CLASSIFICATION: Guideline. This study satisfies Guideline data requirements (81-3) for acute inhalation toxicity for the 40% solution and is acceptable for regulatory purposes.

TOXICITY CATEGORY: III--Caution

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A. MATERIALS

1. Test Compound

Test material: Sodium omadine, 40% solution
Identification numbers: F113D1, SO-8695 8509-P-179H, SO-8697 8509-P-179H
Active ingredient: Sodium omadine
Formulation: 40% in aqueous solution
Purity: 40%
Physical description: Amber liquid
Storage condition: Not reported
Stability: Not reported
Concentration levels: 0.14, 0.58, 0.79, 0.95, and 1.4 mg/L

2. Controls:

None

3. Test Animals

Species: Rat
Strain: Sprague-Dawley
Source: Charles River Laboratories, Inc., Portage, MI. (Animals for each exposure were received separately because the exposures occurred over a 4-month period.)
Sex: Male and female
Age: Young adult (51-72-days-old)
Weight: 234-297 g (males); 178-220 g (females)
Number of animals/concentration: 10 (5/sex)
Housing: Individual
Acclimation period: Not reported
Identification: Ear tag
Feed: Purina Certified Pelleted Rodent Chow #5002 ad libitum except during exposure
Water: Tap water, ad libitum except during exposure
Environmental conditions: Photoperiod: 12 hours light/12 hours dark; other conditions not reported

B. TEST PERFORMANCE

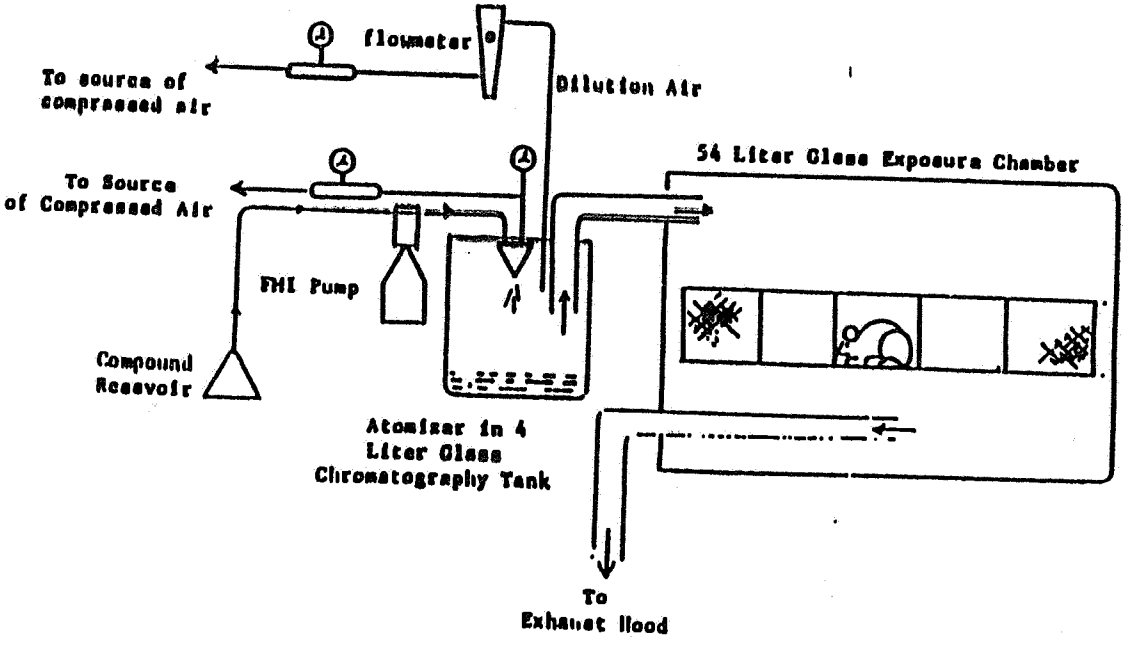
1. Inhalation Chamber

Animals were exposed (whole body) in a 54-L glass dynamic inhalation chamber (Figure 1).

2. Concentration Preparation/Generation of Test Atmospheres

The test material was pumped at a constant rate to an atomizer and into a 4-L container where it was mixed with filtered air prior to entering the inhalation chamber via a 5-cm-diameter pipe.

Figure 1 Schematic Diagram of Generation and Exposure System[a]



[a]Figure 1 extracted from the study report, p. 23.

3. Analytical Determinations

Concentration sampling was conducted at 1-hour intervals by drawing the test atmosphere through a preweighed glass fiber filter for 5 minutes. Exposed filters were treated with $CuSO_4$ to convert sodium omadine to copper omadine. The copper omadine was extracted with methylene chloride and analyzed by high-performance liquid chromatography.

Aerodynamic particle size was determined using an Anderson 8-stage cascade impactor and a flow rate of 28.3 L/min. Measurements were made once per exposure group.

4. Chamber Monitoring

Chamber airflow was monitored and recorded approximately every 30 minutes. Air flow ranged from 27 L/minute to 70 L/minute. Temperature and relative humidity were also recorded every 30 minutes; the temperature range was 21-23°C, and the relative humidity was 39-81%. Oxygen content before exposure was 19.0-21%. Airflow was sufficient to maintain adequate oxygenation.

Particle size determination: The results of the particle size analyzes are presented below:

Group	Nominal Exposure Level (mg/L)	Actual Exposure Level (mg/L)	Equivalent Aerodynamic Diameter (μm)	Geometric Standard Deviation
I	25.9	1.4±0.17	2.5	1.92
II	23.7	0.79±0.183	3.2	2.00
III	6.6	0.14±0.046	2.3	2.28
IV	8.1	0.58±0.095	2.5	2.00
V	18.6	0.95±0.187	3.0	1.95

Data extracted from the study report, pp. 17 and 18.

5. Observation Period

14 days

6. Observation Frequency

Hourly during exposure and twice daily thereafter, once for clinical signs and once for mortality.
Body weight interval: Prior to exposure and at 7 and 14 days postexposure
Gross pathology: YES __X__; NO _____
Histopathology: YES _____; NO __X__

C. RESULTS

1. Mortality

Mortality results are summarized below.

Dosage (mg/L)	Group	(Number Dead / Number Tested) Males	Females	Combined
0.14	III	0/5	0/5	0/10
0.58	IV	0/5	2/5	2/10
0.79	II	3/5	5/5	8/10
0.95	V	0/5	1/5	1/10
1.4	I	3/5	3/5	6/10

Data extracted from the study report, p. 19.

Time and cause of death: All reported mortalities occurred between day 7 and day 14. The cause of death was not noted.

2. Clinical Observations

During, or just after exposure, a marked increase in salivation was observed in most animals. Males exposed to 0.79 or 0.95 mg/L and females exposed to 0.58, 0.79 or 0.95 mg/L of the test material developed hind limb impairment toward the end of the second week; however, hind-limb effects were not observed in the high-concentration group. Animals in the high-concentration group were observed with prostration starting on day 13. Over the remaining observation period the test rats were observed with red material around the facial area, yellow staining around the abdomen and genital areas, and staining on the body surfaces.

3. Body Weights

A concentration-related body weight loss (-58 to -92 g) was observed in males in the three highest concentration groups by the end of the 14-day observation period. Losses were greater during the second week of the observation. Males exposed to a 0.58-mg/L concentration of the test material had a decreased weight gain relative to males exposed to the lowest concentration, which were considered to have normal body weight gains (+102 g). Body weights of females decreased (-51 to -56 g) in the 0.58- and 0.95-mg/L concentration groups by the end of the study. At 0.14 mg/L or 0.58 mg/L, females gained no weight over their pretest weights. Fourteen-day body weight changes were not available for females in the mid-concentration group because of the high incidence of mortality.

4. Gross Necropsy

The remarkable abnormalities of survivors and animals with unscheduled deaths included bright red discoloration of the lungs (3/5 males and 5/5 females at 1.4 mg/L, the highest concentration; 0/5 males and 1/5 females at 0.95 mg/L; and 2/5 males and 1/5 females at 0.79 mg/L). The noted lung abnormalities were not concentration related. Excessive fluid in the intestines was observed in one male and one female at the highest concentration. Dark red fluid in the bladder also occurred in one male exposed to the highest concentration of the test material.

5. LC_{50} Determination

The estimated acute inhalation LC_{50}, calculated by the method of Bliss, was approximately 1.26 mg/L (95% confidence limits, 0.76-2.10 mg/L) in males and 0.81 mg/L (95% confidence limits, 0.45-1.45 mg/L) in females; the acute inhalation LC_{50} in the sexes combined was 1.08 mg/L (95% confidence limits, 0.71-1.66 mg/L). These values correspond to Toxicity Category III--Caution.

D. QUALITY ASSURANCE MEASURES

Was the test performed under GLPs? YES X ; NO ___
A Quality Assurance Statement, signed and dated August 28, 1987, was submitted.

E. REVIEWERS' COMMENTS: The reviewers agree with the study author's findings associated with the determination of the LC_{50} values the sodium omadine.

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Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1-20-95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-5; Primary Dermal Irritation in Rabbits

CHEMICAL: Sodium omadine 40% solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-03

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Primary Dermal Irritation in Albino Rabbits

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370C

STUDY COMPLETED: April 29, 1987

EXECUTIVE SUMMARY: Application of 0.5 ml of sodium omadine 40% solution to the skin of New Zealand White rabbits for 4 hours resulted in slight erythema and edema lasting ≤48 hours. Barely perceptible erythema, but not edema, was observed in 1 animal at 72 hours post-exposure.

CORE CLASSIFICATION: **Acceptable.** The test article purity was not reported. This study satisfies guideline data requirements (81-5) for a primary dermal irritation study on the 40% formulation, and is acceptable for regulatory purposes.

TOXICITY CATEGORY: IV — Caution

Comments: In keeping with HED procedures, the core classification is changed from "Guideline" to "Acceptable." The strain is changed from "Albino" to "New Zealand White." The DER lacked an executive summary, so the preceding summary was generated.

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Primary Dermal Irritation in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn S. Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 400
Project Officer: Caroline Gordon

GUIDELINE SERIES 81-5: Primary dermal irritation

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-5; primary dermal irritation in rabbits

CHEMICAL: Sodium omadine (40% soln)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-03

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Primary Dermal Irritation in Albino Rabbits

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370C

STUDY COMPLETED: April 29, 1987

CONCLUSIONS: Application of 0.5 mL sodium omadine (~40% pure) to the skin of rabbits for 4 hours resulted in slight erythema and edema lasting ≤48 hours. Barely perceptible erythema, but not edema, was observed in 1 animal at 72 hours post-exposure.

CORE CLASSIFICATION: Guideline. This study satisfies guideline data requirements (81-5) for a primary dermal irritation study on the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: IV--Caution

A. MATERIALS

1. Test Compound

Test material: Sodium omadine, 40% solution
Identification number: F113D1
Active ingredient: Sodium omadine
Formulation: 40% solution
Purity: Duplicate samples were determined to be 43.70% and 43.76% test material
Physical description: Yellow liquid
Storage condition: Ambient room temperature and humidity
Stability: Not reported

2. Dose levels

0.5 mL liquid

3. Test Animals

Species: Rabbits
Strain: Albino
Source: Ace Animals
Number of animals: 6
Sex: Not reported
Age: ~8 weeks
Mean body weight: 2.0-3.0 kg
Identification: Cage notation and metal ear tags
Housing: Individually
Acclimation: At least 1 week
Diet: Purina Rabbit Chow #53-21 ad libitum
Water: Ad libitum
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

1. Skin Preparation: Approximately 24 hours prior to testing, the dorsal area of the trunk of each animal was clipped, and one test site (reported to be 6 cm and assumed to be 6 cm^2) was selected.

2. Test Material Application: Test substance was applied to the test site, the area was covered with a gauze patch secured by tape, and the animal's body was wrapped in a semi-occlusive dressing. After 4 hours of exposure, the wrappings and the patch were removed, and residual test material was removed with an appropriate solvent.

3. Observation Period: x 0.5-1 hr x 24 hr x 48 hr
x 72 hr _____ 7 days _____ 10 days
x 14 days

4. Scoring System: Dermal readings were based on the Draize scoring system.

C. REPORTED RESULTS: The incidence of dermal reactions (Grade 2 and Grade 1) compared to the total number of animals is presented below:

Parameter	Incidence at Each Observation Interval (hours) 0.5-1	24	48	72
Erythema				
Grade 2	1/6	1/6	1/6	0/6
Grade 1	3/6	4/6	3/6	1/6
Edema				
Grade 2	2/6	0/6	0/6	0/6
Grade 1	2/6	2/6	1/6	0/6

Slight erythema was observed in 1 rabbit during the first observation period and was evident in a second rabbit during the 24- and 48-hour observation periods. Two rabbits had slight edema at the first observation period. The incidence and severity of the irritation observed in the animals decreased after the 24-hour observation period. Only one animal was observed with dermal irritation (barely perceptible erythema) at the 72-hour observation period.

The study author concluded that sodium omadine produced slight erythema and edema.

Toxicity Category: IV--Caution

D. REVIEWERS' COMMENTS: The reviewers agree with the study author's conclusion that, under the conditions of this study, sodium omadine produced mild dermal irritation.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes (A Quality Assurance Statement was signed and dated April 29, 1987.)

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-6; Dermal Sensitization Study in Guinea Pigs

CHEMICAL: Sodium omadine 40% solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-04

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Guinea Pig Maximization Test (Magnusson-Kligman)

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370F

STUDY COMPLETED: April 29, 1987

EXECUTIVE SUMMARY: Sodium omadine 40% solution was tested in the Magnusson-Kligman guinea pig maximization test up to dose levels which were irritating. The chemical was not a sensitizer under the conditions of the test. No positive control data were provided.

CORE CLASSIFICATION: **Unacceptable.** The test article purity was not reported. This study does not satisfy the guideline data requirements (81-6) for a dermal sensitization study on the 40% formulation, and is not acceptable for regulatory purposes. This study can be upgraded provided positive control data from the same laboratory are supplied. These data must have been generated within a 6-month period under the same testing conditions.

TOXICITY CATEGORY: Not applicable

Comments: In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable." There was no mention of a positive control in this study. The DER lacked an executive summary, so the preceding summary was generated.

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Dermal Sensitization in Guinea Pigs

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 396
Project Officer: Caroline Gordon

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV, Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-6; dermal sensitization study in guinea pigs

CHEMICAL: Sodium omadine (40% soln.)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 402478-04

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® Guinea Pig Maximization Test (Magnusson-Kligman)

AUTHOR: O.M. Moreno

STUDY NUMBER: MB 86-8370F

STUDY COMPLETED: April 29, 1987

CONCLUSIONS: Negative for inducing dermal sensitization when sodium omadine is evaluated using the guinea pig maximization test (Magnusson-Kligman).

CORE CLASSIFICATION: Minimum. This study satisfies the guideline data requirements (81-6) for a dermal sensitization study on the 40% formulation and is acceptable for regulatory purposes.

TOXICITY CATEGORY: Not applicable

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A. MATERIALS

1. Test Compound

Test material: Sodium omadine, 40% solution
Identification number: F113D1
Active ingredient: Sodium omadine
Formulation: 40% solution
Purity: Duplicate samples were determined to be 43.70% and 43.76% test material
Physical description: Yellow liquid
Storage condition: Ambient room temperature and humidity
Stability: Not reported
Date received: September 3, 1986

2. Dose levels

(a) Induction routine A

Dose 1. Freunds Complete Adjuvant (FCA) as received

Dose 2. A 1:10 dilution of the test material (40% sodium omadine solution) in distilled water (dH_2O), yielding a solution containing ≈4% sodium omadine

Dose 3. A 1:1 dilution of dose 2 and FCA, yielding a solution containing ≈2% sodium omadine

(b) Induction routine B

1:10 dilution of the test material (40% sodium omadine solution) in dH_2O, yielding a solution containing ≈4% sodium omadine

(c) Challenge dose

1:20 dilution of the test material (40% sodium omadine solution) in dH_2O, yielding a solution containing 2% sodium omadine

3. Test Animals

Species: Guinea pigs
Strain: Hartley albino
Source: Ace Animals
Number of animals: 10
Sex: Male
Age: Not reported
Mean body weight: Not reported
Identification: Cage notation
Housing: Individually
Acclimation: At least 1 week
Feed: Purina Guinea Pig Chow #5025 ad libitum
Water: Ad libitum
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported

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B. TEST PERFORMANCE

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1. Skin Preparation

(a) Induction site: The shoulders of the test animals were clipped to form a 4x6-cm area that was used for inductions A and B. The site was clipped 48 hours prior to induction and treated with a depilatory cream 24 hours prior to induction. For induction A, six sites were used; two received test material mixed with Freunds Complete Adjuvant (FCA), two received the test material only, and two received FCA only. One injection of each set was on the animal's left side, and the other injection was on the right side.

(b) Challenge site: The right flank was clipped to form a 5x5-cm area between the hip and the ribs. The area was clipped 72 hours prior to the challenge and depilated 48 hours prior to the challenge.

2. Induction Phase

(a) Route of administration: Intradermal injection followed by topical application

(b) Solutions used

Intradermally

Dose 1: 0.1 mL FCA (2 sites)
Dose 2: 0.1 mL test material (2 sites) (=4% sodium omadine in dH_2O)
Dose 3: 0.05 mL test material mixed with 0.05 FCA (two sites) (=2% sodium omadine solution)

Topically: An "irritating dose" (4% sodium omadine solution) (with the addition of 10% sodium lauryl sulphate in petrolatum if the material is not irritating) was added to a 2x4-cm piece of filter paper and applied to the skin.

(c) Frequency of exposure: Once for induction A and once for induction B 7 days later.

(d) Duration of exposure: Induction A was given as an intradermal injection, and the exposure period for induction B was 48 hours.

(e) Observation period: X 24-24.5 hrs X 48 hrs ___ 72 hrs

(f) Rest period, prior to challenge phase: 2 weeks

3. Challenge Phase

(a) Route of administration: Topical

(b) Solutions used: 2% sodium omadine solution.

(c) Exposure duration and frequency: 1 time for a 24-hour period.

(d) Observation period: __X__ 24.5 hrs __X__ 48 hrs _____ 72 hrs

4. Scoring System

Application sites were examined and scored 24 and 48 hours after the challenge dose for erythema and edema.

The following system was used to score the severity of reactions:

0 = No reaction
1 = Scattered mild redness
2 = Moderate or diffuse redness
3 = Intense redness and swelling

The performing laboratory graded the sensitization reaction by the following criteria:

Percentage of animals reacting	Grade	Classification
0-8	I	Weak
9-28	II	Mild
29-64	III	Moderate
65-80	IV	Strong
81-100	V	Extreme

C. REPORTED RESULTS

1. Body Weights

No body weight data were reported.

2. Skin Reactions

(a) Range-finding phase: No data were reported for the range-finding assay.

(b) Induction phase

Induction A: Dermal reactions to the induction procedure are presented in Table 1. Intradermal injection of dose A (not defined) produced grade-2 reactions at all test sites at 24 hours post-exposure and grade-1 or grade-2 reactions 48 hours postexposure, with the exception of one test site that was scored as grade 3. Flaking skin was observed in 3-5 animals at 48 hours, and brown discoloration was observed in 1-3 animals during the 24- and 48-hour observation periods. At 24 hours postexposure, all dose B (not defined) treated areas were scored as grade 2. Brown and/or green discoloration was also noted at all test sites. Forty-eight hours postexposure, bilateral sites on 7 animals were scored as grade-4 reactions; 2 other animals had grade 4 reactions on only one side. The remaining test sites on these animals were scored as grade 2 (moderate or diffuse redness). Induction with dose C (not defined) resulted in one

Table 1. Summary of the Incidence and Severity of Dermal Sensitization Reactions to Sodium Omadine[a]

Test Substance	Observation Period (hours)	Body Side[b]	Number of Animals for Each Grade of Reaction				
			0	1	2	3	4
Induction with Sodium omadine							
Induction A[c]							
Solution A	24	R	0	0	10	0	0
		L	0	0	10	0	0
	48	R	0	4	6	0	0
		L	0	6	3	1	0
Solution B	24	R	0	0	10	0	0
		L	0	0	10	0	0
	48	R	0	0	2	0	8
		L	0	0	2	0	8
Solution C	24	R	0	0	9	1	0
		L	0	0	9	0	1
	48	R	0	1	6	0	3
		L	0	2	6	0	2
Induction B[d]							
Sodium omadine	48	R	0	1	6	3	0
Challenge							
0.1 mL Sodium omadine	24.5	R	8	2	0	0	0
2% solution	48	R	7	3	0	0	0

[a]The data were extracted from the study report, p. 8.
[b]R = right body side; L = left body side
[c]Induction A was a compound intradermal set of doses consisting of three dosing solutions designated as A, B, and C one of which was a 4% solution of sodium omadine, another was Freunds Complete Adjuvant (FCA) and the thi was a 2% sodium omadine solution in 50% FCA.
[d]Induction B was a topical application of an "irritating dose" (4% solution) of sodium omadine.

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each of a grade-3 and grade-4 reaction at 24 hours. At 48 hours, 5 sites on either side were scored as grade 4, and 3 sites were scored as grade 1. All other sites were scored as grade 2. Four to five test sites on each side were brown and/or green, and 2-3 sites were pale 24 hours postexposure. At 48 hours, 6-8 sites were discolored (brown, green, and/or pale). Two animals were observed with flaking skin at the second observation period.

Induction B: Topical application of a 2x4-cm patch occluded for 48 hours resulted in 1/10 grade-1 reactions, 6/10 grade-2 reactions, and 3/10 grade-3 reactions. Three animals were observed with pale skin.

Challenge phase: At 24 hours, 2 animals were observed with grade-1 erythema, and at 48 hours, 3 animals were observed with grade-1 erythema; the remaining sites were negative.

Because the incidence and severity of the responses in the challenge test group were less than observed during the induction phase, the study author concluded that the test material was negative for inducing dermal sensitization.

D. REVIEWERS' COMMENTS: The reviewers agree with the study author's conclusion that sodium omadine did not induce dermal sensitization when tested in the guinea pig maximization test. One reporting deficiency was noted in the study: the test solutions used in induction A are represented as A, B and C in the dermal results section (p. 8 of the study report) but are not further identified, and in the text the solutions are described in two different orders. This did not alter the final interpretation of the study because the response of the challenge reaction was less than the response of any of the test solutions in the induction phase. It was also noted that the data from the range-finding assay were not reported. However, based on the dermal reactions in the induction phase, irritating doses were evaluated.

. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement was signed and dated April 29, 1987.)

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-6; Dermal Sensitization in Humans

CHEMICAL: Sodium omadine (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 403874-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Product Investigations, Inc., Conshohocken, PA

TITLE OF REPORT: Evaluation of the Skin Irritating and Sensitizing Propensities of Sodium OMADINE® Antimicrobial Agent, Sample #H51196A in Humans

AUTHOR: M.V. Shelanski

STUDY NUMBER: PI-4750

STUDY COMPLETED: August 18, 1987

EXECUTIVE SUMMARY: Reported to be negative for inducing dermal sensitization in human volunteers challenged with sodium omadine after exposure to the test material for 4 days/week for 3 weeks and given a 1-week hiatus prior to challenge.

CORE CLASSIFICATION: **Unacceptable.** The test article purity was not reported. This study does not satisfy guideline data requirements (81-6) for a dermal sensitization study for the formulation tested, and is not acceptable for regulatory purposes; however, the study can be upgraded if the purity of the test material is provided.

TOXICITY CATEGORY: Not applicable.

Comments: In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable." This study can be upgraded provided several reporting deficiencies are addressed regarding the test article. The DER lacked an executive summary, so the preceding summary was generated.

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FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Dermal Sensitization in Humans

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 398
Project Officer: Caroline Gordon

GUIDELINE SERIES 81-6: Dermal sensitization

EPA Section Head and Reviewer: Marion Copley, DVM Signature: Marion Copley
Review Section IV, Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-6; dermal sensitization in humans

CHEMICAL: Sodium omadine

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 403874-01

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Product Investigations, Inc., Conshohocken, PA

TITLE OF REPORT: Evaluation of the Skin Irritating and Sensitizing Propensities of Sodium OMADINE® Antimicrobial Agent, Sample #H51196A in Humans

AUTHOR: M.V. Shelanski

STUDY NUMBER: PI- 4750

REPORT ISSUED: August 18, 1987

CONCLUSIONS: Reported to be negative for inducing dermal sensitization in human volunteers challenged with sodium omadine after exposure to the test material for 4 days/week for 3 weeks and given a 1-week hiatus prior to challenge.

CORE CLASSIFICATION: Supplementary. This study does not satisfies guideline data requirements (81-6) for a dermal sensitization study for the formulation tested and is not acceptable for regulatory purposes; however, the study can be upgraded if the purity of the test material is provided.

TOXICITY CATEGORY: Not applicable.

A. MATERIALS

1. Test Compound

Test material: Sodium omadine antimicrobial agent
Identification number: #H51196A
Active ingredient: Sodium omadine
Formulation: Not reported
Purity: Not reported
Physical description: Brown liquid
Storage condition: Not reported
Stability: Stable
Received: June 3, 1987

2. Dose levels

As supplied; 0.2 mL

3. Test Animals

Species: Humans
Source: Not applicable
Number of subjects: 55 (4 subjects did not complete the study)
Sex: 11 males and 44 females
Age: 36-78 years old (males); 21-80 years old (females)
Mean body weight: Not reported
No. volunteers/dose: 55
Exclusion criteria: Illness, history of skin disease, consumption of medication that would interfere with results, or visible skin pathology
Environmental conditions: Volunteers visited the clinic daily

B. TEST PERFORMANCE

1. Skin Preparation: No steps were required to prepare the skin for application of the test material.

2. Test Site: The test material was applied to a 2x2-cm webril pad and placed on the subject's skin (sites were located on the subjects back). Each pad was secured in place with an impermeable adhesive patch.

3. Induction Phase:

(a) Route of administration: Topical

(b) Solutions used:

Test material: 0.2 mL of sodium omadine antimicrobial agent

(c) Frequency of exposure: 4 times weekly (on consecutive days) for 3 weeks

(d) Duration of exposure: 24 hours per exposure

(e) Observation period: 24 hours after every test material application.

(e) Rest period, prior to challenge phase: ≈1 week (twelve subjects received 1-3 addititional doses during the rest period to make up for missed doses during the induction phase.)

(f) Positive control: A positive control was not used.

4. Challenge Phase:

(a) Route of administration: Topical (at naive sites)

(b) Solutions used:

Test material: 0.2 mL sodium omadine antimicrobial agent

(c) Exposure duration and frequency: Once every 24 hours for 4 days

(d) Observation period: __X__ 24 hrs after each application

5. Scoring System: See Appendix A

C. REPORTED RESULTS:

1. Body Weights: Not reported

2. Skin Reactions: The dermal reactions for the test subjects during the induction and challenge phases of the study are presented in Table 1.

(a) Induction phase: Intense erythema with induration or edema lasting <72 hours was observed in 1 volunteer during week 1 and in 3 volunteers during week 2. Intense erythema was observed in 1 volunteer for 1 day during week 3 and moderate erythema was observed 1 volunteer each during week 2 and 3. Faint erythema was observed in 1 volunteer during week 1, in 5 volunteers during week 2, and in 5 volunteers during week 3. On any given test day, 46-55 volunteers had no observable reactions to the test material.

(b) Challenge phase: During the week of the challenge phase, 4 volunteers were observed with faint erythema. On any given challenge day 43-51 volunteers had no observable reactions.

Based on these results the study author concluded that test material in this assay was a weak cumulative dermal irritant but was not a dermal sensitizer.

D. REVIEWERS' COMMENTS: Although the reviewers are in agreement with the study author's reported findings that the test material was not antigenic under the conditions of this assay, the study was compromised because the purity of the test material was not provided. The study can be upgraded if the appropriate information is provided and meets guideline requirements.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes (A quality assurance statement was signed and dated June 3, 1992.)

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Table 1. Summary of the Incidence and Severity of Dermal Sensitization Reactions in Humans to Sodium Omadine

	Observation Period (Hours)	Number of Subjects for Each Reaction Grade[a] 0	1	2	3	4	Total Number of Volunteers[b]
Induction with Sodium Omadine							
Exposure week 1	24	55-54	1	0	0	1	54-55
Exposure week 2	24	53-53	5	1	0	3	54
Exposure week 3	24	52-46	7	1	1	0	49-54
Challenge with Sodium Omadine							
	24	51-43	4	0	0	0	45-51

[a]Skin reaction grades based on the reporting laboratory's scale for irritation (0= no reaction, 1= faint erythema, 2= moderate erythema, 3= intense erythema, and 4 = redness with induration/edema, papule formation or coalescence of discrete elevated areas)

[b]The number of volunteers varied because of absenteeism.

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Appendix A

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Criteria for Grading of Responses: The PI Grading System consisting of a numerical scale of 0 to 7 was used to grade the intensities of the adverse changes, if any, occasioned by the test material's contact with the skin. Though numbers are used to denote the intensity of responses, direction only and not linearity is intended, e.g. Grade 2 denotes a more intense response than Grade 1, but not one that is twice as intense. This must be borne in mind if the grades are used to calculate indices for comparison. A system advocated by the International Contact Dermatitis Research Group (3) for the grading of responses for diagnostic patch test procedures is listed below for comparison.

Response	Visible Change	Grade	
		PI System	ICDRG System
Absent	None	0	-
Inflammation (Stage I)	Redness (Erythema)		
	Very Faint (non-uniform response)	H	+ or IR*
	Faint	1	+
	Moderate	2	+
	Intense	3	+
Inflammation (Stage II)	Redness plus general elevation (induration or edema) on contact site and/or papule formation or coalescence of discrete, elevated areas.	4	+ or IR*
Inflammation (Stage III)	Redness, induration plus vesicle or blister formation.	5	++ or IR*
Inflammation (Stage IV)	Redness, induration, vesicles weeping (serous exudate), and/or extension of response beyond margins of contact site.	6	+++ or IR*
Corrosion	Destruction, necrosis, and/or sloughing of skin.	7	

H = 1/2

IR* = Irritant reactions of different types.

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Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/23/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 82-1, 82-7; Subchronic Oral Toxicity and Neurotoxicity in the Rat

CHEMICAL: Sodium omadine (41.2% purity)

TOX CHEM. NUMBER: 790A

011532

PC CODE: 088004

MRID NUMBER: 407569-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 90 Day Oral (Gavage) Toxicity Study in the Rat (Neurotoxicity)

AUTHOR: Husband, R.F.A., Wood, C.M., and Shirley, E.

STUDY NUMBER: OLA/2/88

STUDY COMPLETED: July 1, 1988

EXECUTIVE SUMMARY (revised): In a subchronic toxicity/neurotoxicity study, sodium omadine (41.2% purity) was administered by oral gavage to groups of 20 male and 20 female Sprague-Dawley rats for 13 weeks at doses of 0, 0.5, 2.0, or 8.0 mg/kg/day. In-cage clinical observations for signs of neurotoxicity were made once before dosing, at 1 and 6 hours after dosing, and daily before dose administration throughout the study. Prior to initiation and during weeks 5 and 13, all animals were given functional tests for potential neurotoxicity (hindlimb grip strength, hindlimb tactile placing response, and landing hindfoot spread test).

At 2.0 mg/kg/day, slight atrophy of the hindlimb skeletal muscle was observed in 5/20 males and 5/20 females, and minimal atrophy was seen in one female. Atrophy of the panniculus muscle was observed in 3/20 females receiving 2.0 mg/kg/day; the atrophy was considered a neurotoxic effect (neurogenic atrophy).

Both males and females dosed at 0, 0.5, and 2.0 mg/kg/day had similar body weights throughout the study. The 8.0 mg/kg/day groups consistently gained less weight than the

other groups, and weighed as much as 21% and 22% less than controls for males and females, respectively. Significant decreases in weight gains were seen for males (30%) and females (47%). The body weight and clinical signs data suggest a steep dose response.

In the high-dose groups, minimum to marked hindlimb atrophy was observed in 95-100% of the males and females (more severe in females), minimal paravertebral muscle atrophy was seen in 2/20 males and 17/20 females, and atrophy of the subcutaneous panniculus muscle was seen in 20/20 males and 17/20 females. Treatment-related neurotoxic signs observed in the high-dose animals consisted of slight hypoactivity, piloerection, ataxia (hindlimb), slight head searching, emaciation, hindlimb paralysis, and hunched posture. As a consequence of severe hindlimb motor dysfunction, 10 high-dose females were sacrificed *in extremis*. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response.

The study LOEL is 2.0 mg/kg/day based on evidence of neurotoxicity in males and females (neurogenic skeletal muscle atrophy) and the NOEL is 0.5 mg/kg/day.

CORE CLASSIFICATION: The study is **Core Guideline** for subchronic toxicity, and satisfies guideline requirements 82-1.

The study is Core **Supplementary** for neurotoxicity, and does not satisfy guideline requirement 82-7 (1991) because cage observations were limited, many of the usual FOB parameters were not performed, grip strength measurements and motor activity were not quantified, guideline procedures for preparation of neural tissues (including perfusion) were not followed, and the histological examination of neural tissues was inadequate.

William Sette (HED neurotoxicologist) requested that another subchronic neurotoxicity study be performed. He also requested an acute neurotoxicity study with a primary focus on histopathologic lesions that might be induced by a single exposure.

Comments: The DER reported significant decreases in body weight gain, but did not discuss body weight.

other groups, and weighed as much as 21% and 22% less than controls for males and females, respectively. Significant decreases in weight gains were seen for males (30%) and females (47%). The body weight and clinical signs data suggest a steep dose response.

In the high-dose groups, minimum to marked hindlimb atrophy was observed in 95-100% of the males and females (more severe in females), minimal paravertebral muscle atrophy was seen in 2/20 males and 17/20 females, and atrophy of the subcutaneous panniculus muscle was seen in 20/20 males and 17/20 females. Treatment-related neurotoxic signs observed in the high-dose animals consisted of slight hypoactivity, piloerection, ataxia (hindlimb), slight head searching, emaciation, hindlimb paralysis, and hunched posture. As a consequence of severe hindlimb motor dysfunction, 10 high-dose females were sacrificed *in extremis*. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response.

The study LOEL is 2.0 mg/kg/day based on evidence of neurotoxicity in males and females (neurogenic muscle atrophy) and the NOEL is 0.5 mg/kg/day.

CORE CLASSIFICATION: The study is **Core Guideline** for subchronic toxicity, and satisfies guideline requirements 82-1.

The study is Core **Supplementary** for neurotoxicity, and does not satisfy guideline requirement 82-7 (1991) because many of the usual FOB parameters were not performed, grip strength measurements and motor activity were not quantified, guideline procedures for preparation of neural tissues were not followed, and the histological examination of neural tissues was inadequate. In addition, a method validation study for FOB parameters should be submitted. The need for a new 90-day neurotoxicity study will be determined by HED following review of the toxicology database on sodium omadine.

Comments: The DER reported significant decreases in body weight gain, but did not discuss body weight.

Although several FOB parameters were omitted, it is doubtful that a repeat study would reveal significantly more information about the neurotoxicity of sodium omadine. Frank, dose-related neurotoxicity was observed along with a clear sex-related difference in sensitivity.

FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Type: Subchronic Oral Toxicity in the Rat (Neurotoxicity)

Study Title: 90 Day Oral (Gavage) Toxicity Study in the Rat

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: [signature] for John Liccione, Ph.D. Date 5/5/94

Independent Reviewer: [signature] William McLellan, Ph.D. Date 5/5/94

QA/QC Manager: [signature] Carol Maczka, Ph.D. Date 5/5/94

[signature] 5/6/94

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 411
Project Officer: Caroline Gordon

SODIUM OMADINE

GUIDELINE SERIES 82-1: Subchronic Oral Toxicity in the Rat
82-7: Subchronic Neurotoxicity in Rat

EPA Reviewer: Linnea Hansen, Ph.D.
Review Section IV, Toxicology Branch I
Health Effects Division (H-7509C)

Signature: Linnea Hansen
Date: 5/26/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division (H-7509C)

Signature: Marion Copley
Date: 5/31/94

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral Toxicity in the Rat (Neurotoxicity) (82-1, 82-7)

MRID NUMBER: 407569-01

TOX. CHEMICAL NO.: 790A

PC CODE: 088004

TEST MATERIAL: Sodium omadine

SYNONYM: Sodium pyrithione; sodium-2-pyridinethiol-1-oxide

STUDY NUMBER: OLA/2/88

SPONSOR: Olin Corporation
New Haven, Connecticut

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 90 Day Oral (Gavage) Toxicity Study in the Rat (Neurotoxicity)

AUTHOR(S): Husband, R.F.A., Wood, C.M., and Shirley, E.

REPORT ISSUED: July 1, 1988

EXECUTIVE SUMMARY: In a subchronic toxicity/neurotoxicity study, sodium omadine was administered by oral gavage to groups of 20 male and 20 female Sprague-Dawley rats for 13 weeks at doses of 0, 0.5, 2.0, or 8.0 mg/kg/day. In-cage clinical observations for signs of neurotoxicity were made once befor dosing, at 1 and 6 hours after dosing, and daily before dose administration throughout the study. Prior to initiation and during weeks 5 and 13, all animals were given functional tests for potential neurotoxicity (hindlimb gri strength, hindlimb tactile placing response, and landing hind-foot spread test).

At 2.0 mg/kg/day, slight atrophy of the hindlimb skeletal muscle was observed in 5/20 males and 5/20 females and minimal atrophy was seen in one female. Atrophy of the panniculus muscle was observed in 3/20 females receiving 2.0 mg/kg/day; the atrophy was considered a neurotoxic effect (neurogenic atrophy).

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In addition, at 8.0 mg/kg/day, significant decreases in weight gains were seen for males (30%) and females (47%). Minimum to marked hindlimb atrophy was observed in 95-100% of males and females (more severe in females), minimal paravertebral muscle atrophy was seen in 2/20 males and 17/20 females, and atrophy of the subcutaneous panniculus muscle was seen in 20/20 males and 17/20 females. Treatment-related neurotoxic signs observed in the high-dose animals consisted of slight hypoactivity, piloerection, ataxia (hindlimb), sight head searching, emaciation, hindlimb paralysis, and hunched posture. As a consequence of severe hindlimb motor dysfunction, 10 high-dose females were sacrificed in extremis. Effects on neuromuscular function included significant decreases in landing foot spread, hindlimb grip strength, and hindlimb tactile placing response. **The study LOEL is 2.0 mg/kg/day based on evidence of neurotoxicity in males and females (neurogenic muscle atrophy) and the NOEL is 0.5 mg/kg/day.**

CORE CLASSIFICATION: The study is core guideline for subchronic toxicity and satisfies guideline requirements 82-1.

The study is core supplementary for neurotoxicity and does not satisfy guideline requirement 82-7 (1991) because many of the usual FOB parameters were not performed, grip strength measurements and motor activity were not quantitated, guideline procedures for preparation of neural tissues were not followed, and the histological examination of neural tissues was inadequate. In addition, a method validation study for FOB parameters should be submitted. The need for a new 90-day neurotoxicity study will be determined by HED following review of the toxicology database on sodium omadine.

Special Review Criteria (40 CFR 154.7): None

A. MATERIALS:

1. Test Material: Sodium omadine

   Chemical formula: Not reported

   Description: 41.2% aqueous solution of sodium pyrithione as pale amber liquid

   Batch number: 8508-P-166H

   Stability: Stable for at least 1 week

   Storage: Dark at room temperature

2. Dosing Regimen

   Rats were dosed by oral gavage for 7 days per week for 13 weeks with aqueous solutions of sodium omadine with 0.5, 2.0, or 8.0 mg/kg/day at a dose volume of 10 mL/kg. Vehicle controls received distilled water. Individual doses were adjusted daily based on body weight. Dosing solutions were prepared weekly by dilution of the stock (41.2% solution) material.

3. Test Material Analyses for Purity and Stability

The study authors indicated that the aqueous solution of sodium omadine consisted of 41.2% sodium pyrithione based on a letter from the sponsor; the letter (with details of the assay used to quantitate the test material in the solutions) was not provided in the report. The test material was reported by the Sponsor to be stable in solutions prepared fresh each day. Dosing solutions were analyzed weekly for 12 weeks of the study; overall mean concentrations were within 10% of target for each dose level. The range of concentrations of the 0.5-, 2.0-, and 8.0-mg/kg/day dosing solutions were 98.2-115.7%, 85.7-113.6%, and 80.2-120.1% of nominal values, respectively. The analytical method utilized to measure the sodium omadine in the solutions was not specified.

4. Animals

Species: Rat
Strain: Crl:CD(SD)BR(VAF plus)
Age and weight at initiation: Age not reported; males -- 110-156 g; females -- 105-147 g
Source: Charles River Limited, Margate, England
Housing: Individual
Environmental conditions: Temperature: 19-26°C
Humidity: 33-88%
Photoperiod: 12-hour light/dark cycle (extremes occurred only occasionally)

B. Study Design:

1. Animal assignmnet

Following a 12-day acclimatization period, animals were randomly assigned to the following test group using a randomization procedure that stratified the animals by body weight:

Group	Dose Level (mg/kg/day)	Number of Animals (13 Weeks)	
		Males	Females
Control	0	20	20
Low dose	0.5	20	20
Mid dose	2.0	20	20
High dose	8.0	20	20

Dose selection: Rationale not provided

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2. Diet

SQC Rat and Mouse Maintenance Diet No. 1, Expanded, Special Diet and tap water ad libitum.

3. Statistics

Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used in the statistical analysis of all parameters. When necessary, transformation of data was performed prior to analysis. Ranks of data were analyzed by Bennett's method; intergroup differences were examined with a chi-square test. Significant differences between treatment and control groups were determined by Student's t-test. Statistical tests for trend with dose were performed. For parametric data, William's test was used: Shirley's test was used for rank data. Statistical significance was at <0.05 or better.

4. Quality Assurance

A signed Good Laboratory Practice Compliance Statement and a signed Quality Assurance Statement were provided in the study report. A signed flagging statement was not included.

C. METHODS AND RESULTS

1. General Observations

Animals were observed each day for clinical signs of toxicity and mortality.

Observations to evaluate neurotoxicity were made on all animals once before the start of treatment, again about 1 and 6 hours after the first dose and daily before dose administration throughout the study. The following home cage observations were made:

Posture	Staining of eyes, nose, and mouth
Tremors	Piloerection
Convulsions	Salivation
Bizarre behavior	Vocalization
Fecal composition Gait	Circling
Respiration	Compulsive licking
Pupil size	Head searching
Lachrymation	Head flicking

Results: Ten high-dose females were sacrificed in extremis because of severe debilitation resulting from severe hindlimb ataxia or total paralysis of the hindlimbs during weeks 4-14; seven were sacrificed by week 9.

Compound-related clinical signs were limited to the high-dose males and females, with signs being more severe in the females. Slight hypoactivity and/or piloerection were observed in 10 of 20 high-dose males and 10 of 20 high-dose females at day 1 (2.5-6 hours postdosing). In addition, slight ataxia (hindlimb) was observed in one high-dose male and one high-dose female at day 1. Also, two high-dose males exhibited very slight to slight head searching at day 1, while another male showed whole body tremors. From day 2 (females) or day 76 (males) on, 5 of 20 high-dose males and 9 of 20 high-dose females also developed slight hypoactivity and/or piloerection. Emaciation (8 of 20 males from day 54 on; 17 of 20 females from day 16 on), hunched posture (8 of 20 males from day 53 on; 14 of 20 females from day 26 on), and abdominal distention (6 of 20 males from day 51 on; 5 of 20 females from day 46 on) were observed in the high-dose animals of both sexes. In addition, mild ataxia was seen in 3 of 20 high-dose males from day 75 on. Ataxia progressing to severe restriction of hindlimb movement or total hindlimb paralysis was observed in 11 of 20 high-dose females from day 21 on.

2. Functional Tests

The following functional tests for assessing potential neurotoxicity were performed on all animals prior to the initiation of the study and during weeks 5 and 13. Testing was performed before daily dose administration.

(a) Hindlimb grip strength. Hindlimb grip strength was assessed using a grid cage lid; each rat was place don the lid and then pulled away by lifting the thorax and removing the animal vertically. A subjective rating scale was used to evaluate grip strength responses. For each animal, a rating of -2 (no response), -1 (weak response), +1 (strong response), or +2 (exaggerated response) was scored. Behavioral response in the treated animals were compared to those of controls at respective intervals.

(b) Hindlimb tactile placing response. This test was performed by positioning the animal towards the top edge of a cage at an angle of approximately 30° from the horizontal plane. As the abdomen contacts the surface, the animal responds by raising hindlimbs to assert its grip. A subjective rating scale was used to evaluate tactile placing responses. For each animal, a rating of -2 (no response), -1 (weak response), +1 (strong response), or +2 (exaggerated response) was scored. Behavioral responses in the treated animals were compared to those of controls at respective intervals.

(c) Landing hindfoot spread test. Muscle tone was assessed by using the Edwin-Parker Motor Function Test. Briefly, the animal was maintained in a horizontal position with dorsal side uppermost and with the nose 32 cm above a bench. The hindfeet were marked with ink; the animal was then dropped onto paper,

and the position of the fourth digit of each hindlimb on landing was marked. The distance between the two marks was recorded. This procedure was repeated three times and the mean of four measurements was calculated for each animal.

The usual complete FOB examination recommended in the 1991 Neurotoxicity Test Guidelines was not conducted. The following measurements or observations were not made

Manipulative observations (none)
Physiological measures
  Temperature
  Body tone
Open field observance
Response observations
  Auditory response
  Approach response
  Righting reflex
  Pupil response
  Touch response
  Pain response
Neuromuscular tests
  Forelimb grip strength

Motor activity testing was not conducted in this study.

Results

(a) Foot Spread. Table 1 presents the results of the landing foot spread test with means adjusted for baseline values. Compared to controls, the high dose of sodium omadine (8.0 mg/kg/day) decreased mean foot spread (adjusted for baseline value) in both sexes at week 5 ($p<0.05$) and week 13 ($p<0.001$). In the high-dose males, the decreases were 12.3% and 34.4% at weeks 5 and 13, respectively; for the females, the decreases were 17.0% and 23% at weeks 5 and 13, respectively. The test for trend indicated statistical significance at week 5 for females and at week 13 for males and females.

(b) Hindlimb grip strength. Data on hindlimb grip strength were statistically evaluated as rank order data following adjustment for baseline values; rank order data are summarized in Table 2. Results showed that the high dose of sodium omadine (8.0 mg/kg/day) significantly ($p<0.01$ by the chi-square test, z-test, and William's test) decreased grip strength in males at week 13 when compared to that of the controls at week 13. The mean hindlimb grip strength scores for the control and high-dose males at week 13 were -1.4 and -1.95, respectively. There were no significant effects on hindlimb grip strength in the high-dose males at week 5, or in the high-dose females at any time interval. There were no significant effects in the low- or mid-dose animals of either sex.

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TABLE 1. Adjusted Mean Hind Foot Spread (mm) for Rats Fed Sodium Omadine for 90 Days[a,b]

Week	Dose Groups (mg/kg/day)			
	0	0.5	2.0	8.0
		Males		
5	99.3 (20)	100.9 (20)	102.6 (20)	87.1* (20)
13	103.8 (20)	9.12* (20)	99.4 (20)	68.1***,## (20)
		Females		
5	77.6 (20)	80.3 (20)	77.2 (20)	64.5*,# (20)
13	88.5 (20)	80.4 (20)	82.1 (20)	68.3***,## (11)

[a]Data extracted from Study No. OLA/2/88, Tables 7, 8, and 9 and Appendices 15-17 and 25. The values in parenthesis are the number of animals tested.
[b]Mean foot spread values adjusted for pre-treatment values.

#Significantly different from control ($p<0.05$) by William's test for trend.
##Significantly different from control ($p<0.01$) by William's test for trend.
*Significantly different from control ($p<0.05$).
**Significantly different from control ($p<0.01$).
***Significantly different from control ($p<0.001$).

TABLE 2. Ranks of Observation of Hindlimb Grip Strength and Tactile Placing Response in Rats Fed Sodium Omadine for 90 Days[a]

Dose mg/kg/day	Hindlimb Grip		Tactile Placing Response	
	Males	Females	Males	Females
0	47.5	36.46	49.6	36.8
0.5	42.7	36.36	44.2	36.3
2.0	38.8	34.38	41.3	37.3
2.8	33.0**	37.41	27.0**	31.5

[a]Data from Appendix 25, pp. 298-299. Based on 20 males in all groups and 20 females in the control, 0.5 and 2.0 mg/kg/day groups and 11 females in the 2.8 mg/kg/day group. No explanation of the derivation of these numbers from the scores (-2, -1, +1, +2) was provided.

**Statistically significant with the William's test for trend.

(c) Hindlimb tactile placing response. Data on tactile placing response were also statistically evaluated as rank order data and adjusted for baseline values. Results revealed that tactile placing response was significantly decreased in the high-dose males at weeks 5 ($p<0.05$) by chi-square test and William's test) and 13 ($p<0.001$) by the z-test) when compared to that of controls at the respective interval. The mean hindlimb tactile placing response scores for the control and high-dose males at week 5 were -1.4 and -1.75, respectively. The mean hindlimb tactile placing response scores for the control and high-dose males at week 13 were -0.8 and -1.9, respectively. Although tactile placing response in the mid-dose males was slightly less than that of controls at week 5 ($p<0.05$ by the z-test and William's test), this effect was not observed at week 13.

3. Body Weight

Individual body weight data were recorded on the first day of dosing and weekly thereafter.

Results - Statistical analyses were provided for data on body weight gain (adjusted for initial body weight) over the 13-week study period; results are summarized in Table 3. Overall mean body weight gains were significantly ($p<0.001$) lower than those of controls in high-dose males (30%) and females (49%). The decrease in mean body weight gains was compound related. Mean body weight gains in the low-and mid-dose animals were comparable to those of controls throughout the treatment period.

4. Food consumption: Mean food consumption data per cage were recorded weekly.

Results - Decreases (approximately 4–16% in males and 4–23% in females) in mean food consumption (g/rat/week) as compared to controls were noted in the high-dose males and females from weeks 3 through 13 (data not presented). Mean total food consumption (g/rat) in the high-dose animals for weeks 1–13 (results summarized in Table 4) was lower (9% in males; 10% in females) than that of controls. No statistical analysis of the data was provided.

5. Ophthalmologic Examinations

Ophthalmoscopic examinations were performed on all rats prior to treatment and on control and high-dose animals at week 13. Eyes were examined using both direct and indirect ophthalmoscopes. Prior to examination, the pupils of each animal were dilated with a mydriatic agent.

Results - No treatment-related ophthalmologic effects were found.

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TABLE 3. Mean Body Weight Gain (g ± SD) for Rats fed Sodium Omadine for 90 Days[a,b]

Week	Dose Groups (mg/kg/day)			
	0	0.5	2.0	8.0
		Males		
0-13	296.2±35.3 (294.0)[c]	305.6±32.8 (306.6)	301.7±30.9 (301.2)	207.8±47.1*,# (207.4) ↓ 30%
		Females		
0-13	121.6±23.6 (120.9)	118.4±19.9 (119.8)	117.4±23.6 (118.9)	68.5±23.7*,# (61.0) ↓ 49%

[a]Data extracted from Study No. OLA/2/88, Appendices 2 and 25.
[b]Mean body weight gains (± SD) for weeks 0-13 were calculated by the reviewers from individual animal data.
[c]Mean body weight gains for weeks 0-13 adjusted for initial body weights.

*Significantly different from control ($p<0.001$) using the t-test.
#Significantly different from control ($p<0.01$) by William's test for trend.

TABLE 4. Mean Total Food Consumption (g) for Rats Fed Sodium Omadine for 90 Days[a]

	Dose Groups (mg/kg/day)			
Week Interval	0	0.5	2.0	8.0
		Males		
1-13	2373	2383	2356	2171
		Females		
1-13	1676	1689	1687	1503

[a]Data extracted from Table 2, page 33, Volume 1, Subchronic Toxicity Study with Sodium Omadine.

6. Clinical Pathology

Hematological and clinical chemistry analyses were performed on 10 rat/sex/group prior to treatment, and at weeks 5 and 13. Blood was collected from the retro-orbital sinus. All animals were fasted prior to analyses. The parameters checked (X) below were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocyte count (RETIC)
Red cell morphology
X Leukocyte differential count
Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
X Coagulation: activated partial thromboplastin time (APTT)
X Prothrombin time

* Recommended by Subdivision F (November 1984) Guidelines

Results - There were no changes of toxicological significance in hematology parameters. Slight decreases in hemoglobin content (4.5-6.7% at the mid dose; 6.7-10.4% at the high dose), red blood cell count (4.7-6.8% at the mid dose; 7.0-8.8% at the high dose), and PCB (3.0-6.9% at the mid dose; 6.7-7.9% at the high dose) were noted in the mid- and/or high-dose animals of both sexes at week 13; however, the values were within the normal range.

(b) Clinical chemistry

Electrolytes

X Calcium*
X Chloride*
X Magnesium
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
X Creatinine phosphokinase
X Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)
Glutamate dehydrogenase

Other

X Albumin*
Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
Globulins
X Glucose*
X Total bilirubin*
X Direct bilirubin
X Total protein*
X Protein electrophoresis
Phospholipid
Triglycerides

* Recommended by Subdivision F (November 1984) Guidelines

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Results - There were no clinical chemistry changes of toxicological importance.

(c) Urinalysis

Urinalysis was performed on 10 rats/sex/group prior to treatment and at weeks 5 and 13. The parameters checked (X) below were examined.

X Appearance*	X Sediment (microscopic)	X Bilirubin*
X Volume*	X Protein*	X Blood
X Specific gravity*	X Glucose*	Nitrate
X pH*	X Ketones	Urobilinogen

* Recommended by Subdivision F (November 1984) Guidelines

Results - There were no compound-related effects on urinalysis parameters.

7. Sacrifice and Pathology

Following 13 weeks of treatment, all rats were sacrificed by carbon dioxide asphyxiation and necropsied. Brains were not perfused in situ at sacrifice to have proper fixation for histologic examination of neural tissues. Tissues indicated by a check (X) below were examined histologically in all control and high-dose animals, and in all animals that were sacrificed moribund during the study. In addition, gross lesions, lungs, kidneys, liver, skeletal muscle, thymus, skin, and testes were examined histologically in all dose groups. Also, paravertebral muscles (included in spinal cord sections) and the subcutaneous panniculus muscle were examined in control and high-dose animals. To evaluate potential neuropathological effects of sodium omadine, the following tissues from control and high-dose animals were processed, embedded in paraffin, and examined with special staining techniques: (1) brain and spinal cord (three sections) - luxol fast blue/cresyl fast violet, and (2) sciatic nerve (unilateral) - solochrome cyanine. Double-checked (XX) organs were weighed for rats sacrificed by design.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain*
X Salivary glands*	XX Heart	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen*	X Eyes (optic nerve)*
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	
X Colon*		Glandular
X Rectum*	XX Kidneys*	
XX Liver*	X Urinary bladder*	XX Adrenals*
Gallbladder*	XX Testes*	Lacrimal gland
X Pancreas*	X Epididymides	X Mammary gland*
	X Prostate	XX Thyroids*
Respiratory	X Seminal vesicle	XX Parathyroids*
	XX Ovaries	Harderian glands
X Trachea*	X Uterus*	
XX Lung*		
Larynx		

Other

X Bone (sternum and femur)*
X Skeletal muscle (hindlimb)*
X Skin (including panniculus muscle)*
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights

Absolute liver weights were similar in all groups of males; in females there was a significant decrease in the group receiving 8 mg/kg/day (88% of control; significant at 5% using the t-test but no trend). The liver weights adjusted for body weight (ANCOVA) were 23% higher than controls ($p<0.001$ Student t-test) in males receiving 8 mg/kg/day. However, in females, the liver weights adjusted for body weight were also significantly increased (12% higher than controls; $p<0.01$ with the Student's t-test and $p<0.01$ for trend with the Williams test). The effects on liver weights are considered secondary to the decreased weight gains at termination and are not a direct cause of compound administration. Furthermore, there were no histopathologic correlations to indicate the changes are of any toxicologic importance. No important changes in brain weight were observed in dosed rats.

(b) Gross pathology

Emaciation and wasting of the skeletal muscle (particularly hindlimb muscle) were observed in the high-dose females that

were sacrificed in extremis. Skeletal muscle wasting (primarily hindlimb muscles) was also noted in 16 of 20 high-dose males and 10 of 10 high-dose females sacrificed at termination of the study. This wasting may have reflected neurogenic atrophy.

(c) Microscopic pathology

Table 5 summarizes treatment-related histopathological findings. The most notable finding was bilateral atrophy of the upper hindlimb muscles in the high-dose males and females. Minimal, moderate, or marked bilateral atrophy of the upper hindlimb muscles was observed in 19 of 20 high-dose males and 20 of 20 high-dose females; the atrophy was reported to be more severe in the females. Also, minimal atrophy was noted in 1 of 20 mid-dose females, and slight atrophy was noted in 5 of 20 high-dose males and 5 of 20 high dose females. The atrophy was characterized by reduction in the diameter of muscle fibers, irregular staining of fibers, an increase in the number of sarcolemmal nuclei, and fatty replacement of muscle fibers. These changes are typical of diffuse atrophy.

Minimal atrophy of the paravertebral muscles (examined only in control and high-dose animals) was seen in 2 of 20 high-dose males and 17 of 20 high-dose females. Atrophy of the subcutaneous panniculus muscle was observed in 17 of 20 high dose males, 20 of 20 high-dose females, and 3 of 20 mid-dose females.

Histological examination of the brain, spinal cord, and sciatic nerve revealed no abnormalities.

Histologic examination of other tissues did not indicate any increase of incidence of findings that were of biological importance. Atrophy of the thymus was seen in 5/20 high-dose females but in no control or lower dose animals; this may be related to stress or general poor condition of the animals. Statistical analysis of histologic data were not conducted.

D. DISCUSSION

The design and conduct of the study were adequate for a subchronic toxicity study in rats (82-1a), but the study did not fulfill the requirements of the neurotoxicity study guidelines (83-7) proposed in 1991.

There were major problems with the neurotoxicity portion of the study. Although in cage clinical observations appear to have been relatively thorough for detecting signs of neurotoxicity, there were no open-field studies. Motor activity was not quantitated and the grip strength measurement used a subjective ranking rather than a quantitative measure No data were provided on general stimuli such as removal from the cage; arousal and startle, and auditory and visual stimuli and pain perception

TABLE 5. Selected Microscopic Lesions for Rats Fed Sodium Omadine for 90 Days[a,b]

Parameter	Dose Level (mg/kg/day)			
	0	0.5	2.0	8.0
Males				
Skeletal muscle (hind limb)	(20)	(20)	(20)	(20)
Atrophy - Slight	0	0	5	0
- Minimal	0	0	0	9
- Moderate	0	0	0	9
- Marked	0	0	0	1
Paravertebral muscles	(20)	(20)	(20)	(20)
Atrophy - Minimal	0	0	0	2
Females				
Skeletal muscle (hind limb)	(20)	(20)	(20)	(20)
Atrophy - Slight	1	0	5	0
- Minimal	0	0	1	4
- Moderate	0	0	0	8
- Marked	0	0	0	8
Paravertebral muscles	(20)	(20)	(20)	(20)
Atrophy - Minimal	0	0	0	17

[a]Data extracted from Table 12, page 49, Volume 1, Subchronic Toxicity Study with Sodium Omadine.
[b]Numbers in parentheses indicate number of animals examined.

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were not tested. Other parameters such as body temperature, rearing activity, righting ability and forelimb strength were not measured. However, the study was initiated in 1987 and it was reported that the guidelines in FR50 No. 18 (1985) Subpart G Neurotoxicity 790.60 50 were followed (e.i., FOB).

Histopathologic examination of neural tissues was not adequate since tissues were not fixed by in-situ perfusion or embedded in plastic. In addition, insufficient samples of tissues were taken from major brain regions to be assured of thorough examination. Six levels of sectioning are required to be assured of an adequate examination. Optic nerve, tibial and sural nerves should be examined in addition to the sciatic nerve.

The study did show that at 8.0 mg/kg/day, sodium omadine the animals displayed sedation in hindlimb grip strength and tactile placing response (males) and a decreased landing foot splay (males and females); in addition several clinical signs (in-cage) indicating a neurotoxic effect were observed as early as day 1 of dosing.

The most notable histopathologic effect in high-dose males and females was minimal to marked bilateral atrophy of hindlimb muscles. Slight atrophy was present in several males and females receiving 2.0 mg/kg/day and minimal atrophy in one female at 2.0 mg/kg/day. Minimal atrophy of the paravertebral muscles was observed in 2/20 males and 17/20 females receiving 8.0 mg/kg/day and atrophy of the panniculus muscle (skin) was seen in 17 males and 20 females at 8.0 mg/kg/day and 3/20 females at 2.0 mg/kg/day. Atrophy of these muscles is considered to be secondary to neurogenic atrophy and is considered a neurotoxic effect. Based on slight atrophy of the hindlimb skeletal muscle the study LEL is considered as 2.0 mg/kg/day and the NOEL is 0.5 mg/kg/day.

Note: In this study, it appears that the MTD was not reached because the only effect observed was an increase in epidermal hyperplasia at the high dose. A 28-day study was conducted in mice but not submitted. The reference to it is in the mouse study itself. I am inclined to ask for the study, but Roger thinks that it may be a waste of time. Therefore, I have started an argument that an increase in dose will decrease the absorption rate of the chemical because of the probability that the increased dose will increase epidermal hyperplasia, thus probably decreasing absorption. There is one major error in this DER. There were 2 dermal subchronic studies conducted with this chemical; a 28-day study in the mouse and a 90-day study in the rat. The 90-day study in the rat had low NOEL's and the effects were neurotoxicity effects. There is no mention anywhere of the effects for the 28-day mouse study. In the executive summary of the DER, the preliminary study that was mentioned as being the one from which the dose levels were selected is the mouse study, but the effects and dose levels mentioned were really for the rat study, not the mouse study. I have made the correction in the discussion section of my supplementary DER (see next page).

Reviewed By: Pamela Hurley, Toxicologist Pamela Hurley 7/12/94
Section I, Tox. Branch (7509C)
Secondary Reviewer: Roger L. Gardner, Section Head
Section I, Tox. Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Carcinogenicity Study - Mouse
(Supplementary DER)

SHAUGHNESSY NO./TOX. CHEM. NO.: 088004 / 790A

ACCESSION NO./MRID NO.: 421008-01

DP BARCODE/SUBMISSION NO.: D177620, D190969; S417070, S440249

TEST MATERIAL: Sodium omadine (41.2% aqueous solution)

SYNONYMS: Sodium pyrithione; sodium 2-pyridinethiol-1-oxide; RD 8702

STUDY NUMBER: OLA/7/90

SPONSOR: Olin Corporation, Stamford, CT 06904

TESTING FACILITY: Toxicol Laboratories Ltd., Ledbury, Herefordshire, England

TITLE OF REPORT: 80-Week Dermal Carcinogenicity Study in the Mouse

AUTHOR(S): R.F.A. Husband, A.J. Newman, P.N. Lee

REPORT ISSUED: 2/20/91

DISCUSSION: Sodium omadine was tested in an 80-week dermal carcinogenicity in mice at 0, 5, 15 or 40 mg/kg/day. The only effect observed was an increase in epidermal hyperplasia at the skin application site at 40 mg/kg/day. The original executive summary states that the highest dose was considered adequate to assess carcinogenicity based on a 13-week dermal study in mice where atrophy of the hind limb muscles was observed at 15 and 50 mg/kg/day in females and 50 mg/kg/day in males. This study was a **rat** study, not a mouse study. There was a 28-day dermal study conducted in mice, but the data were not available. Since there was no appreciable systemic toxicity, it appears that the mice in this study could have tolerated higher dose levels. However, a new study will not be required for the following reasons:

- It is not likely that repeating the study with a higher dose level will provide any additional data because the increase in dose will probably increase the epidermal hyperplasia. An increase in epidermal hyperplasia will likely decrease the amount of chemical being absorbed. In mice, a dermal

absorption study exists which was rejected in the 1984 Registration Standard. In this study, only about 10-18% of the administered radiolabelled dose was recovered; less than 1% in the urine and feces and 9-17% during washing after 72 hours. Either the majority of the compound was deposited throughout the body or retained on the skin in spite of the washing procedure. There were no data on whether or not the chemical was retained in the tissues. However, in an oral rat metabolism study, less than 0.8% of an administered dose was retained in the tissues after 4 days and 1.3 - 2.1% was retained in the carcass. There was no evidence of bioaccumulation. Therefore, it is likely that the chemical is not retained in the tissues in mice either. Although the dermal absorbtion study in mice was rejected because it did not provide enough information as to where the chemical was retained, it does give an indication that the absorption rate in mice is fairly low to begin with.

- The rat combined chronic gavage/carcinogenicity study showed no evidence of carcinogenicity. This study was conducted up to toxic levels. The rat study was conducted up to a dose level of 3.5 mg/kg/day and indicated a NOEL of 0.5 mg/kg/day and an LEL of 1.5 mg/kg/day based on degeneration of the skeletal muscle of the hind limbs in both sexes at 1.5 mg/kg/day and up and decreases in body weight and body weight gain, increase in nerve fiber degeneration in the sciatic nerve and in the spinal cord and an increased incidence of retinal atrophy at 3.5 mg/kg/day.

- The NOEL for the subchronic gavage study in the rat was also 0.5 mg/kg/day and the LEL 2.0 mg/kg/day (tested up to 8.0 mg/kg/day) based on atrophy of the hindlimb skeletal muscle and the panniculus muscle at 2.0 mg/kg/day and above and decreases in body weight gain, atrophy of the paravertebral muscle, clinical signs of neurotoxicity, decreases in landing foot splay, hindlimb grip strength and hindlimb tactile placing response.

  Sodium omadine was also tested in a 90-day dermal study in rats at 0, 5, 15 or 50 mg/kg/day. The NOEL was 5 mg/kg/day and the LEL was 15 mg/kg/day based on atrophy of the hind-limb muscles and subdermal panniculus muscles (15 mg/kg/day in females, 50 mg/kg/day in males); decreased weight gain, atrophy of the paravertebral muscle, clinical signs of neurotoxicity and degeneration of some sciatic nerve fiber muscles at 50 mg/kg/day. The chemical was not a skin irritant in rats.

  On the basis of the results from the 2 subchronic studies, it appears that the amount of sodium omadine that was absorbed via the dermal route in rats was approximately 10%

of the amount absorbed via the oral route. Thus, in mice, it is likely to have a low absorption rate as well.

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 82-3; Subchronic Dermal Toxicity in Rats

CHEMICAL: Sodium omadine (41.2% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 409362-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 90 Day Dermal Toxicity Study in the Rat

AUTHOR: Taupin, P.J.Y. and Wood, C.M.

STUDY NUMBER: OLA/5/88

STUDY COMPLETED: November 3, 1988

EXECUTIVE SUMMARY: Sodium omadine (41.2% purity) was administered dermally to groups of Sprague-Dawley rats (20/sex) daily for 90 days at dosage levels of 0, 5, 15, or 50 mg/kg body weight/day. There was no evidence of dose-related dermal irritation. Dose-related clinical signs seen in high-dose females included emaciation, hunched posture, stiff hindlimbs, incoordination, and tremors. Among the males, one high-dose rat was emaciated; there were no neurologic signs.

Males and females dosed at 0, 5, and 15 mg/kg/day had similar body weights throughout the study. The 50 mg/kg/day males and females consistently gained less weight than the other groups, and weighed as much as 14% and 23% less than controls, respectively. At termination, high-dose body weights were 9% and 17% less than controls for males and females, respectively. Food consumption was not affected.

There were no dose-related effects on eye health or clinical pathology. Statistically significant increases in relative brain, pituitary, heart, lung, liver, kidney, and spleen weights in the high-dose males and females were attributed to retarded growth. There were no dose-related effects on absolute organ weights. The only dose-related gross lesion was

wasting of the hindlimb skeletal muscle in 3/20 mid-dose females, and in 2/20 males and 19/20 females in the high-dose. The gross findings were confirmed histopathologically as a reduction of muscle fiber diameter, fatty replacement, and an increase in the number of sarcolemmal nuclei. The subcutaneous panniculus muscle displayed atrophy in the mid-dose females and the high-dose males and females. In addition, degeneration of sciatic nerve fibers and minimal atrophy in the paravertebral muscles was seen in 10/20 high-dose females. Degenerated fibers showed a loss of myelin.

NOEL = 15 mg/kg/day in males, and 5 mg/kg/day in females.
LOEL = 50 mg/kg/day in males and 15 mg/kg/day in females based on atrophy of the hindlimb muscles and subcutaneous panniculus muscles.

At 50 mg/kg/day, both sexes had decreased weight gain compared to controls, and females showed minimal atrophy of the paravertebral muscle, neurotoxic symptoms, and degeneration of some sciatic nerve fiber bundles.

CORE CLASSIFICATION: **Core Guideline.** The study satisfies the guideline requirements (82-3) for a dermal subchronic study.

Comments: The DER lacked an executive summary, so the preceding summary was generated.

FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Title:
90 Day Dermal Toxicity Study in the Rat

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: William L. McLellan Date 10/22/93
William McLellan, Ph.D.

Independent Reviewer: John Liccione Date 10/22/93
John Liccione, Ph.D.

QA/QC Manager: Sharon A. Segal Date 10/22/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 2-124/403
Project Officer: Caroline Gordon

EPA Reviewer: William B. Greear, M.P.H., DABT Signature: William B. Greear 2/28/94
Review Section IV, Toxicology Branch I Date: _____
Health Effects Division

EPA Section Head: Marion Copley, D.V.M., DABT Signature: Marion Copley
Review Section IV, Toxicology Branch I Date: 3/1/94
Health Effects Division

DATA EVALUATION REPORT

STUDY TYPE: Subchronic dermal toxicity in rats

TEST MATERIAL: Sodium omadine

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 409362-01

SYNONYMS: Sodium pythrithione; sodium 2-pyridinethiol-1-oxide; RD 8702

STUDY NUMBER: OLA/5/88

SPONSOR: Olin Corporation, Stamford, CT 06904

TESTING FACILITY: Toxicol Laboratories Ltd., Ledbury, Herefordshire, England

TITLE OF REPORT: 90 Day Dermal Toxicity Study in the Rat

AUTHORS: Taupin, P.J.Y. and Wood, C.M.

REPORT ISSUED: November 3, 1988

CONCLUSIONS: Sodium omadine was administered dermally to groups of Sprague-Dawley rats (20/sex) daily for 90 days at dosage levels of 0, 5, 15, or 50 mg/kg body weight/day.

NOEL = 5 mg/kg/day

LOEL = 15 mg/kg/day in females and 50 mg/kg/day in males based on atrophy of the hind-limb muscles and subdermal panniculus muscles

In addition, at 50 mg/kg/day both sexes had a decreased weight gain compared to controls, females showed minimal atrophy of the paravertebral muscle, neurotoxic symptoms and degeneration of some sciatic nerve fiber bundles. Sodium omadine was not a skin irritant.

CORE CLASSIFICATION: Core Guideline. The study satisfies the guideline requirements (82-3) for a dermal subchronic study.

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A. MATERIALS AND METHODS

1. Test Article Description

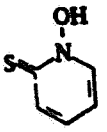
Name: Sodium omadine

Lot number: 8508-P-166H

Purity: Aqueous solution 41.2%

Physical property: Pale amber liquid

Chemical structure.



Storage: Room temperature in the dark in plastic screw top drum

Stability: Confirmed stable before study initiation under conditions of use in this study

2. Dose Formulation and Application

Dosing solutions were prepared weekly by dilution of the 40% aqueous solution of the test compound (as received) with distilled water. Dosing formulations at all three doses were analyzed at weeks 1, 4, 7, 10, and 13. The dosing volume was 1 mL/kg body weight and the amount administered was based on the body weight of each rat prior to dosing on each day. The application sites (about 10% of the body surface) on the dorsal surface of the animals were clipped free of hair 24 hours before treatment began, and the sites were clipped as often as necessary to keep them free of hair. The dose was applied with autopipet and spread with a glass rod. The application site was covered with a gauze patch under aluminum foil held in place with a self-adhesive bandage (Hypertie). Exposure was for 6 hours/day. The application sites were not washed.

Results: At the five intervals of analysis, the concentration ranges for formulations of 5, 15, or 50 mg/mL were 99-112%, 108-118%, and 106-118% of nominal. The mean doses (±SD) were 5.4 (±0.26), 16.8 (±0.66), or 55.7 (±2.40) mg/kg of body weight/day.

The stability of the formulations was tested in other studies. Homogeneity was not checked since the test material was completely soluble in water.

3. Animals

Species: Rat

Strain: Crl: CD(SD)BR® (VAF plus)

Age: Not provided

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Weight at initiation: Males, 217-285 g; females 157-217 g

Source: Charles River (UK) Limited, Margate, England

Group assignment: Animals were found to be healthy on arrival. They were acclimated for 11 days to laboratory conditions. A health check group of 10/sex was included. They were sacrificed after blood and urine sampling for clinical pathology baseline data. Animals were allocated randomly to the following groups:

Test Group	Doses (mg/kg body weight)	Number of Animals	
		Males	Females
1,5 Control	0	20	20
2,6 Low-dose (LDT)	5	20	20
3,7 Mid-dose (MDT)	15	20	20
4,8 High-dose (HDT)	50	20	20

Animals were individually caged and housed in an environmentally controlled room with a temperature range of 19-24°C and humidity range of 45-75% and a 12-hour light/dark cycle. On two days during the study the upper range of temperature exceeded 24°C (26°C and 28°C). Food (SQC Rat and Mouse Maintenance Diet from Special Diet Services, Witham, England) and tap (mains) water were available ad libitum.

Rationale for dose selection: Not provided.

4. Statistics

Body weight, hematological, and absolute organ weight data were analyzed using ANOVA. If between group differences were significant at the 5% level, pairwise t-tests were used for analyses of differences between control and treatment groups. Clinical chemistry data were tested using the Kruskal-Wallis test for between group differences; significant differences between the control and treatment groups used the Wilcoxon rank sum test.

5. Quality Assurance

A Quality Assurance Statement, signed and dated November 3, 1988, was provided. A GLP Compliance Statement and a statement of No Data Confidentiality Claims were also present.

B. METHODS AND RESULTS

1. Clinical Observations

Mortality checks were performed twice daily, and all rats were examined once a day for changes in condition or behavior. Skin at the application site was assessed daily just before dose

application. The skin reactions were scored for erythema/eschar and for edema using the Draize scoring method. Clinical observations were recorded weekly.

Results:

Mortality - Two animals, a female receiving 5 mg/kg/day and a male receiving 50 mg/kg/day, died shortly after blood sampling in week 5. The cause of death was ether overdosage.

Toxicity - Emaciation was observed in 5/20 high-dose females at week 3 and all these females by week 4; it persisted in most through weeks 10-13. From week 7 onwards hunched posture was observed in 10/20 high-dose females and stiff hind limbs were observed in 15/20 high-dose females. Incoordination was observed in one high-dose female during weeks 6-10 and tremors in another high-dose female only at week 9. One male receiving 50 mg/kg/day appeared emaciated; no males showed neurologic symptoms. Fur staining and hair loss were observed fairly frequently but were not treatment related. Other signs were infrequent and not test material related.

Skin Reactions - Scabs were seen at the site of skin application in 3 males and 10 females. They were primarily observed in the first 2 weeks of the study, were not dose related and may be due to removal of hair by skin clipping. Barely perceptible erythema (grade 1) was observed on one day in three mid-dose and one high-dose male. Well-defined erythema (grade 2) was observed in one mid-dose female (2 days only); barely perceptible erythema was observed on occasion in one control female, one low-dose female, one mid-dose female, and six high-dose females. These isolated responses were reported by the study authors to be no more than expected from the repeated usage of occlusive dressings.

2. Body Weights and Food Consumption

Body weights were taken daily for dose adjustment and were recorded weekly. Food consumption was measured weekly.

Results: Table 1 summarizes data on mean body weights and weight gains at selected intervals. A decrease in weight gain was observed in high-dose males and was most marked during weeks 3 and 4 of the study; the mean gain was 20 g in the high-dose males compared to 54 g for controls. High-dose females lost an average of 19 g during week 4. At study termination, mean weights were 91% and 83% of controls in high-dose males and females, respectively. Overall weight gain in high-dose males was 79.1% of control weight gain, and high-dose females gained only an average of 10 g compared to 57 g (17.5%) for controls. No important effects on weight gain were seen at 5 or 15 mg/kg/day in either sex.

Table 1. Summary Data of Group Mean Body Weights and Group Weight Gains for Rats Dermally Administered Sodium Omadine for 90 Days[a]

Dosage (mg/kg/day)	Mean Weights in Grams at Week				Weight Gain in Grams Between Weeks[b] (percent of control)		
	1	4	8	14	1-4	1-8	1-14
				Males			
0	253	335	395	444	82	142	191
5	254	335	395	442	81(98.8)	141(99.3)	188(98.4)
15	253	334	391	433	81(98.8)	138(97.2)	180(94.2)
50	253	308	346	404*	55(67.1)	93(65.5)	151(79.1)
				Females			
0	197	220	241	254	23	44	57
5	198	222	244	257	24(104.3)	46(104.5)	59(103.5)
15	200	227	241	251	27(117.4)	41(93.2)	51(89.5)
50	201	193	190	211**	-8(-)	-11(-)	10(17.5)

[a]Source: study no. OLA/5/88, Table 1, pp. 25-26
[b]Weight gain data calculated from mean body weight data.

*Significantly different from control value, $p \leq 0.01$
**Significantly different from control value, $p \leq 0.001$

Food consumption was not markedly affected in dosed males or females. Although it was slightly depressed during weeks 3-6 in high-dose males compared to controls, the overall food consumption (14 weeks) was 97% of control. In high-dose females, food consumption was 84.6%, 88.4%, and 92.1% of control during weeks 3, 4, and 5, respectively, but overall food consumption was 98% of the control value.

3. Ophthalmoscopic Examination

Both eyes of all animals were examined at the start of the study and prior to termination. The examinations used both direct and indirect ophthalmoscopes after instillation of a mydriatic agent (2% w/v homatropine hydrobromide).

Results: No treatment-related abnormalities or changes were observed. Variations that occurred were related to trauma of orbital sinus bleeding or were normal variations.

4. Clinical Pathology

Blood samples were drawn from 10 rats/sex/group toxicity groups by retroorbital sinus puncture in weeks 5 and 13. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit (HCT)*	X Leukocyte differential count
X Hemoglobin (HGB)*	Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	X Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*	X Mean corpuscular volume (MCV)
X Platelet count*	X Prothrombin time and partial thromboplastin time
X Reticulocyte count (RETIC)	
Red cell morphology	

*Recommended by Subdivision F (November 1984) Guidelines

Results: No effects on hematology parameters were observed and all individual animal values appeared to be within the normal range for rats of this strain.

(b) Blood (Clinical) Chemistry

Electrolytes	Other
X Calcium*	Albumin*
X Chloride*	Albumin/globulin ratio
X Phosphorus*	X Blood creatinine*
X Potassium*	X Blood urea nitrogen*
X Sodium*	X Cholesterol (total)*
	Globulins
	X Glucose*
Enzymes	X Protein Electrophoreses
	X Total bilirubin*
X Alkaline phosphatase (ALP)	Direct bilirubin
Cholinesterase	X Total protein*
X Creatine phosphokinase	Triglycerides
Lactic acid dehydrogenase	
X Serum alanine aminotransferase (ALAT)*	
X Serum aspartate aminotransferase (ASAT)*	
X Gamma glutamyl transferase (GGT)	

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related effects on any clinical chemistry parameters were observed.

(c) Urinalysis: Urine samples were collected at the same intervals as the blood samples (and from the same rats). Urine was collected overnight from rats deprived of water. The checked (X) parameters were examined.

X Appearance*	X Sediment (microscopic)	X Bilirubin*
X Volume*	X Protein*	X Blood*
X Specific gravity*	X Glucose*	Nitrate
X pH*	X Ketones*	X Urobilinogen

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related effects on urinary parameters were observed.

5. Sacrifice and Pathology

Each animal received a complete necropsy. Any abnormalities were reported with details of location, color, shape, and size. Necropsies were conducted over 6 working days. The tissues checked (X) below were preserved in formalin (except the eyes which were fixed in Davidson's fluid), and the double-checked (XX) organs were weighed. Histology was performed on the specified tissues from all control and high-dose animals. The lungs, liver, kidneys, testes, all gross lesions, treatment site skin, and all masses were examined in low- and mid-dose groups. The following additional tissues were examined from the low- and mid-dose groups: hind limb skeletal muscle, skin-subcutaneous panniculus muscle, spinal cord-paravertebral muscle (females only); the sciatic nerve from mid-dose females was also examined. Tissues that were not processed, stained, and examined were retained.

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Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain* (four levels)
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Lymph nodes* (submandibular)	X Spinal cord*[1] (three levels)
X Stomach*	XX Spleen*	XX Pituitary*
X Duodenum*	X Thymus*	X Eyes* (optic nerve)
X Jejunum*		
X Ileum*		
X Cecum*		
X Colon*		
X Rectum*	Urogenital	Glandular
XX Liver*		
X Gallbladder*	XX Kidneys*	XX Adrenals*
X Pancreas*	X Urinary bladder*	X Lacrimal gland
	XX Testes*	X Mammary gland
Respiratory	X Epididymides	XX Thyroids* with parathyroids
	X Prostate*	X Harderian glands
X Trachea*	X Seminal vesicle	
XX Lungs*	XX Ovaries*	
	X Uterus*	

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin* (treated and untreated)[2]
X All gross lesions and masses*

*Recommended by Subdivision F (November 1984) Guidelines
[1]Including paravertebral muscles
[2]Including subcutaneous panniculus muscles

(a) Organ Weights

No effects of treatment on absolute organ weights were observed. The relative organ weights (as percentage of body weight) were significantly increased for the brain, pituitary, heart, lungs, liver, kidneys, and spleen of high-dose males and females and for the testes of males. This was caused by a 10% decrease in the terminal body weights in males and a 20% decrease in females in the high-dose groups as compared to controls. The relative weight of liver was also slightly but significantly increased (10%) in mid-dose females. These increases were attributed to growth retardation alone.

(b) Macroscopic Pathology

The only finding related to dosing was wasting of the hind-limb skeletal muscle which was grossly observed in 3/20 females at 15 mg/kg/day and in 2/20 males and 19/20 females at 50 mg/kg/day.

(c) Microscopic Pathology

Table 2 summarizes the incidence of frequent histologic findings. All other findings were incidental. Atrophy of the upper hind-limb skeletal muscle was observed in high-dose males and mid- and high-dose females. Slight atrophy was also observed in one mid-dose male. Incidence and severity of atrophy were greater in high-dose females than in high-dose males. The atrophy was characterized by a reduction of diameter of muscle fibers, fatty replacement, and an increase in the number of sarcolemmal nuclei. The subcutaneous panniculus muscle displayed atrophy in the same groups; no atrophy was seen in controls, low-dose females, or mid-dose males. Minimal atrophy was seen in the paravertebral muscles of 10 high-dose females but not in other groups. Degeneration of sciatic nerve fibers was seen in 10/20 high-dose females but in no other group of females or in any males. These changes involved only some of the bundles of nerve fibers in the trunk of the sciatic nerve. With solachrome cyamine staining there was loss of myelin in the degenerating fibers but no effects on myelin in adjacent fibers.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study was adequately conducted and reported. The summary data that were validated were supported by individual animal data. The test compound was not a skin irritant at the levels tested. Barely perceptible erythema (grade 1) was occasionally seen in some control and dosed rats. Only two rats on study (mid-dose females) exhibited grade 2 erythema (well-defined erythema), but this was observed only on one study day. These skin findings are assessed by the reviewers to be the result of the occlusive bandage and not related to dosing. The effects on atrophy of the hind-limb muscles were more severe in females than in males. These effects correlate with neurotoxicity. In this study, degeneration of fibers in the sciatic nerve was evident only in the high-dose females. Other studies have used more sensitive parameters to evaluate neurotoxic effects.

The effects on body weights indicated that the dosing levels were appropriate in this study. At the highest dose, the decreases in body weights, which were not accompanied by a decrease in food consumption, were clear-cut but not severe enough to compromise survival, cause secondary effects on the neurotoxic symptoms, or exacerbate the atrophy of hind-limb musculature.

Table 2. Representative Histologic Findings in Rats Dermally Administered Sodium Omadine for 90 Days[a]

Site/Finding	Dosage (mg/kg/day)							
	Males				Females			
	0	5	15	50	0	5	15	50
Skeletal muscle (hind limb)	(20)[b]	(20)	(20)	(19)	(20)	(20)	(20)	(20)
Atrophy:								
Slight or minimum	0	0	1	11	0	0	17	1
Moderate	0	0	0	6	0	0	0	9
Marked	0	0	0	0	0	0	0	10
Total	0	0	1	17	0	0	17	20
Panniculus muscle	(20)	(-)	(20)	(20)	(20)	(20)	(20)	(20)
Atrophy (not graded)	0	-	0	17	0	0	9	20
Paravertebral muscle	(20)	(-)	(-)	(20)	(20)	(-)	(-)	(20)
Atrophy (minimal)	0	-	-	0	0	0	0	10
Sciatic nerve	(20)	(20)	(20)	(20)	(20)	(1)	(20)	(20)
Degeneration	0	0	0	0	0	0	0	10
Skin (treatment site)	(20)	(-)	(-)	(20)	(20)	(-)	(-)	(20)
Epidermal hyperplasia	6	-	-	7	2	-	-	5

[a]Source: Study No. OLA/5/88, Appendix 19, pp 165-182.

[b]The numbers in parentheses are the number examined histologically.

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 82-4; Subchronic Inhalation Toxicity in Rodents

CHEMICAL: Sodium Omadine 40% Aqueous Solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 411782-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Thirteen Week Subchronic Inhalation Toxicity Study on Sodium Omadine in Rats

AUTHOR: Ulrich, C.E.

STUDY NUMBER: 397-042

STUDY COMPLETED: May 3, 1989

EXECUTIVE SUMMARY: Sodium Omadine 40% Aqueous Solution was administered by whole-body inhalation to male and female Sprague-Dawley rats for 6 hours/day, 5 days/week, for 13 weeks at analytical concentrations of 0.00046, 0.0011, and 0.0038 mg/l. The high concentration of 0.0038 mg/l was increased to 0.0081 mg/l at week 6 because of the lack of signs of toxicity. Air control groups were included. Particle size EAD's were 1.1-1.4 μm with GSD's of 1.81-2.09.

Systemic NOEL = 0.0081 mg/l in males
Systemic NOEL = 0.0011 mg/l in females
Systemic LOEL = 0.0081 mg/l in females based on clinical signs of hindlimb dysfunction, histopathologic skeletal muscle regeneration, and decreases in female body weight and body weight gain.

CORE CLASSIFICATION: **Core Minimum.** This study satisfies the guideline requirements for a subchronic inhalation study (82-4) in rodents. Food consumption data were not

reported. Data on food intake could be useful since body weight was affected. Test article purity was not reported.

Comments: The DER lacked an executive summary, so the preceding summary was generated. The penned corrections added by the secondary reviewer read as follows:

"TOX Chemical Number: 790A"

"Purity: 40%"

011532

This is considered a FINAL. HAND WRITTEN CHANGES were done by EPA PERSONEL.
JCR 7/16/94

DATA EVALUATION REPORT

SODIUM OMADINE

Study Title: Thirteen Week Subchronic Inhalation Toxicity Study on Sodium Omadine in Rats

Study Type: Subchronic Inhalation Toxicity in Rodents

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: John Liccione, Ph.D. Date 9/2/93

Independent Reviewer: William McLellan, Ph.D. Date 9/2/93

QA/QC Manager: Sharon Segal, Ph.D. Date 9/3/93

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 402
Project Officer: Caroline Gordon

Guideline Series 82-4: Subchronic Inhalation Toxicity in Rodents 011532

EPA Reviewer: John Bolden M.S.
Review Section III, Toxicology Branch I,
Health Effects Division (H-7509C)

Signature:
Date: 7/26/94

Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I,
Health Effects Division (H-7509C)

Signature:
Date: 7/26/94

DATA EVALUATION REPORT

STUDY TYPE: Subchronic inhalation toxicity in rodents

MRID Number: 411782-01

TOX Chemical Number: 790A

HED Project Number:

TEST MATERIAL: Sodium omadine

SYNONYM: Sodium pyrithione; sodium-2-pyridinethiol-1-oxide

STUDY NUMBER: 397-042

SPONSOR: Olin Corporation, New Haven, Conn.

TESTING FACILITY: International Research and Developmental Corporation, Mattawan, Michigan

TITLE OF REPORT: Thirteen Week Subchronic Inhalation Toxicity Study on Sodium Omadine in Rats

AUTHOR: Ulrich, C.E.

REPORT ISSUED: May 3, 1989 (study date completion)

CONCLUSIONS: Sodium omadine (analytical concentrations: 0.00046, 0.0011, 0.0038 mg/L) was administered by whole-body inhalation to male and female Sprague-Dawley rats for 6 hours/day, 5 days/week, for 13 weeks. The high concentration of 0.0038 mg/L was increased to 0.0081 mg/L at week 6 because of the lack of signs of toxicity. Air control groups were included.

NOEL (systemic effect) in females = 0.0011 mg/L
NOEL (systemic effect) in males = 0.0081 mg/L

LOEL (systemic effect) in females = 0.0081 mg/L based on clinical signs of hindlimb dysfunction and histological effects in the skeletal muscle (regeneration).

Other treatment-related effects in the high-concentration females included decreases in mean body weight and overall body weight gain.

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CORE CLASSIFICATION: Core minimum. This study satisfies the guideline requirements for a subchronic inhalation study (82-4) in rodents . However, food consumption data were not reported. Data cn food intake would be useful since body weight was affected.

A. MATERIALS, METHODS, AND RESULTS

1. Test Material Description

Name: Sodium omadine

Composition: 40% aqueous solution of sodium pyrithione

Lot number: Not reported

Purity: 40%

Physical property: Amber liquid

Stability: Not reported

Storage conditions: Below 55°C

2. Test Material Analyses for Purity and Stability

The purity and stability of the test material were not determined in the study.

3. Generation of Exposure Atmosphere

All groups were exposed simultaneously in four 1-m^3 glass and stainless steel exposure (whole-body) chambers. Aerosol atmospheres containing sodium omadine were generated by metering liquid test material (diluted in distilled deionized water) with an FMI pump from a reservoir to an atomizer mounted in an 3.6-L atomization chamber. The atomizer was operated by compressed air. The diluted test material solutions were prepared weekly.

4. Analysis of Exposure Atmosphere

Actual concentrations for all dose groups were determined each exposure day by high-performance liquid chromatography (HPLC). Samples of the test atmospheres were drawn through glass-fibre filters. During sampling, volumes were measured by dry gas meters. The airflow rates for sample collection ranged from 1 to 8 L/min. Sample duration was approximately 5 hours. Weekly mean analytical exposure concentrations and their standard deviations were calculated. Nominal concentrations were also calculated. Prior to analysis, sodium omadine was converted to a strongly bonded copper complex, which was then extracted in methylene chloride and analyzed

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by HPLC. In addition, aerosol concentrations for each chamber were qualitatively determined every 20 minutes per hour with an automated sampling system and light-scattering aerosol monitor; this procedure served to assess proper operation of the generation system.

To confirm test atmosphere homogeneity, test material concentrations in each exposure chamber and from five specified locations in each chamber were evaluated; the results were compared to a reference location (i.e., the location used for routine sampling during the study). Particle-size distributions for all exposure levels were determined prior to initiation of exposure and once every other week during the exposure period using an Andersen cascade impactor.

Mean inhalation exposure target and analytical levels of the test atmospheres are presented in Table 1, along with the particle-size analysis. Actual exposure concentrations were within 10% of the target levels. The Equivalent Aerodynamic Diameter (EAD) determined in the study ranged from 1.1 μm to 1.4 μm, and GSDs ranged from 1.81 μm to 2.09 μm. Distributions of the test material in the chambers was determined to be uniform (86-111% of the reference location; data not shown); these data indicated that the droplets were of respirable size.

5. Chamber Monitoring

Chamber airflow rate was monitored at approximately hourly intervals during each exposure day. Temperature and relative humidity were measured at approximately hourly intervals during each exposure day.

The airflow rate, as a daily average, ranged from approximately 120 to 250 L/min. The relative humidity mean values (±S.D.) for dose groups 1, 2, 3 and 4 were 63±15.13%, 64±13.70%, 65±13.54%, and 63±9.05%, respectively. The temperature (mean±S.D.) for dose groups 1, 2, 3, and 4 were 23±0.73°C, 22±1.09°C, 23±1.33°C, and 22±0.83°C, respectively.

6. Animals

Species: Rat
Strain: Sprague-Dawley albino (Charles River CD)
Age and weight at study initiation: 7 weeks; males -- 226-254 g; females -- 161-181 g
Source: Charles River Breeding Laboratories, Inc., Portage, Michigan
Housing: Individual
Environmental conditions: Temperature and humidity conditions were not reported; however, it was reported that these parameters were in accordance with DHEW standards. The Photoperiod was a 12-hour light/dark cycle.

Animals were acclimated to laboratory conditions for 16 days and were randomly assigned to the following test groups using a computer-randomization procedure that stratified the animals by body weight:

TABLE 1. Inhalation Exposure Chamber Data for a 13-week Subchronic Inhalation Study with Sodium Omadine in Rats[a]

Parameter	Target Concentration (x 10^{-3} mg/L)			
	0[b]	0.5	1.0	4.0[c] 7.5[d]
Mean (± SD) Nominal Concentration (mg/m^3)	NA[e]	2.1 ± 0.47	3.3 ± 0.31	10.0 ± 0.73[c] 23.7 ± 5.24[d]
Mean (± SD) Analytical Concentration (mg/m^3)	NA	0.46 ± 0.10	1.1 ± 0.31	3.8 ± 0.31[c] 8.1 ± 1.74[d]
Mean EAD[f] (μm)	NA	1.3	1.1	1.4
Mean GSD[g] (μm)	NA	1.81	1.94	2.09

[a]Data extracted from page 30 of the study report
[b]Air control
[c]Weeks 1-6
[d]Weeks 7-14
[e]NA = Not applicable
[f]Equivalent Aerodynamic Diameter
[g]Geometric Standard Deviation

Group	Target Concentration (mg/L)[b]	Number of Animals (13 weeks)[a] Males	Females
1 (air control)	0	15	15
2 (low)	0.0005	15	15
3 (mid)	0.0010	15	15
4 (high)	0.0040	15	15
	0.0075	15	15

[a]Animals were exposed 6 hours/day, 5 days/week, for 13 weeks.
[b]Following 6 weeks of exposure, the high-concentration of 0.0040 mg/L increased to 0.0075 mg/L because of lack of signs of toxicity.

Dose selection: Two range-finding studies were performed. The first range-finding study was performed as Phase I of the main study. The second range-finding study was carried out as a separate study (IRDC Study No. 397-048). Summary results of both studies were provided in the present study. In the first range-finding study, rats were exposed to sodium omadine at mean exposure concentrations of 0.0109, 0.0208, or 0.0427 mg/L for approximately 23 days. The mean EAD ranged from 2.9 to 5.1 μm, and the GSD ranged from 2.10 to 2.41 μm. Poor growth rate was observed in all treated animals. Impairment of hindlimb function was observed in 6 of 10 males and 6 of 10 females administered 0.0109 mg/L sodium omadine, and in 3 of 10 males and 4 of 10 females administered 0.0208 mg/L. This effect was not seen in either the control animals or animals treated with 0.0427 mg/L. Two high-concentration females died on study day 6; another died on day 8. In addition, one high-concentration female died on day 14. At day 13, one low-concentration male and four low-concentration females died. The study author indicated that the mid-concentration level of 0.0208 mg/L was reduced to 0.0014 mg/L during week 2. However, during week 3 of the study, deaths occurred in the low-concentration group (six males, six females), mid-concentration group (five males, six females), and high-concentration group (two males, five females). The exposures were terminated at day 23. These results prompted a second range-finding study in which rats were exposed (5 days/week for 4 weeks) to sodium omadine at concentrations of 0, 0.000042, 0.000110, 0.000340, 0.01120, or 0.003030 mg/L. Particles were within the respirable range. Impairment of hindlimb function was observed in 5 of 10 females exposed to 0.003030 mg/L after 3 weeks of exposure; one female died after 19 days of exposure. There were no treatment-related effects on body weight, gross findings, or on the histology of the respiratory tract and skeletal muscle. Based on these findings, target concentrations of 0.0005, 0.0010, and 0.0040 mg/L were chosen for the 13-week subchronic study.

7. Statistics

For continuous data, statistical analyses were conducted by Bartlett's test for homogeneity, analysis of variance, and Dunnett's t test. Nonparametric analyses were performed by the Kruskal-Wallis one-way analysis of variance, followed by the Mann-Whitney U-test.

8. Quality Assurance

A Quality Assurance Statement (signed and dated 5/1/89) was provided in the study report. The Quality Assurance Statement indicated that the study complied with Good Laboratory Practice Standards. A flagging statement was included.

B. METHODS AND RESULTS

1. General Observations

Animals were observed twice each day, prior to and after exposure, for mortality and clinical signs of toxicity. In addition, animals received a detailed physical examination once each week.

Results

There were no treatment-related deaths. One mid-concentration female died as a result of an accident.

Slight, bilateral impairment of hindlimb function was observed in 4 of 15 high-concentration females. This clinical effect occurred in three females during week 13; in the other female it occurred during weeks 10-13. Hindlimb function was normal in control, low-concentration, and mid-concentration males and females and in the high-concentration males.

2. Body Weights and Food Consumption

Individual body weights were recorded prior to initiation of exposure and weekly thereafter. Food consumption data were not reported.

Results

Body weight: Table 2 summarizes data on mean body weights at selected intervals and overall mean body weight gains. Statistically significant decreases (8.5-11.6%) in mean body weights, compared to controls, were observed in the high-concentration females during weeks 11-13. Mean body weights in the high-concentration females were lower (0.4-3.6%) than those of controls during weeks 7-10, but the difference was not statistically significant. Mean body weights in the low- and mid-concentration females were similar to those of controls. Overall mean body weight gain in the high-concentration females was 28% lower than the control mean. Mean body weights in the low-concentration males were slightly (0.2-2.7%) lower than those of controls between weeks 5 and 8, and between weeks 10 and 13; at

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TABLE 2. Mean Body Weights (g ± S.D.) at Selected Intervals and Overall Mean Body Weight Gain for Rats Exposed to Sodium Omadine by Inhalation for 13 weeks[a]

Week	Analytical Concentration (x 10^{-3} mg/L)			
	0[b]	0.46	1.1	3.8[c] 8.1[d]
		Males		
1	273 ± 11.4	273 ± 9.9	271 ± 15.6	268 ± 11.6
3	331 ± 14.8	331 ± 15.0	342 ± 14.9	331 ± 18.6
5	382 ± 19.3	377 ± 24.5	390 ± 29.1	375 ± 27.1
7	401 ± 28.7	394 ± 26.4	416 ± 27.5	398 ± 32.2
9	436 ± 30.9	395 ± 33.6[e]	459 ± 33.4	435 ± 39.4
11	461 ± 39.1	451 ± 25.1	478 ± 37.1	456 ± 42.1
13	478 ± 30.3	468 ± 35.3	497 ± 41.5	478 ± 43.2
0-13[f]	237.07 ± 26.91	228.93 ± 36.03	253.40 ± 36.50	237.13 ± 37.74
		Females		
1	187 ± 7.7	187 ± 11.0	186 ± 8.5	188 ± 7.0
3	223 ± 12.4	224 ± 10.0	222 ± 13.1	221 ± 7.8
5	250 ± 17.3	250 ± 13.5	247 ± 12.4	243 ± 13.5
7	250 ± 15.8	259 ± 14.5	253 ± 13.5	249 ± 13.1
9	274 ± 18.6	279 ± 15.0	279 ± 16.0	270 ± 13.8
11	281 ± 20.5	285 ± 19.0	284 ± 18.3	257 ± 23.8[e]
13	292 ± 21.7	296 ± 18.7	296 ± 18.2	258 ± 27.9[e]
0-13[f]	118.07 ± 26.77	125.80 ± 17.28	125.93 ± 14.84	85.33 ± 26.06

[a]Data extracted from Table 7 of the study report
[b]Air control
[c]Weeks 1-6
[d]Weeks 7-14
[e]Significantly different from control group ($p \leq 0.01$)
[f]Mean body weight gain calculated by reviewers

week 9, the mean body weight was 9.4% lower ($p<0.01$) than that of controls. Overall mean body weight gain in the low-concentration males was 3.4% lower than those of controls. Mean body weights in the mid- and high-concentration males were slightly higher or similar to controls.

Food consumption: Food consumption data were not reported.

3. Ophthalmologic Examinations

Ophthalmoscopic examinations were conducted on all animals prior to treatment and on 10 rats/sex/group at weeks 6 and 13.

There were no treatment-related ocular effects.

4. Clinical Pathology

After 6 weeks of treatment and prior to the terminal sacrifice, blood samples were taken from the orbital sinus of 10 rats/sex/group for hematology and clinical chemistry analysis. The animals were fasted overnight. The parameters checked (X) below were examined.

(a) Hematology

X	Hematocrit (HCT)*		Leukocyte differential count
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation: thromboplastin time (PT)
X	Reticulocyte count (RETIC)		
	Red cell morphology		

* = Recommended by Subdivision F (November 1984) Guidelines

Results: Although a slight (7.5%) but statistically significant ($p<0.05$) decrease in mean hemoglobin levels was observed in the high-concentration females at week 6 when compared to controls, values were within the normal range. Also, mean hemoglobin levels were similar to controls at week 13.

(b) Blood (clinical) chemistry

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
Magnesium	X Blood creatinine*
X Phosphorus*	X Blood urea nitrogen*
X Potassium*	X Cholesterol*
X Sodium*	X Globulins
	X Glucose*
Enzymes	X Total bilirubin*
	Direct bilirubin
X Alkaline phosphatase (ALP)	X Total protein*
Cholinesterase	Triglycerides
X Creatine phosphokinase	
Lactic acid dehydrogenase	
X Serum alanine aminotransferase (SGPT)*	
X Serum aspartate aminotransferase (SGOT)*	
X Gamma glutamyltransferase (GGT)	
X Ornithine carbamoyl-transferase	

* = Recommended by Subdivision F (November 1984) Guidelines

Results: There were no changes of toxicological significance in clinical chemistry parameters.

(c) Urinalysis

Urinalysis was performed on 10 rats/sex/group at weeks 6 and 13. The parameters checked (X) below were examined.

X Appearance*	X Sediment (microscopic)	X Bilirubin*
X Volume*	X Protein*	X Blood
X Specific gravity*	X Glucose*	X Nitrite
X pH*	X Ketones	X Urobilinogen

* = Recommended by Subdivision F (November 1984) Guidelines

Results: There were no changes of biological importance in urinalysis parameters.

5. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subject to gross pathological examination. The tissues checked (X) below were collected from control and high-concentration animals for histological examination. In addition, the lungs, nasal turbinates, trachea, and gross lesions were examined microscopically in the low- and mid-concentration animals. The double-checked (XX) organs were weighed.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	X Spleen*	X Eyes (optic nerve)*
X Jejunum*	X Thymus*	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum*	XX Kidneys*	X Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland*
Gallbladder*	XX Testes*	X Thyroids*
X Pancreas*	X Epididymides	X Parathyroids*
	X Prostate	X Harderian glands
Respiratory	X Seminal vesicle	
	XX Ovaries	
XX Trachea*	X Uterus*	
XX Lung*		
X Nasal turbinates (3 levels)		
Pharynx		
X Larynx		

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin*
X All gross lesions and masses*

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights

Relative weights of the brain, heart, adrenals, lungs, and liver were significantly increased in the high-concentration females and are ascribed to the lower body weights in this group.

(b) Gross pathology

No gross lesions attributable to exposure to sodium omadine were found.

(c) Microscopic pathology

The only treatment-related histopathological change was regeneration (trace) of the skeletal muscle in three of four high-concentration females that also displayed clinical signs of hindlimb dysfunction. The histological change consisted of an increase in the number of sarcolemma cells per unit area. In addition, one of the high-dose females (animal no. 48045) showed

large pale inclusions in several of the myofibers suggestive of a degenerative change.

D. DISCUSSION

The design and conduct of the study were adequate. However, data regarding the purity of the test material were not provided. Also, food consumption data were absent; food intake data may be useful in the interpretation of body weight changes observed in the high-concentration females. Therefore, this study is classified core minimum.

Four of 15 female rats exposed by inhalation to the high concentration of sodium omadine (0.0038/0.0081 mg/L) showed clinical signs of slight, bilateral impairment of hindlimb motor function during the latter part of the treatment period. Three of the four high-concentration females also exhibited regeneration (graded as trace) of the skeletal (thigh) muscle. In addition, large pale inclusions in several of the myofibers were present in one of the high-concentration females suggesting degenerative changes in the skeletal muscle. Since skeletal muscle regeneration is indicative of a repair process, it is possible that the females may have tolerated a higher concentration level. There were no lesions in the brain, spinal cord, or sciatic nerve. Clinical signs of slight, bilateral impairment of hindlimb motor function were also noted in a subchronic dietary study in rats (MRID 407569-01); this effect was seen in male and female rats administered 8.0 mg/kg/day (high dose) of sodium omadine by oral gavage. In addition, functional tests (i.e., landing foot splay, hindlimb grip strength, and hindlimb tactile placing response) confirmed the clinical signs of hindlimb motor dysfunction in the subchronic oral study. Because of the severity of hindlimb motor dysfunction in female rats dosed orally with 8.0 mg/kg/day sodium omadine, 10 of 20 females were sacrificed during the study. The most notable histological effect found in the subchronic oral study was bilateral atrophy of the hinclimb muscles in the high-dose males and females. No corresponding histopathological changes in the brain, spinal cord, or sciatic nerve were found.

Other treatment-related effects in the high-concentration females included decreases in mean body weight and overall body weight gain.

Based on clinical signs of hindlimb dysfunction and histological effects in the skeletal muscle (i.e., regeneration) in females, the LOEL for systemic toxicity in females is 0.0081 mg/L. The NOEL in females is 0.0011 mg/L. No treatment-related effects were observed in males.

Reviewed by: John E. Whalan JW 1-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 83-1; Chronic Oral Toxicity in Nonrodents (Monkeys)

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.41% and 40.5% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 411781-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corp., Mattawan, MI

TITLE OF REPORT: One Year Oral Toxicity Study in Cynomolgus Monkeys

AUTHOR: Johnson, D.E.

STUDY NUMBER: 397-047

STUDY COMPLETED: April 14, 1989

EXECUTIVE SUMMARY (revised): Sodium Omadine 40% Aqueous Solution (41.41% and 40.5% purity) was administered in water by gavage to groups of 5 male and 5 female Cynomolgus monkeys for 1 year at dose levels of 0, 5, 25, or 150 mg/kg/day. The dose level of 150 mg/kg/day was lowered to 75 mg/kg/day at week 6 because of adverse effects on survival. No explanation was offered for selecting this species as the test system.

No evidence of toxicity was seen at the 5 mg/kg/day dose other than emesis in some monkeys. Emesis was observed in all monkeys at higher doses. Male body weights were unaffected by dosing, but female body weights were decreased as much as 8%, 17%, and 23% at the 5, 25, and 75/150 mg/kg/day doses, respectively. At 150 mg/kg/day, one female was sacrificed *in extremis* at week 6. At 75 mg/kg/day, one male and one female died at weeks 13 and 35, respectively; the cause of death was not apparent for either animal. Clinical signs noted in the dead female and sacrificed female included prostration, decreased activity, emesis, thinness, weak appearance, and cold extremities. Emesis and ptyalism were seen in the male that died. Hematologic changes (i.e., decreases in erythrocyte count, hemoglobin, and hematocrit levels) were slight and considered of minor toxicological importance. The defined doses are as follows:

NOAEL = 5 mg/kg/day
LEL = 25 mg/kg/day (emesis, decreased female body weight)

CORE CLASSIFICATION: The study is **Core Minimum** and satisfies the minimal guideline requirements (83-1b) for a chronic oral study in nonrodents. The choice of monkeys as the test system instead of dogs is unusual, and no justification was offered. Although a one year study cannot be regarded as chronic (lifetime) exposure for a monkey any more than for a dog, it is acceptable from a regulatory standpoint since cancer endpoints are not at issue. Food consumption data were not reported. These data would be useful since the body weight gain was affected.

Comments: No explanation was offered for selecting Cynomolgus monkeys as the test system for a chronic study. Monkeys are rarely used because they are expensive and dangerous to handle. They are especially poorly suited for a long-term gavage study.

The DER states that a NOEL could not be determined. The low-dose of 5 mg/kg/day was defined as the LEL on the basis of decreased body weight gain in both sexes. This is incorrect.

All dosed males slowly gained weight over the course of the study, and their weights remained comparable. The body weights of the control males were similar to the dosed groups during the first half of the study, but during the second half, their body weights took an upswing — probably because of some iatrogenic effect. Since the control values were atypical, and there was no dose-relationship among the dosed groups, this cannot be considered a toxic response.

In the females, there was a dose-related decrease in body weight during much of the study. The control weights did not take an upswing as seen in the males. Compared to controls, female body weights were decreased as much as 12% at 25 mg/kg/day, and 23% at 75 mg/kg/day (HDT). Body weight gain in the females was an unreliable indicator; the values were exaggerated because the controls gained so little weight over the course of the study (0.2 kg).

The penned corrections added by the secondary reviewer read as follows:

"The cause of death was not apparent for either animal."

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FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Type: Chronic Oral Toxicity in Nonrodents

Study Title: One Year Oral Toxicity Study in Cynomolgus Monkeys

Prepared for:

Office of Pesticide Programs
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Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 393
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Signature: William B. Greear
Date: 1.Jan 3, 1994

Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I,
Health Effects Division (7509C)

Signature: Marion Copley
Date: 5/8/94

DATA EVALUATION REPORT

STUDY TYPE: Chronic Oral Toxicity in Nonrodents

MRID NUMBER: 411781-01

TOX CHEMICAL NUMBER: 790A

PC NUMBER: 088004

TEST MATERIAL: Sodium Omadine

SYNONYM: Sodium pyrithione; sodium-2-pyridinethiol-1-oxide

STUDY NUMBER: 397-047

SPONSOR: Olin Corporation, New Haven, Conn.

TESTING FACILITY: International Research and Development Corporation
Mattawan, Michigan

TITLE OF REPORT: One Year Oral Toxicity Study in Cynomolgus Monkeys

AUTHOR: Johnson, D.E.

REPORT ISSUED: April 14, 1989

EXECUTIVE SUMMARY: Sodium omadine was administered in water by gavage to groups of 5 male and 5 female cynomolgus monkeys for 1 year at dose levels of 0, 5, 25, or 150 mg/kg/day. The dose level of 150 mg/kg/day was lowered to 75 mg/kg/day at week 6 because of adverse effects on survival.

At 5 mg/kg/day decreased body weight gains were seen throughout the study in both sexes. At the higher doses emeses was observed in most animals and body weight gains were generally more severely depressed that at 5 mg/kg/day. At 75 mg/kg/day one male and one female died at weeks 13 and 35, respectively. *The cause of death* At 150 mg/kg/day one female was sacrificed in extremis at week 6. Clinical signs noted in the female that was sacrificed and in the female that died included prostration, decreased activity, emesis, thinness, weak appearance, and cold extremities. Emesis and ptyalism were seen in the male that died. Emesis was observed in most of the low-dose animals, and in all of the mid- and high-dose

were not apparent for either animal.

animals. Hematological changes (i.e., decreases in red blood cell count, hemoglobin, and hematocrit levels) were slight and considered of minor toxicological importance.

The LEL of 5 mg/kg/day is based on decreased body weights. A NOEL was not determined.

CORE CLASSIFICATION: The study is Core Minimum and satisfies the minimal guideline requirements (83-1b) for a chronic oral study in non rodents. Food data consumption were not reported. These data would be useful since the body weight gain was affected.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Sodium omadine

Composition: 40% aqueous solution of sodium pyrithione

Batch number: IRDC 9180 and 9180B

Physical property: Amber liquid

Purity: 41.41% (Batch No. 9180)
40.5% (Batch No. 9180B)

Stability: Stable for at least 29 days when stored at room temperature

Storage: Room temperature in capped amber containers

2. Dosing Regimen: Monkeys were dosed by oral gavage for 7 days per week for at least 1 year with aqueous solutions of sodium omadine at 5, 25, or 150 mg/kg/day at a dosing volume of 1.0 ml/kg (followed by a rinse with 5 mL of deionized water). The high-dose of 150 mg/kg/day was reduced to 75 mg/kg/day on day 7 of study week 6 because of effects on survival. Vehicle controls received deionized water. Dosing solutions were corrected for the active ingredient. Doses were adjusted weekly based on the most recent body weight. Dosing solutions were prepared by diluting the stock solution weekly for weeks 1 through 5, and every 4 weeks thereafter.

3. Test Material Analyses for Purity and Stability

The stability of the test material in the dosing solutions prepared during week 1 was determined (by HPLC) from samples stored at room temperature for 0, 8, 15, and 29 days. The stability of the test material in the dosing solutions prepared during weeks 2, 3, 4, and 5 was determined from samples stored at room temperature for 0 and 8 days. Beginning at week 6, stability analyses of dosing solutions were performed every 4 weeks of the study from samples stored at room temperature for 0, 22, and/or 29 days.

TABLE 3. ... ody Weight Gains (kg ± SD) of Monkeys Administered Sodium ... by Gavage for 1 Year[a]

Dose (mg/kg/day)	Mean Body Weight Gains at Selected Intervals		
	0-13 weeks	26-52 weeks	0-52 weeks
	Males		
0	0.02 ± 0.13	0.66 ± 0.46	0.96 ± 0.71
5	0.18 ± 0.15	0.32 ± 0.23	0.32 ± 0.28
25	-0.22 ± 0.22	0.34 ± 0.11	0.18 ± 0.33
75	-0.05 ± 0.13	0.20 ± 0.14	0.15 ± 0.21
	Females		
0	-0.08 ± 0.13	0.12 ± 0.08	0.16 ± 0.13
5	-0.14 ± 0.05	0.10 ± 0.20	0.00 ± 0.20
25	-0.28 ± 0.22	0.14 ± 0.09	0.06 ± 0.18
75	-0.53 ± 0.39	0.07 ± 0.15	-0.17 ± 0.21

[a]Body weight gain data calculated by the reviewers from individual animal data

(a) Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation: activated partial thromboplastin time (APTT)
X	Reticulocyte count (RETIC)		Prothrombin time
	Red cell morphology		

* = Recommended by Subdivision F (November 1984) Guidelines

Note: Bone marrow smears were prepared from all monkeys. In order to confirm the absorption of test material additional blood was obtained from each animal at termination for determination of 2-methylsulfonylpyridine levels.

Results

Table 4 summarizes selected hematology data. Decreases in red blood cell count (14-18% in males; 13-20% in females), as well as hemoglobin (13-17% in males; 13-17% in females) and hematocrit (14-16% in males; 15-18% in females) levels were noted in the high-dose males and females when compared to controls; the decreases reached statistical significance ($p<0.05$ or $p<0.01$) at various study intervals. Decreases in red blood cell count (18-19% in males; 10-15% in females), and hemoglobin (13-17% in males; 11-14% in females) and hematocrit (12-17% in males; 10-13% in females) levels were also noted in the mid-dose animals; the decreases were statistically significant ($p<0.05$ or $p<0.01$) at various study intervals. Based on historical control data on red blood cell counts (provided in the study report), the decreases in red blood cell counts were within the normal range. In addition, there were no signs of hemolysis or changes in the cellularity in the bone marrow smears. Therefore, the hematological changes are considered to be of minor toxicological importance.

TABLE 4. Selected Hematology Parameters for Monkeys Administered Sodium Omadine by Gavage for 1 Year[a,b]

Parameter/ Month	Dose Groups (mg/kg/day)							
	Males				Females			
	0	5	25	150/75[c]	0	5	25	150/75[c]
Erythrocytes ($x10^6/mm^3$)								
0	6.68 ± 0.580	6.49 ± 0.305	6.27 ± 0.478	6.77 ± 0.418	6.30 ± 0.340	6.29 ± 0.444	6.17 ± 0.279	6.24 ± 0.276
1	6.69 ± 0.357	6.07 ± 0.557*	5.51 ± 0.247**	5.47 ± 0.229**	6.47 ± 0.136	5.70 ± 0.589*	5.50 ± 0.335**	5.18 ± 0.222**
3	5.89 ± 0.720	5.88 ± 0.216	5.14 ± 0.173	5.59 ± 0.353(4)[d]	5.97 ± 0.281	5.37 ± 0.346*	5.21 ± 0.209**	5.03 ± 0.335**(4)
6	6.54 ± 0.494	5.88 ± 0.197*	5.31 ± 0.158**	5.65 ± 0.292**(4)	6.08 ± 0.435	5.75 ± 0.324	5.47 ± 0.295*	5.32 ± 0.177**(4)
12	6.31 ± 0.355	5.77 ± 0.282*	5.12 ± 0.296**	5.46 ± 0.297**(4)	5.74 ± 0.136	5.32 ± 0.249	5.06 ± 0.378**	4.73 ± 0.133**(3)
Hemoglobin (g/dL)								
0	12.4 ± 0.45	12.3 ± 0.49	11.9 ± 0.59	13.2 ± 1.11	11.6 ± 0.86	12.0 ± 1.22	11.6 ± 0.50	12.0 ± 0.95
1	12.6 ± 0.65	11.9 ± 1.18	10.6 ± 0.65**	10.5 ± 0.82**	12.2 ± 0.82	11.2 ± 1.23	10.5 ± 0.25**	10.1 ± 0.61**
3	13.0 ± 0.71	13.1 ± 0.97	11.3 ± 0.60*	12.2 ± 1.05(4)	12.9 ± 1.00	12.0 ± 0.81	11.5 ± 0.42*	11.2 ± 0.93*(4)
6	12.7 ± 0.85	11.9 ± 0.91	10.6 ± 0.31**	11.0 ± 0.61*(4)	11.8 ± 1.18	11.8 ± 0.58	10.9 ± 0.40	11.0 ± 0.41(4)
12	12.7 ± 0.64	12.1 ± 0.79	10.7 ± 0.48**	11.1 ± 0.51**(4)	11.8 ± 0.82	11.3 ± 0.72	10.6 ± 0.61	10.0 ± 0.66*(3)
Hematocrit(%)								
0	42.8 ± 2.11	43.2 ± 1.69	41.6 ± 2.58	44.6 ± 3.44	40.9 ± 3.50	42.3 ± 3.88	40.2 ± 1.95	42.3 ± 2.98
1	45.6 ± 2.05	42.7 ± 3.79	38.9 ± 1.71**	38.5 ± 1.86**	44.5 ± 2.59	40.7 ± 3.95	38.6 ± 1.42**	36.7 ± 1.73**
3	42.0 ± 3.08	42.5 ± 2.56	37.0 ± 0.83*	39.5 ± 2.93(4)	42.3 ± 2.82	39.4 ± 2.75	37.6 ± 1.61*	35.7 ± 2.27**(4)
6	44.0 ± 2.52	41.1 ± 2.16	36.7 ± 1.38**	37.8 ± 1.34**(4)	41.0 ± 4.50	40.3 ± 2.33	37.7 ± 1.85	36.7 ± 1.20(4)
12	42.2 ± 1.59	40.1 ± 2.91	35.4 ± 1.67**	36.4 ± 1.98**(4)	38.6 ± 2.38	37.2 ± 2.14	34.7 ± 2.08*	32.8 ± 0.87**(3)

[a]Data extracted from Table 4, pages 64-68, study report
[b]Data based on 5 monkeys/sex/group unless otherwise indicated
[c]The dose of 150 mg/kg/day was administered through week 6; 75 mg/kg/day was administered thereafter
[d]Number in parenthese indicates number monkeys/sex/group

*Significantly different from control at $p<0.05$
**Significantly different from control at $p<0.01$

(b) Blood (clinical) chemistry

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
Magnesium	X Blood creatinine*
X Phosphorus*	X Blood urea nitrogen*
X Potassium*	X Cholesterol*
X Sodium*	X Globulins
	X Glucose*
Enzymes	X Total bilirubin*
	Direct bilirubin
X Alkaline phosphatase (ALP)	X Total protein*
Cholinesterase	Protein electrophoresis
X Creatine phosphokinase	Phospholipid
Lactic acid dehydrogenase	Uric acid

X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

* = Recommended by Subdivision F (November 1984) Guidelines

Results

There were no changes of toxicological significance in clinical chemistry parameters.

(c) Urinalysis

Urinalysis was performed on all monkeys/sex/group prior to treatment, and at months 1, 3, 6, and 12. The parameters checked (X) below were examined.

X Appearance*	X Sediment (microscopic)	X Bilirubin*
X Volume*	X Protein*	X Blood
X Specific gravity*	X Glucose*	X Nitrite
X pH*	X Ketones	X Urobilinogen

* = Recommended by Subdivision F (November 1984) Guidelines

Results

There were no changes of toxicological significance in urinalysis parameters.

5. Sacrifice and Pathology

Following 12 months of treatment, all surviving monkeys were sacrificed and necropsied. Animals that died during the study or that were sacrificed before the end of the study also received a complete gross examination. Tissues checked (X) below were examined

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histologically. In addition, double-checked (XX) organs were weighed for monkeys sacrificed by design.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen*	X Eyes (optic nerve)*
X Jejunum*	X Thymus*	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum*	XX Kidneys*	Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland*
X Gallbladder*	XX Testes*	XX Thyroids*
X Pancreas*	X Epididymides	XX Parathyroids*
	X Prostate	Harderian glands
Respiratory	Seminal vesicle	
	XX Ovaries	
X Trachea*	X Uterus*	
X Lung*		
Larynx		

Other

X Bone (rib)*
X Skeletal muscle (thigh)*
X Skin*
X All gross lesions and masses*

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights

There were no organ weight changes of biological importance. The increases in relative (to body) liver and kidney weights noted in treated males and females are ascribed to decreases in body weights. The increase in absolute adrenal weights in the high-dose females was not accompanied by pathological changes.

(b) Gross pathology

No gross lesions attributable to administration of sodium omadine were found.

(c) Microscopic pathology

There were no microscopic lesions attributed to administration of sodium omadine.

C. DISCUSSION

The design and conduct of the study were adequate. However, food consumption was not measured; food intake data may be useful in the interpretation of body weight gain changes observed in the treated animals. Measurements of the plasma levels of 2-methylsulfonyl-pyridine indicated that the test material was absorbed following oral administration.

One high-dose female administered 150 mg/kg/day sodium omadine by gavage for 6 weeks was sacrificed in extremis as the result of apparent toxicity; clinical signs noted prior to sacrifice included prostration, thinness, cold extremities, weak appearance, ptyalism, and emesis. Consequently, the 150-mg/kg/day dose level was reduced to 75 mg/kg/day at week 6. However, deaths occurred in one high-dose male (week 13) and one high-dose female (week 35). These results indicate that the administration of 150 mg/kg/day dose may have exceeded the maximum tolerated dose. The cause of the deaths in the monkeys was not ascertained. Clinical observations noted in the high-dose female that died at week 35 included prostration, decreased activity, emesis, thinness, and cold extremities. Moderate ptyalism and emesis were seen in the high-dose male that died at week 13.

Emesis was observed in the treated animals, and occurred within 15-30 minutes of dosing. The incidence of emesis was higher in the mid- and high-dose animals when compared to the low-dose animals. Also, the frequency of emesis was reported to be higher in the mid- and high-dose animals. Mean body weight gains were depressed in the low-, mid-, and high-dose monkeys at several intervals of the study. Moreover, the decreases in mean body weight gains were dose-dependent in the treated females at weeks 0-13 and 0-52. Hematological changes were slight and were considered of minor toxicological importance.

Hindlimb motor dysfunction and/or hindlimb muscle atrophy were observed in a subchronic oral study in rats (MRID # 407569-01), a subchronic inhalation study in rats (MRID # 411782-01), a chronic toxicity/oncogenicity study in rats (MRID # 421009-01), and in a 90-day dermal study in rats (MRID # 409362-01). These effects were not observed in the present study, indicating a possible species difference.

Based on decreases in body weight gains in the low-, mid-, and high-dose monkeys, the LOEL for systemic toxicity is 5 mg/kg/day. A NOEL for depressed body weight gain was not determined.

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SODIUM OMADINE

Page _____ is not included in this copy.

Pages 127 through 128 are not included in this copy.

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_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

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Reviewed by: John E. Whalan JW 4-20-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner 4-20-95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 83-2; Dermal Carcinogenicity Study in Mice

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.2% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 421008-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 80-Week Dermal Carcinogenicity Study in the Mouse

AUTHOR: R.F.A. Husband, A.J. Newman, and P.N. Lee

STUDY NUMBER: OLA/7/90

STUDY COMPLETED: February 20, 1991

EXECUTIVE SUMMARY (revised): In an 80-week dermal carcinogenicity study, Sodium Omadine 40% Aqueous Solution (41.2% purity) was administered topically to groups of 50 male and 50 female CD-1 mice at dosage levels of 0, 5, 15, or 40 mg/kg/day.

At 40 mg/kg/day, an increase in the incidence of epidermal hyperplasia at the application site was seen in males (20% compared to 0% in controls, $p < 0.01$) and in females (20% compared to 6% for controls; nonsignificant by pairwise comparison but a significant trend, $p < 0.05$). No systemic toxicity was observed. Under the conditions of the study, dermal application of sodium omadine did not induce any benign or malignant neoplasms.

The 40 mg/kg/day dose is defined as a free-standing systemic NOEL, based on the range-finding study. The dermal NOEL is 15 mg/kg/day. The dermal LEL is 40 mg/kg/day based on an increase in epidermal hyperplasia at the skin application site. The Health Effects Division RfD Committee considered the doses in this study inadequate to assess carcinogenicity.

CORE CLASSIFICATION: This study is classified **Core Supplementary**, so it does not satisfy the minimum requirement (83-2) for a dermal oncogenicity study in rodents. While it is clear that the mice could have been given a higher dose, the thickened skin may have slowed absorption. The absence of systemic toxicity can be attributed to the unpredictable nature of a steep dose-response curve.

Comments: The Executive Summary in the DER states that, "The highest dose was considered adequate to assess carcinogenicity based on a 13-week dermal study in mice where atrophy of the hindlimb muscles was observed at 15 and 50 mg/kg/day in females and 50 mg/kg/day in males." The study alluded to was performed in rats, not mice.

011532

FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Title:
80 Week Dermal Carcinogenicity Study in the Mouse

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
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Principal Reviewer: William L. McLellan Date 3/15/94
William McLellan, Ph.D.

Independent Reviewer: Cinn Rose for Date 3/15/94
John Liccione, Ph.D.

QA/QC Manager: Date 3/15/94
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 2-124/392
Project Officer: Caroline Gordon

Guideline Series 83-2: Dermal Oncogenicity in Rodents

EPA Reviewer: William Greear, M.P.H.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: William B. Greear
Date: 4/9/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Marion Copley
Date: 4/11/94

DATA EVALUATION REPORT

STUDY TYPE: Dermal oncogenicity study in mice

TEST MATERIAL: Sodium omadine

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 421008-01

SYNONYMS: Sodium pyrithione; sodium 2-pyridinethiol-1-oxide; RD 8702

STUDY NUMBER: OLA/7/90

SPONSOR: Olin Corporation, Stamford, CT 06904

TESTING FACILITY: Toxicol Laboratories Ltd., Ledbury, Herefordshire, England

TITLE OF REPORT: 80-Week Dermal Carcinogenicity Study in the Mouse

AUTHORS: R.F.A. Husband, A.J. Newman, and P.N. Lee

REPORT ISSUED: February 20, 1991

EXECUTIVE SUMMARY: In an 80 week dermal oncogenicity study, sodium omadine was administered topically to groups of 50 male and 50 female CD-1 mice at dosage levels of 0, 5, 15, or 40 mg/kg/day.

At 40 mg/kg/day an increase in the incidence of epidermal hyperplasia at the skin application site was seen in males (20% compared to 0% in controls, $p<0.01$) and in females (nonsignificant by pairwise comparison but a significant trend, $p<0.05$); 20% at the high dose compared to 6% for control. No systemic toxicity was observed.

The dermal LEL of 40 mg/kg/day is based on an increase in epidermal hyperplasia at the skin application site and the dermal NOEL is 15 mg/kg/day. The systemic NOEL is 40 mg/kg/day.

Under the conditions of the study, dermal application of sodium omadine did not induce any benign or malignant neoplasms. The highest dose was considered adequate to assess carcinogenicity based on a 13-week dermal study in mice

where atrophy of the hind limb muscles was observed at 15 and 50 mg/kg/day in females and 50 mg/kg/day in males.

The study is classified Core Minimum and satisfies the minimum requirement (83-2) for a dermal oncogenicity study in rodents.

A. MATERIALS AND METHODS

1. Test Article Description

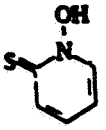
Name: Sodium omadine

Lot number: 8508-P-166H

Purity: Aqueous solution 41.2%

Physical property: Pale amber liquid

Chemical structure:



Storage: Room temperature in the dark in plastic, screw top drum

Stability: Stable under conditions of storage

2. Dose Preparation

The test compound was corrected for active ingredient content and an appropriately weighed amount was diluted with distilled water and mixed by shaking. Test article formulations were prepared weekly and daily dispensed aliquots were discarded following dosing. Samples of each formulation (including controls) were analyzed for concentration prior to dosing and every third week during the study. The stability of the test material in the 5- and 40-mg/mL dosing solutions was confirmed over 15 days. Testing for homogeneity was not necessary because the test article forms a true solution.

Results: The test compound was stable over 15 days of storage. The mean analyzed concentrations (±SD) were 5.312 (±0.168), 15.774 (±0.562), and 42.254 (±1.108) for the theoretical concentrations of 5, 15, or 40 mg/kg/day.

3. Animals

Species: Mouse

Strain: Crl:CD-1® (ICR)BR VAF Plus

Age: Approximately 28 days old on receipt and 41 days old at initiation of dosing

Weight at initiation: Males weighed 19-31 grams and females weighed 18-27 grams.

Source: Charles River (UK) Limited, Margate, England.

Group assignment: Animals were acclimated to laboratory conditions for 13 days and confirmed suitable for use by two health examinations and microscopic examination of kidneys, liver, and lungs from a health-check group of five/sex. The mice were assigned randomly to the following groups after excluding those at the extremes of the weight range:

Test Group	Doses (mg/kg body weight)	Number of Animals	
		Males	Females
1. Control	0	50	50
2. Low-dose	5	50	50
3. Mid-dose	15	50	50
4. High-dose	40	50	50

Rationale for dose selection: Dose levels for the study were chosen by the sponsor based on a 13-week dermal study with rats and a 28-day dermal study in mice (Toxicol reports numbers OLA/5/88 and OLA/6/87). The high range in these studies was 50 mg/kg. Results of the 28-day study were not provided. The 13-week dermal study in rats had a NOEL of 5 mg/kg/day. Atrophy of hind-limb muscles was observed at 15 and 50 mg/kg/day in females and at 50 mg/kg/day in males (MRID No. 409362-01).

Treatment: The application sites on the dorsal surface of the animals (about 10% of the body surface) were clipped free of hair prior to dosing and by regular clipping as frequently as required. Test compound was dispensed to the test site (1 mL/kg) once daily with an autopipet and spread with a glass rod. Test sites were not occluded or washed. Control groups received a dose of 1 mL/kg distilled water, and doses for the treated groups were adjusted according to the most recently recorded body weights.

Animals were individually caged in environmentally controlled rooms with a temperature range of 11-27°C and a relative humidity range of 22-90% for the first 50 weeks. A room change (completed in 1 day) was mandated at week 50 because of the need for major air conditioning maintenance. Thereafter the temperature and humidity ranges were 16-23°C and 39-74%, respectively. The rooms had a 12-hour dark/light cycle. The animals received SQC Rat and Mouse Maintenance Diet #1 from Special Diet Services, Witham, England, and tap (mains) water was available ad libitum.

4. Statistics

Body weight and absolute organ weight were analyzed for variance using Bartlett's est. If variance was homogeneous, data were further analyzed using ANOVA. If variances were heterogeneous, a log transformation was performed. For data that were still non-parametric, the Wilcoxon rank sum test was used. Hematology and clinical chemistry data were analyzed using the Kruskal-Wallis one-way analysis of variance. Body weight data were analyzed at 8-week intervals, and body weight gain data were analyzed for the overall study.

Survival data and incidence data were analyzed by the method of Peto (IARC method) using a Microvax computer. Both trend and Chi square analyses were performed. For histologic lesions of kidney, liver, lung, and muscle and other tissues examined in all animals in all groups, the number of tissues examined was the denominator. For tissues designed by protocol to be examined only in decedents in the low- and mid-dose groups or when an abnormality was present post-mortem, the number of animals (not tissues examined) was used as the denominator. In these cases, controls and high-dose animals were analyzed based on decedents plus terminals, and for low- and mid-dose animals, analysis was based on decedents only.

When incidences of histologic findings were low, age-adjusted exact tests were used in preference to Chi square tests. Statistics were performed separately by sex and also combined by sexes.

5. Quality Assurance/Compliance

A Quality Assurance Statement, signed and dated February 20, 1991, was provided and included dates of inspections. A GLP Compliance Statement and Flagging Statement (dated June 6, 1991) were also provided.

B. METHODS AND RESULTS

1. Clinical Observations

Mortality checks were performed twice daily, and all mice were examined once a day for changes in condition or behavior. Beginning at week 27, all animals were palpated weekly for masses and details of location, size, and consistency were recorded. Clinical observations were recorded weekly.

Results: Survival was not affected by topical application of sodium omadine. Survival was 82%, 88%, 90%, and 84% in male groups receiving 0, 5, 15, or 40 mg/kg body weight/day, respectively. Female survival was 72%, 72%, 84%, and 74% in the same dose groups, respectively. At 52 weeks, survival ranged between 92% and 98% in all groups.

Clinical signs were present at background incidence levels in all treated groups. No treatment-related distribution of palpable masses was observed in any dose group. During the study only

12 animals were observed with palpable masses. Only four of the masses seen in life were confirmed as neoplasms. Two were benign and two were malignant.

2. Body Weights and Food Consumption

Each animal was weighed on the first day of dosing, weekly for 16 weeks, and every month thereafter. Food consumption was recorded weekly for 16 weeks and every fourth week thereafter.

Results: The mean body weights and body weight gains were not affected by dermal dosing in either sex.

Food consumption was not affected by dermal dosing. Overall food consumption was decreased 5% compared to controls, but this was not considered in high-dose males to be related to application of sodium omadine. Overall food consumption values in all other groups of males and in treated females were within 1% of control values.

3. Ophthalmoscopic Examination

Ophthalmoscopic examinations were not conducted.

4. Clinical Pathology

Blood samples ~~was~~ were drawn by orbital sinus puncture from 10 mice/sex/group during weeks 52 and 80 for differential leukocyte counts. No other hematology parameters were examined. Clinical chemistry and urinalysis were not required.

Results: No treatment-related effects or trends were observed at either week 52 or week 80 in the differential leukocyte counts.

5. Sacrifice and Pathology

All animals that died or were sacrificed moribund and all animals sacrificed at termination received a complete necropsy. The tissues checked (X) below were preserved in formalin (except the eyes which were fixed in Davidson's fluid), and the double-checked (XX) organs were weighed. Histology was performed on the specified tissues from all control and high-dose animals and all decedents. The lungs, liver, kidneys, all gross lesions, and all masses suspected of being tumors were examined. Tissues not processed, stained, and examined were retained. Skin at the treatment site was subsequently processed from all animals in the low- and medium-dose groups and examined microscopically.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue[1]	X Aorta*	XX Brain* (4 levels)
X Salivary glands*	X Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes* (submandibular and mesenteric)	X Pituitary*
X Duodenum*	X Spleen*	X Eyes* (optic nerve)
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	Glandular
X Colon*		
X Rectum*	XX Kidneys*	X Adrenals*
XX Liver*	X Urinary bladder*	Lacrimal gland
X Gallbladder*	XX Testes*	X Mammary gland (females only)
X Pancreas*	X Epididymides	X Thyroids* with parathyroids
	X Prostate*	X Harderian glands
Respiratory	X Seminal vesicle	
	X Ovaries*	
X Trachea*	X Uterus*	
X Lungs*	Ureters[1]	
	Urethra[1]	

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin* (treated and untreated areas)
X All gross lesions and masses*

*Recommended by Subdivision F (November 1984) Guidelines

[1]Stored tissues not examined histologically

(a) Organ Weights

Minor reductions in kidney weights were observed in treated females, but they are not considered of toxicological importance. In high-dose females, the mean absolute kidney weight was 90% of control (0.51 g) and body weight-related values (as percent of body weight) were 92% of control. Relative weights were significantly decreased ($p<0.01$) in all treated female groups. There were no corresponding changes in males.

(b) Macroscopic Pathology

No treatment-related gross findings were indicated. No apparent dose trends were seen. All of the findings were normal for the species and strain.

(c) Microscopic Pathology

Nonneoplastic: The only significant dose-related change was an increase in the incidence of minimal epidermal hyperplasia at the treated skin site. Skin was examined from all animals on test (50/group/sex). Epidermal hyperplasia was seen in 4% of mid-dose males and 20% of high-dose males compared to 0% control (significant trend and significant at $p<0.01$ by pairwise comparison). In females, the incidences were 6%, 6%, 12%, and 20% at doses of 0, 5, 15, or 40 mg/kg/day, respectively; there was a significant trend ($p=0.05$) but no significance in females using pairwise comparison. Nonneoplastic findings at other sites were not increased in dosed groups compared to controls, and no positive dose-trends were seen.

Neoplastic: Table 1 summarizes the incidence of neoplasms of the liver, lungs, and lymphoreticular system. No treatment-related increase in neoplasms at any site was observed. With the exception of these tabulated neoplasms, the majority of malignant or benign neoplasms were only observed in one or less animals per group for controls and treated animals. Leiomyosarcoma in the uterus was observed in 3/50 control females but in none of the treated animals.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study was adequately conducted and reported. None of the variations from protocol were sufficient to interfere with interpretation of results (e.g., increased temperature and humidity due to air conditioner malfunction).

The rationale for dose selection was reasonable. However, it is possible that the mice would have tolerated a higher dose since it was not obvious that any systemic toxicity was caused by dosing. The only clear effect was minimal hyperplasia of the epidermis at the site of skin application. Slight decreases in kidney weights (a decrease 30-60-mg compared to controls) were not considered related to test substance application. The incidence of neoplasms in the livers of males was similar to the range of incidence in untreated laboratory historical controls (12-20% for hepatocellular adenoma in males with a mean of 15.5%; 4-16% for hepatocellular carcinoma with a mean of 10%. Similarly, the incidence of lung tumors in both sexes and lymphoma in females were within the normal range provided for the testing laboratory (See Appendix 11 of report attached).

Under the conditions of the study, sodium omadine did not cause an increase in benign or malignant tumors at any site. However, the mice might have been able to tolerate a higher dose.

Table 1. Neoplastic Lesions in Liver, Lungs and Reticuloendothelial System of Mice Dermally Treated with Sodium Omadine for 18 Months[a,b]

Organ/Neoplasm	Topical Dose (mg/kg/day)							
	Males				Females			
	0	5	15	40	0	5	15	40
Liver	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Hepatocellular carcinoma	1	2	2	3	1	0	0	0
Hepatocellular adenoma	6	7	8	3	1	0	0	0
Adenoma/Carcinoma	7	9	10	6	2	0	0	0
Lung	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Pulmonary carcinoma	2	5	1	3	2	0	1	1
Pulmonary adenoma	7	4	4	5	3	5	2	6
Adenoma/Carcinoma	9	9	5	8	5	5	3	7
Lymphoreticular System[c]								
Malignant lymphoma	0	0	1	3	8	5	6	6
Histiocytic sarcoma	1	1	2	1	6	3	1	2

[a]Source: Study No. OLA/7/90, Appendix 8, pp 56-62

[b]The numbers in parentheses are the number of animals for which tissues were examined.

[c]For the lymphoreticular system the number of animals was 50/group.

SODIUM OMADINE

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Pages 140 through 148 are not included in this copy.

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_____ Identity of product inert ingredients.

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X FIFRA registration data.

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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.

Reviewed by: John E. Whalan JW 3-23-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner 3-23-95
Section I, Tox. Branch I (7509C)

NOTE: A study report was obtained to assess the suitability of the high-dose (40 mg/kg/day) in the main study. There is no MRID number since the study report was not officially submitted for review.

STUDY TYPE: Range-finding Study for a Dermal Carcinogenicity Study in Mice

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.9% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: N/A

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 28-Day Dermal Dose Rangefinding Study in the Mouse

AUTHOR: I.N. Robinson

STUDY NUMBER: OLA/6/87

STUDY COMPLETED: June 1987

EXECUTIVE SUMMARY: A range-finding study was performed to assist in selecting doses for the main study. Groups of 5 male and 5 female CD-1 mice were dermally dosed with Sodium Omadine 40% Aqueous Solution (41.9% purity) for 28 consecutive days at 0, 1, 5, 25, or 50 mg/kg/day.

A control male was found dead on day 8; the cause of death was not determined. A moribund high-dose male was sacrificed on day 28 when it was found laterally recumbent with partial paralysis, piloerection, incoordination, and tachypnea. It was found to have pale kidneys and a thickened brown stomach lining.

No erythema or edema was observed at the dosing sites. There were no dose-related effects on body weight, food consumption, gross pathology, or organ weights.

CORE CLASSIFICATION: Since range-finding studies are neither guideline studies nor bound by the GLP requirements, a core classification is not necessary. It is worth noting that this study received Quality Assurance review.

Discussion on Dose Selection:

There was no evidence of toxicity in the 28-day dermal mouse range-finding study other than one moribund high-dose mouse. The moribund mouse was probably a sensitive individual responding to a chemical with a steep dose response curve. If the high dose mice had been dosed over several months, it is likely one or more additional mice could have turned moribund. On the basis of this study, the laboratory determined that the high-dose in the chronic study should be between 25 and 50 mg/kg/day. A dose of 40 mg/kg/day was selected.

In a 13-week dermal rat study, a dose of 15 mg/kg/day induced atrophy of the hindlimb muscles. It was rational to expect mice to have a systemic response when given 3-times this dose (i.e. 40 mg/kg/day). Considering the test article's steep dose response, a greater dose in the mouse chronic study may have proved lethal.

JW 3-17-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner
Section I, Tox. Branch I (7509C)

Ron Gardner 3/22/95

STUDY TYPE: Guideline 83-3; Dermal Developmental Toxicity in Rabbit

CHEMICAL: Sodium Omadine 40% Aqueous Solution (43.8% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 404872-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Dermal Developmental Toxicity Study in New Zealand White Rabbits with Sodium Omadine®

AUTHOR: K.A. Keller

STUDY NUMBER: 397-044

STUDY COMPLETED: December 11, 1987

EXECUTIVE SUMMARY: In a developmental toxicity study, New Zealand White rabbits were given sodium omadine by daily dermal application for 6 hours at doses of 0, 1, 2.5, or 5 mg/kg/day on gestation days 6-19, inclusive. Although there was no evidence of maternal or fetal toxicity at any dose, the 5 mg/kg/day dose is defined as a free-standing NOEL since a range-finding dose of 7.5 mg/kg/day was frankly toxic.

CORE CLASSIFICATION: **Core Minimum.** There was no evidence of maternal or fetal toxicity. The doses were based upon a range-finding study in which rabbits were dosed at 1, 3, 7.5, 15, and 30 mg/kg/day. No toxicity was observed at 1 and 3 mg/kg/day, yet death, moribundity, and excessive maternal weight loss were observed in the other dose groups. On the basis of survival and body weight effects, a high-dose of 5 mg/kg/day in the main study appears to have been a prudent choice. The absence of maternal and fetal toxicity can be attributed to the unpredictable nature of a steep dose-response curve. A 10 mg/kg/day dose would likely have been too toxic.

Comments: The DER lacked an executive summary, so the preceding summary was generated. The Study Type is changed to include the route of administration (dermal).

The only evidence of maternal toxicity cited in the DER was dose-related changes in body weight gain of as much as 52%, yet the DER also states that, "Body weights were similar to control for all dose groups throughout the study." This reason for this apparent contradiction can be seen below. Table 1, Revised (below) includes two intervals discussed in the text of the DER but missing from DER Table 1 (DER page 6). Table 1A presents absolute body weights.

As is typical for rabbits, there was very little weight gain during gestation. Taking into account the 3% weight difference on gestation day 0, the high-dose does remained within 2% of control weights throughout gestation. When body weight gain percentages are calculated from data as stable as this, even minor variations can be profoundly exaggerated and easily misconstrued.

Table 1 (Revised)
Body Weight Gain (Δ%)

Gestation Days	0 mg/kg/day	1 mg/kg/day	2.5 mg/kg/day	5 mg/kg/day
0-6	146	144 (-1%)	137 (-6%)	158 (8%)
6-13	121	93 (-23%)	89 (-26%)	58 (-52%)
13-20	209	164 (-22%)	183 (-12%)	142 (-32%)
6-20	329	257 (-22%)	272 (-17%)	200 (-39%)
20-24	111	71 (-36%)	91 (-18%)	111 (0%)
0-29	577	535 (-7%)	510 (-12%)	528 (-8%)

Table 1A
Body Weight (Δ%)

Gestation Day	0 mg/kg/day	1 mg/kg/day	2.5 mg/kg/day	5 mg/kg/day
0	3460	3531 (+2%)	3382 (-2%)	3362 (-3%)
6	3606	3675 (+2%)	3519 (-2%)	3520 (-2%)
13	3727	3768 (+1%)	3608 (-3%)	3578 (-4%)
20	3935	3932 (0%)	3791 (-4%)	3720 (-5%)
24	4046	4003 (-1%)	3881 (-4%)	3831 (-5%)
29	4037	4058 (+1%)	3892 (-4%)	3820 (-4%)

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Developmental Toxicity (Rabbit)

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Pia Lindström Date 12/10/93
Pia Lindström, D.V.M.

Independent Reviewer Date Dec 10, 1993
Sanju Diwan, Ph.D.

QA/QC Manager Sharon A. Segal Date 12/10/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 390
Project Officer: Caroline Gordon

EPA Reviewer: Myron Ottley, Ph.D. Signature: MSOttley
Review Section IV, Toxicology Branch I/HED Date: 2/14/94

EPA Section Head: Marion Copley, D.V.M. Signature: MCopley
Review Section IV, Toxicology Branch I/HED Date: 2/24/94

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity (Rabbit); Guideline Series 83-3

EPA IDENTIFICATION NUMBERS

PC Code: 088004

Tox Chem. No.: 790 A

MRID No.: 404872-01

TEST MATERIAL: Sodium omadine

SYNONYM: Sodium pyrithione

SPONSOR: Olin Corporation, Cheshire, CT

STUDY NUMBER: 397-044

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Dermal Developmental Toxicity Study in New Zealand White Rabbits with Sodium Omadine®

AUTHOR: K.A. Keller

REPORT ISSUED: December 11, 1987

CONCLUSIONS: In a developmental toxicity study New Zealand White rabbits were administered sodium omadine via a single daily dermal application for 6 hours at doses of 0, 1, 2.5, or 5 mg/kg/day on gestation days (GDs) 6-19, inclusive.

Maternal NOEL = not determined
Maternal LOEL = 1 mg/kg/day based on decreased body weight gain

Developmental NOEL = 5 mg/kg/day
Developmental LOEL = not determined

CORE CLASSIFICATION: Minimum Data. This study meets the minimum data requirements [83-3] for a developmental toxicity study in rabbits. Although maternal body weight data were not statistically analyzed, percent decrease

below the control group was of such magnitude that clear maternal toxicity during the dosing period was demonstrated at all dose levels. Other deficiencies as noted on page 9 did not alter the classification of this study for regulatory purposes.

A. MATERIALS

Test Compound

Purity:	43.8%
Description:	Amber liquid
Sample number:	F113D
Receipt date:	December 24, 1986
Contaminants:	None reported
Storage:	Not reported

Vehicle: Deionized water

Test Animals

Species:	Rabbit
Strain:	New Zealand White
Source:	Hazleton Research Products, Inc., Denver, PA
Age:	Approximately 4.5 months on GD 0
Weight:	2968-4052 g on GD 0
Males used:	Proven males from the same source as the females

B. STUDY DESIGN

This study was designed to assess the potential of sodium omadine to cause developmental toxicity in rabbits after a single daily dermal dose on GDs 6-19, inclusive.

Mating: Following 47 days of acclimation, females were artificially inseminated with sperm collected from proven resident males. The semen was collected using an artificial vagina, examined for sperm motility, and diluted with 3 mL of 0.9% sodium chloride. Approximately 3 weeks before insemination, females were injected with 50 U.S.P. units of human chorionic gonadotropin. Immediately after insemination, females were injected with an additional 100 U.S.P. units of human chorionic gonadotropin. The day of insemination was considered to be GD 0.

Animal husbandry: Animals received food (Purina Certified Rabbit Chow® #5322) in gradually increasing amounts until approximately 2 weeks before study initiation; from this point through the end of the study, they received food ad libitum. Tap water was available ad libitum throughout the study. A 12-hour light/dark cycle was maintained. Temperature was maintained at 64°-74°F, and humidity was maintained at 38%-65%.

Group arrangement: Animals were assigned to the following dose groups using a computer-generated randomization procedure based on body weight:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	20
Low-dose	1	20
Mid-dose	2.5	20
High-dose	5	20

Dose administered: Doses were prepared as needed. Single daily dermal doses were applied from GD 6 through 19 in a volume of 3.0 mL/kg. Frequency of preparation and storage of the dosing solutions were not reported. Individual doses were calculated based on the most recently recorded body weight data. The back of each animal was clipped before administration of the test material. The test material was administered using a blunt-tip syringe, and each animal was fitted with a plastic collar immediately after application. After 6 hours of exposure, the collars were removed and the test site was blotted with absorbent tissues and water to prevent ingestion. Analysis for concentration of the dosing solutions was conducted three times throughout the study. Analyses for stability and homogeneity of the test material in the vehicle were not conducted.

Dose rationale: Doses were selected based on the results of a range-finding study in which rabbits were administered the compound dermally at dose levels of 1, 3, 7.5, 15, and 30 mg/kg/day. Maternal toxicity was manifested at ≥7.5 mg/kg/day as premature death and excessive weight loss. Developmental toxicity was not reported.

Observations: Animals were observed twice daily for mortality and moribundity, and once daily for clinical signs. In addition, animals were scored once daily for signs of dermal irritation (including erythema, edema, atonia, desquamation, fissures, coriaceousness, eschar, and exfoliation). Body weight data were recorded on GDs 0, 6, 13, 20, 24, and 29. Food consumption was not recorded. On GD 29, animals were sacrificed by an injection of sodium pentobarbital and litters were delivered by cesarean section. Examination of the does at sacrifice included the following:

- Gross pathology observations of the abdominal and thoracic cavities as well as all internal organs
- Number of corpora lutea
- Number of implantation sites
- Numbers of resorptions (early and late) and live and dead fetuses

Uteri from apparently nonpregnant animals were stained with ammonium sulfide to detect early embryonic loss.

Examination of all live fetuses included the following:

- Individual fetal weight and sex
- External anomalies
- Visceral anomalies including brain by mid-coronal slice and heart using a modification of the method described by Staples (1974)
- Skeletal anomalies using a method similar to that described by Dawson (1926)

Statistical analysis: The following methods were used.

- Sex ratio--Chi Square with Yates' correction
- Proportion of litters with malformations--Fisher's Exact test
- Proportion of dead and resorbed fetuses and postimplantation losses--Mann-Whitney U-test
- Numbers of corpora lutea, implantations, and live fetuses and mean fetal body weights--ANOVA, Bartlett's test, and t-test (as described by Steel and Torrie, 1960)

Compliance: The following statements were provided.

- A signed Statement of No Data Confidentiality Claims, dated January 8, 1987
- A signed but not dated Statement of Compliance with EPA GLPs
- A signed Quality Assurance Statement, dated December 10, 1987

C. RESULTS

Test Material Analysis

Concentration analysis revealed values ranging from 89% to 111% of target. Analyses for stability and homogeneity were not reported.

Maternal Toxicity

Mortality: No mortality was observed at any dose level.

Abortion: No compound-related abortions were observed at any dose level. One female at 1 mg/kg/day aborted on GD 25. The abortion was considered to be due to stress associated with an accidental injury. Details of the injury were not provided.

Clinical observations: No compound-related clinical signs (including dermal irritation at the application site) were observed at any dose level.

Body weight: Compound-related effects on body weight gain were observed at all dose levels. A summary of body weight gain data for selected intervals is presented in Table 1. Body weight gain was 23%, 26%, and 52% lower than control during GDs 6-13 and 22%, 12%, and 32% lower than control during GDs 13-20 at 1, 2.5, and 5 mg/kg/day, respectively (data not shown). When determined for the entire dosing period (GDs 6-20), mean body weight gain was 22%, 17%, and 39% lower than control at 1, 2.5, and 5 mg/kg/day (Table 1). Body weights were similar to control for all dose groups throughout the study. Body weight and body weight gain data were not statistically analyzed.

Gross pathology observations: No compound-related gross pathology was observed at any dose level.

Cesarean section observations: No compound-related effects were observed at any dose level. A summary of cesarean section observations is presented in Table 2.

Developmental Toxicity

No compound-related effects were observed at any dose level. A summary of external, visceral, and skeletal malformations is presented in Table 3.

External examinations: External malformations in the control group consisted of one fetus with multiple head malformations and one fetus from a different litter with spina bifida. At 1 mg/kg/day, two fetuses from the same litter had ectrodactyly. At 2.5 mg/kg/day, one fetus had syndactyly. At 5 mg/kg/day, one fetus had ethmocephaly. External variations were limited to tarsal flexure and hemorrhagic iris and occurred in the control, low-dose, and high-dose groups.

Visceral examinations: Visceral malformations in the control group consisted of one fetus with interventricular septal defect and bulbous heart. At 1 mg/kg/day, one fetus had a retroesophageal aortic arch. At 2.5 mg/kg/day, one fetus had gallbladder agenesis. At 5 mg/kg/day, one fetus had interventricular septal defect and bulbous heart and another fetus from a different litter had a missing adrenal gland. Visceral variations, occurring in all dose groups, included left carotid arising from the innominate, missing azygous lung lobes, gallbladder hypoplasia, retroesophageal right subclavian, and accessory left subclavian.

Skeletal examinations: Skeletal malformations in the control group consisted of three fetuses (two litters) with vertebral malformations with or without associated rib malformations and two fetuses (two litters) with spherical enlargement of a rib. At 1 mg/kg/day, one fetus had a rib malformation, two fetuses (two litters) had spherical enlargement of a rib, three fetuses (three litters) had interrupted ossification of a rib, one fetus had fused skull bones, and one fetus had forked scapulae. At 2.5 and 5 mg/kg/day, one fetus each had spherical enlargement of a rib. Skeletal variations, occurring in all dose groups, included bipartite/accessory skull bones, extra ribs, 7th cervical ribs, 13th rudimentary ribs, 25th and 27th presacral vertebrae, incomplete ossification of various bones, fused sternebrae, and centrum variations.

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TABLE 1. Mean Body Weight Gain (g ± s.d.) of Rabbits Exposed to Sodium Omadine during GDs 6-20[a,b]

Dose Group (mg/kg/day)	Prior to Dosing Period (GDs 0-6)	Dosing Period (GDs 6-20)	Post-Dosing Period (GDs 20-24)	Post-Dosing Period (GDs 24-29)	Gestation Period (GDs 0-29)
0	146 ± 57.2	329 ± 113.0	111 ± 74.5	-9 ± 115.0	577 ± 177.2
1	144 ± 69.3	257 ± 90.5 (22%)	71 ± 151.4	26 ± 78.3	535 ± 174.6 (7%)
2.5	137 ± 74.6	272 ± 97.1 (17%)	91 ± 103.4	11 ± 144.2	510 ± 149.0 (12%)
5	158 ± 43.2	200 ± 141.4 (39%)	111 ± 119.4	59 ± 114.1	528 ± 142.8 (8%)

[a]Data were extracted from Study No. 397-044, Table 2.

[b]Number in parenthesis represent percent decrease below control.

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TABLE 2. Cesarean Section Observations in Rabbits Exposed to Sodium Omadine during GDs 6-20[a]

Parameter	Observation for Each Dose Level (mg/kg/day) 0	1	2.5	5
No. animals mated	20	20	20	20
No. animals pregnant	17	19	17	18
Pregnancy rate (%)	85	95	85	90
Maternal wastage				
No. died/nonpregnant	0	0	0	0
No. died/pregnant	0	0	0	0
No. nonpregnant	3	1	3	2
No. aborted	0	1	0	0
Does with live litters	16	17	17	18
Total corpora lutea	192	201[b]	187	190
Corpora lutea/doe	12.0 ± 2.6	11.8 ± 2.9	11.0 ± 2.7	10.6 ± 3.6
Total implantations	126	120	124	116
Implantations/doe	7.4 ± 3.3	6.7 ± 2.4	7.3 ± 2.3	6.4 ± 2.0
Total live fetuses	113	103	116	109
Live fetuses/doe	6.6 ± 3.1	5.7 ± 2.7	6.8 ± 2.1	6.1 ± 2.0
Total resorptions	13	17	8	7
Early resorptions	11	16	6	7
Late resorptions	2	1	2	0
Resorptions/doe[c]	0.8 ± 1.3	0.9 ± 1.4	0.5 ± 0.6	0.4 ± 0.8
Total dead fetuses	0	0	0	0
Fetal weight/litter (g)	43.4 ± 7.7	45.1 ± 5.9	43.8 ± 4.6	45.6 ± 5.4
Preimplantation loss (%)	35	41	34	39
Postimplantation loss (%)	10	14	7	6
Sex ratio (% male)	51	55	44	54

[a]Data were extracted from Study No. 397-044, Table 3 and Appendix B.

[b]One doe had regressing corpora lutea and was not included in calculation.

[c]Calculated by the reviewers; not statistically analyzed

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TABLE 3. Incidences of Fetal Malformations Rabbits Exposed to Sodium Omadine during GDs 6-20[a,b,c]

Findings	Dose Level (mg/kg/day) 0	1	2.5	5
No. fetuses examined	113 (16)	103 (17)	116 (17)	109 (18)
External Malformations				
Spina bifida	1	0	0	0
Mandibular agnathia	1	0	0	0
Astomia	1	0	0	0
Aglossia	1	0	0	0
Ethmocephaly	0	0	0	1
Malpositioned nares	1	0	0	0
Ablepharia	1	0	0	0
Ectrodactyly	0	2 (1)	0	0
Syndactyly	0	0	1	0
Malformed brain	1	0	0	0
Total no. fetuses with any external malformation	2 (2)	2 (1)	1	1
Visceral Malformations				
Interventricular septal defect	1	0	0	1
Bulbous aortic arch	1	0	0	1
Retroesophageal aortic arch	0	1	0	0
Absent adrenal gland	0	0	0	1
Gallbladder agenesis	0	0	1	0
Total no. fetuses with any visceral malformation	1	1	1	2 (2)
Skeletal Malformations				
Fused skull bones	0	1	0	0
Vertebral malformation with/without an associated rib malformation	3 (2)	0	0	0
Rib malformation	0	1	0	0
Interrupted ossification of a rib	0	3 (3)	0	0
Spherical enlargement of a rib	2 (2)	2 (2)	1	1
Forked scapulae	0	1	0	0
Total no. fetuses with any skeletal malformation	5 (4)	8 (7)	1	1
Total no. fetuses with any malformation	8 (6)	10 (8)	2 (2)	3 (3)

[a]Data were extracted from Study No. 397-044, Table 4 and Appendix C.

[b]More than one type of malformation may be found in one fetus.

[c]Numbers in parenthesis indicate number of litters.

D. DISCUSSION/CONCLUSIONS

Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. All but two criteria were satisfied: food consumption data were not reported and the test material was not analyzed for stability and homogeneity.

Test Material Analyses

Analyses for concentration revealed values within ±10% of nominals. Stability and homogeneity analyses were not performed. However, concentration analyses (conducted three times during the study) indicated that the dosing solutions were stable and homogeneous for the duration of the study.

Maternal Toxicity

Compound-related maternal toxicity was observed in all dose groups as evidenced by a decrease in body weight gain during the dosing period. Consequently, the LOEL for maternal toxicity was 1 mg/kg/day; the NOEL was not determined.

Developmental Toxicity

Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity was 5 mg/kg/day; the LOEL was not determined.

Study/Reporting Deficiencies

Maternal body weight and weight gain data were not statistically analyzed. Results of such an analysis would further strengthen the conclusion of maternal toxicity at all dose levels. Gravid uterine weights were not recorded. Consequently, corrected maternal body weight and weight gain could not be calculated. Food consumption data were not reported. While this precluded a complete evaluation of toxicity, other endpoints (i.e., body weight gain) show that the test compound is toxic at the lowest dose level tested.

E. CORE CLASSIFICATION: Minimum Data

Maternal NOEL = not determined
Maternal LOEL = 1 mg/kg/day (based on decreased body weight gain)

Developmental Toxicity NOEL = 5 mg/kg/day
Developmental Toxicity LOEL = not determined

F. RISK ASSESSMENT: Not applicable

ATTACHMENT I

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83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	YES	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	YES	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	Y/N	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	YES	Individual daily observations.
8.	YES	Individual body weights.
9.	NO	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	YES	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with an asterisk (*) are supplemental, may not be required for every study.

JW 3-23-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner
Section I, Tox. Branch I (7509C)

Roger Gardner 3/23/95

NOTE: A study report was requested to substantiate a free-standing NOEL of 5 mg/kg/day in the main study. There is no MRID number since the study report was not officially submitted for review.

STUDY TYPE: Range-finding Study for a Dermal Developmental Toxicity in Rabbit

CHEMICAL: Sodium Omadine 40% Aqueous Solution (purity not reported)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: N/A

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Range-Finding Dermal Developmental Toxicity Study in New Zealand White Rabbits with Sodium Omadine®

AUTHOR: Not reported.

STUDY NUMBER: 397-043

STUDY COMPLETED: July 21, 1987

EXECUTIVE SUMMARY: A range-finding study was performed to assist in selecting doses for the main study. The protocol for the range-finding study resembled the main study. Groups of 5 pregnant New Zealand White SPF rabbits were assigned to 6 groups. They were dermally dosed by non-occlusive topical application between gestation days 6 and 19 at doses of 0 (water control), 1, 3, 7.5, 15, and 30 mg/kg/day. A toxic response at 7.5 mg/kg/day could justify defining 5 mg/kg/day as a free-standing NOEL in the main study.

Clinical signs observed in the 7.5 mg/kg/day group included stools that were small, absent, or soft; stained nose, mouth, and/or anogenital area; alopecia; and excessive salivation. No gross lesions were found in this group. All groups, including controls, had dermal lesions.

CORE CLASSIFICATION: Since range-finding studies are neither guideline studies nor bound by the GLP requirements, a core classification is not necessary. It is worth noting that this study received Quality Assurance review. The study report listed moribundity, unsteady gait, convulsions, loss of righting reflex, and labored breathing as clinical signs in the 7.5 mg/kg/day group; this is an error.

Discussion on Dose Selection:

The patterns of mortality and moribundity were as follows:

	Dermal Dose (mg/kg/day)					
	0	1	3	7.5	15	30
Died/sacrificed *in extremis*	0	0	0	1	2	4
Moribund	0	0	0	0	1	1

The following table presents the body weights during gestation in the range-finding study. The 1 and 3 mg/kg/day groups were virtually unaffected. The 7.5 mg/kg/day group weights decreased by 11% between gestation days 6 and 13, compared to the controls. After dosing ceased, this group regained its weight. A similar response was seen in the 15 mg/kg/day group. The 30 mg/kg/day group had significantly greater decreases in weight.

	Dermal Dose (mg/kg/day)					
Gestation Day	0	1	3	7.5	15	30
0	3912	3850 (-2%)	4108 (+5%)	4310 (+10%)	4036 (+3%)	4275 (+9%)
6	3974	3958 (0%)	4361 (+10%)	4550 (+14%)	4314 (+9%)	4351 (+9%)
13	4017	3994 (-1%)	4276 (+6%)	4121 (+3%)	4057 (0%)	3900 (-3%)
20	3883	3939 (+1%)	4152 (+7%)	4002 (+3%)	3931 (+1%)	3360 (-13%)
24	3839	3940 (+3%)	4202 (+9%)	4138 (+8%)	3914 (+2%)	3237 (-16%)
29	3732	3929 (+5%)	4134 (+11%)	4262 (+14%)	4038 (+8%)	3090 (-17%)

As stated in the range-finding study final report, "Premature deaths and substantial weight loss in the 7.5, 15, and 30 mg/kg/day groups precluded selection of these dosage levels for

a developmental toxicity study. No maternal toxicity was noted at the 1 and 3 mg/kg/day levels." On the basis of survival and body weight effects, a high-dose of 5 mg/kg/day in the main study appears to be a prudent choice. The absence of maternal and fetal toxicity can be attributed to the unpredictable nature of a steep dose-response curve. A 10 mg/kg/day dose would likely have been too toxic.

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Reviewed by: John E. Whalan JW 3-17-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner
Section I, Tox. Branch I (7509C) 3/22/95

STUDY TYPE: Guideline 83-4; Gavage Reproductive Toxicity in Rats

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.2% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410972-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: Sodium Omadine Rat Two-Generation Reproduction Toxicity Study

AUTHOR: P. Ridgway and C.M. Wood

STUDY NUMBER: CLA/9/88

STUDY COMPLETED: January 24, 1989

EXECUTIVE SUMMARY: In a two-generation reproduction study, Crl:CD(SD)BR rats received Sodium Omadine 40% Aqueous Solution (41.2% purity) by gavage at dose levels of 0, 0.5, 1.5, or 3.5 mg/kg/day. The highest dose level was changed from 4.5 mg/kg/day to 3.5 mg/kg/day after 3 weeks of dosing because of marked toxicity at 4.5 mg/kg/day.

Parental NOEL = 0.5 mg/kg/day
Parental LOEL = 1.5 mg/kg/day in females, and 3.5 mg/kg/day in males based on increased incidence of histologic atrophy in the upper hindlimb skeletal muscles (reduction in fiber diameter) in F_1 females (3/25), F_0 males (7/23), and F_1 males (9/25).

Additional parental effects seen at 3.5 mg/kg/day included increased histologic atrophy in the upper hindlimb skeletal muscles in F_0 females (19/24), and F_1 females (20/23); and significantly decreased body weight in F_0 and F_1 females.

Reproductive NOEL = 1.5 mg/kg/day
Reproductive LEL = 3.5 mg/kg/day based on slightly decreased number of pups per litter born in both generations (possibly a consequence of reduced mating success due to

hindlimb atrophy), delayed development in pups from both generations (including open ears and eyes and startle response), and decreased pup body weight and weight gain in both sexes.

CORE CLASSIFICATION: **Minimum** data. Test article homogeneity and stability were not reported. A parental NOEL was not determined.

Comments: The DER lacked an executive summary, so the preceding summary was generated. The study classification can be found in two locations in the DER — pages 2 and 12. On page 2, the study is listed as "Core Supplementary Data — Upgradable" because of the lack of homogeneity and stability analyses, and historical control data. On page 12, it is listed as "Minimum Data" without further qualifications.

The DER requested that historical data be submitted in hopes of explaining anomalies in male mating and fertility indices in the F_0 high-dose males and all the F_1 male groups, and in the number of pups born per high-dose litter. Upon further evaluation and discussion with Roger Gardner, it is apparent that historical data would add little insight. Atrophy of the hindlimb muscles in males could potentially have a profound effect on mating success. Although the mating and fertility indices for the F_0 males was reduced, it was within the range seen in all the F_1 male groups. The number of pups born per high-dose litter was slightly reduced, but not enough to be considered a dose-related effect.

The DER also cited the lack of homogeneity and stability analyses. Although this information should have been included in the study report, it is obvious from other studies of the same product that homogeneity and stability were not a problem.

The Parental NOEL and LOEL values differ from the original DER. They were changed at the request of the RfD Peer Review Committee because excessive salivation was not considered to be definitive evidence of neurotoxicity. The core classification for this study is **Core Minimum.**

The penned corrections added by the secondary reviewer read as follows:

Page 11: No historical control data were submitted (mating indices - males, number of pups born/litter).

FINAL

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DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer Pia Lindström Date 12/10/93
Pia Lindström, D.P.H.

Independent Reviewer Sanju Diwan Date Dec 10, 1993
Sanju Diwan, Ph.D.

QA/QC Manager Sharon Segal Date 12/10/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 391
Project Officer: Caroline Gordon

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Guideline Series 83-4: Reproductive Toxicity

EPA Reviewer: Myron Ottley, Ph.D.
Review Section IV, Toxicology Branch I/HED
Signature: MS Ottley
Date: 2/14/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I/HED
Signature: M. Copley
Date: 2/24/94

DATA EVALUATION REPORT

STUDY TYPE: Reproductive Toxicity; Guideline Series 83-4

EPA IDENTIFICATION NUMBERS

PC Code: 088004

TOX CHEM. NUMBER: 790 A

MRID NUMBER: 410972-01

TEST MATERIAL: Sodium omadine

SYNONYM: Sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

STUDY NUMBER: OLA/9/88

TESTING FACILITY: Toxicol Laboratories Limited, Herefordshire, England

TITLE OF REPORT: Sodium Omadine Rat Two-Generation Reproduction Toxicity Study

AUTHORS: P. Ridgway and C.M. Wood

REPORT ISSUED: January 24, 1989

CONCLUSIONS: In a two-generation reproduction study, Crl:CD(SD)BR rats received sodium omadine by gavage at dose levels of 0, 0.5, 1.5, or 3.5 mg/kg/day. The highest dose level was changed from 4.5 mg/kg/day to 3.5 mg/kg/day after 3 weeks of dosing because of marked toxicity at 4.5 mg/kg/day.

Parental NOEL = not determined
Parental LOEL = 0.5 mg/kg/day based on excessive salivation after dosing

Additional parental effects included increased atrophy of hindlimb muscles in F_0 males, F_0 females, and F_1 males (3.5 mg/kg/day) and F_1 females (3.5 and 1.5 mg/kg/day) and significantly decreased body weight in F_0 females and F_1 females (3.5 mg/kg/day).

Reproductive NOEL = 1.5 mg/kg/day
Reproductive LOEL = 3.5 mg/kg/day based on a slightly decreased number of pups per litter born in both generations and delayed development (open ears and eyes and startle response) in pups from both generations.

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CLASSIFICATION: Core Supplementary Data - Upgradable. This study does not meet the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats because results from homogeneity and stability analyses were not reported and no historical control data were submitted. The submitter may wish to supply the missing information, at which time the Agency may reevaluate the data. (see p. 11)

A. MATERIALS

Test Compound

Purity:	41.2%
Description:	Transparent amber liquid
Batch number:	8508-P-166H
Date received:	February 3, 1987
Contaminants:	None reported
Storage:	Ambient temperature

Vehicle: Distilled water

Test Animals

Species:	Rat
Strain:	Crl:CD(SD)BR
Source:	Charles River (UK) Limited, Margate, England
Age:	Six weeks at receipt
Weight:	F_0 males--225-258 g on week 1
	F_0 females--171-196 g on week 1

B. STUDY DESIGN

This study was designed to assess the potential of sodium omadine to cause reproductive toxicity when administered continuously by gavage for two successive generations.

Mating: After 10 days of acclimatization followed by 11 weeks of daily dosing via gavage, F_0 females were mated with males from the same group in a ratio of 1:1 until sperm was observed in a vaginal smear. All females that did not mate within the first 7 days were mated with a different male (that had previously mated) from the same group for a maximum of 14 days. After 17 weeks of treatment, F_1 animals were mated in the same manner as F_0 animals. Sibling matings were avoided.

Animal husbandry: All females were vaccinated against Sendai virus. Rodent diet (SQC R and M No.3 Breeder diet) and tap water were available *ad libitum*. Temperature and humidity were maintained at 22°±3°C and 50%±20%, respectively. There were at least 16 air changes per hour and a 12-hour light/dark cycle was maintained.

Group arrangement: F_0 animals were distributed using a stratification technique based on body weights. The groups were as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	25	25	25	25
Low dose	0.5	25	25	25	25
Mid dose	1.5	25	25	25	25
High dose	4.5/3.5[a]	25	25	25	25

[a]The highest dose level was changed from 4.5 mg/kg/day to 3.5 mg/kg/day after 3 weeks of dosing because of marked toxicity at 4.5 mg/kg/day (decreased body weight gain and increased clinical signs).

Dose administered: The test material was dissolved in distilled water and administered by gavage at a volume of 10 mL/kg body weight for two consecutive generations. Dosing solutions were prepared weekly (storage conditions were not reported). Analysis for concentration of the dosing solutions was performed every three weeks throughout the study. Analyses for homogeneity and stability were not reported although the protocol stated that stability was to be tested prior to study initiation.

Dose rationale: Doses were selected based upon the results of a range-finding study (Study No. OLA/8/87). The results of this study were not presented.

Observations: Observations were made daily for mortality, moribundity and clinical signs of toxicity. Body weight and food consumption data were recorded weekly for males and weekly during premating, on gestation days (GDs) 0, 7, 14, and 20, and on lactation days (LDs) 0, 7, 14, and 21 for females.

The following data were recorded for each litter:

- External physical anomalies
- Clinical signs, litter size, and confirmation of sex daily
- Individual pup weight at birth and on LDs 4, 7, 14, and 21
- Developmental landmarks (opening of ears on LD 3, static righting reflex on LD 5, and opening of the eyes and startle response on LD 15)

Pregnancy status of apparently non-pregnant females was confirmed by abdominal palpation.

On Day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups, stillborn pups, and pups dying during lactation were subjected to gross necropsy. Twenty-five male and 25 female F_1 pups were randomly selected as F_1 parental animals. Twenty randomly selected

females from the control group were test mated with F_1 males that had failed to mate.

Parental females were sacrificed and necropsied after weaning of their respective litters. Parental males were sacrificed and necropsied following the mating period. The following tissues were preserved in 10% formalin and processed for histological examination from animals in the control and high-dose groups and from any animal which failed to mate. Histological examination was also performed on testes from all F_0 males and on skeletal muscle from all animals in both sexes and generations.

- Vagina
- Uterus
- Ovaries
- Testes
- Epidiymides
- Skeletal muscle
- Coagulating gland
- Pituitary gland
- Prostate
- Seminal Vesicles
- Epididymides

In addition, brain, sciatic nerve, spinal cord and paravertebral muscles were preserved from all animals. These tissues from control and high-dose groups were processed for histological examination after a 90-day study in rats with sodium omadine demonstrated neurotoxicity and effects on skeletal muscle.

Statistical analysis: The following analyses were conducted.

- Body weight, food consumption, gestation length, total number of pups born, developmental landmarks, and pup body weight--ANOVA and Student's t test
- Mating, fertility, and gestation indices and number of estrous cycles required for mating--Fisher's exact test
- Live birth, viability, lactation, and cumulative survival indices and sex ratios--Kruskal-Wallis test

Compliance: The following statements were provided.

- A signed Statement of No Data Confidentiality Claims, dated March 23, 1989
- A signed Statement of Compliance with EPA, OECD, and UK Compliance Programme GLPs dated February 2, 1989
- A signed Quality Assurance Statement, dated February 2, 1989

C. RESULTS

Test Material Analysis

Analyses of dosing solutions revealed concentrations ranging from 94.4% to 111.1% of target. Homogeneity and stability analyses were not reported.

Parental Toxicity

Mortality: Mortalities/moribund sacrifices were observed at 3.5 mg/kg/day in females from both generations and were probably compound related. In the F_0 generation, one female was sacrificed moribund on day 87 after demonstrating the following clinical signs: hunched posture; abdominal, peri-orbital, and peri-nasal staining; impaired hindlimb mobility; and rapid breathing. Incidental deaths consisted of two males from the control group for which no clinical signs were observed prior to death.

In the F_1 generation, two females at 3.5 mg/kg/day were sacrificed moribund, one on day 225 and one on day 235. Prior to sacrifice, both females exhibited hindlimb paralysis, emaciation, ataxia, hunched posture, and increased respiration rate. Incidental deaths consisted of one male and one female from the control group that died 3 and 4 days respectively, after weaning. These animals were immediately replaced.

Clinical observations: Compound-related clinical signs were observed in a dose-related manner in both sexes and all dose groups. In the F_0 generation, excessive salivation after dosing was observed in 8, 25, and 25 males and 1, 25, and, 25 females at 0.5, 1.5, and 3.5 mg/kg/day, respectively.

In the F_1 generation, excessive salivation after dosing was observed in all males and females at 1.5 and 3.5 mg/kg/day. In addition, two females at 3.5 mg/kg/day experienced emaciation, slight ataxia, hunched posture, and/or increased respiration rate.

Body weight: Compound-related effects in body weight were observed at 3.5 mg/kg/day in females of both generations. Summaries of body weight data for selected intervals are presented in Tables 1, 2, and 3. Detailed results are discussed below. Body weight gain data were not provided.

In the F_0 generation among males at 3.5 mg/kg/day, body weight was significantly below control (91%-97%) starting at week 3 and continuing through the end of the study. Among females at 3.5 mg/kg/day, body weight was significantly below control for weeks 3-9 and 12 of premating (90%-96%); on GDs 7, 14, and 20 (91%-92%); and on LDs 0, 7, 14, and 21 (92%-94%).

In the F_1 generation among males, no significant differences between groups were noted in body weight. Among females at 3.5 mg/kg/day, body weight was significantly below control for weeks 4-5 and 14-17 of premating (92%-95%); on GDs 0, 7, 14, and 20 (88%-91%); and on LDs 0, 7, 14, and 21 (90%-94%).

Food consumption: No compound-related effects on food consumption (g/animal/day) were observed in either sex or generation. Sporadic deviations from control were noted in most dose groups but were not considered to be biologically relevent. In the F_1 females at 3.5 mg/kg/day, food consumption was significantly below control for weeks 12-16 of premating. A similar decrease was not noted in F_1 males

Table 1. Body Weight (g ± S.D.) During the Premating Period for Rats Receiving Sodium Omadine for Two Successive Generations[a]

Week of Treatment	Mean Body Weights at Each Dose Level (mg/kg/day) 0	0.5	1.5	3.5
F_0 Males				
1	242 ± 9	242 ± 9	242 ± 9	242 ± 9
2	279 ± 12	280 ± 13	285 ± 11	281 ± 14
4	364 ± 13	359 ± 22	368 ± 18	351 ± 23*
8	447 ± 24	443 ± 38	453 ± 31	422 ± 39**
11	495 ± 30	488 ± 44	503 ± 41	462 ± 42**
F_0 Females				
1	183 ± 7	183 ± 6	183 ± 7	183 ± 6
2	196 ± 8	198 ± 8	197 ± 8	198 ± 10
4	220 ± 11	221 ± 11	221 ± 12	202 ± 19***
8	253 ± 17	257 ± 18	256 ± 18	241 ± 21*
11	263 ± 18	269 ± 20	269 ± 22	256 ± 23
F_1 Males[b]				
4	53 ± 5	54 ± 5	52 ± 7	50 ± 5
8	265 ± 27	269 ± 33	268 ± 27	264 ± 27
11	379 ± 31	385 ± 46	387 ± 33	374 ± 31
14	437 ± 37	451 ± 52	453 ± 39	434 ± 37
17	487 ± 38	503 ± 58	504 ± 43	474 ± 46
F_1 Females[b]				
4	50 ± 6	52 ± 6	48 ± 5	46 ± 5**
8	186 ± 17	185 ± 16	186 ± 20	184 ± 14
11	233 ± 21	233 ± 20	235 ± 26	225 ± 17
14	261 ± 24	260 ± 20	265 ± 34	247 ± 19*
17	277 ± 26	276 ± 21	286 ± 42	255 ± 23*

[a]Data were extracted from Study No. OLA/9/88, Tables 1, 2, 10, and 11.

[b]Week of treatment also refers to age of animals.

*Significantly different from control ($p \leq 05$)

**Significantly different from control ($p \leq 0.01$)

***Significantly different from control ($p \leq 0.001$)

Table 2. Body Weight (g ± S.D.) During Gestation for Rats Receiving Sodium Omadine for Two Successive Generations[a]

Gestation Day	Mean Body Weights at Each Dose Level (mg/kg/day) 0	0.5	1.5	3.5
F_0 Generation-F_1 litters				
0	266 ± 17	276 ± 19	275 ± 23	251 ± 16
7	282 ± 19	294 ± 20	288 ± 26	260 ± 18**
14	307 ± 19	318 ± 21	309 ± 26	279 ± 15***
20	365 ± 22	379 ± 25	362 ± 30	332 ± 21***
F_1 Generation-F_2 litters				
0	276 ± 27	270 ± 18	275 ± 22	252 ± 24**
7	295 ± 28	290 ± 21	293 ± 27	264 ± 26***
14	318 ± 29	312 ± 21	317 ± 28	281 ± 24***
20	369 ± 31	372 ± 27	371 ± 40	330 ± 26***

[a]Data were extracted from Study No. OLA/9/88, Tables 2 and 11.

*Significantly different from control ($p \leq 0.05$)

**Significantly different from control ($p \leq 0.01$)

***Significantly different from control ($p \leq 0.001$)

Table 3. Body Weight (g ± S.D.) During Lactation for Rats Receiving Sodium Omadine for Two Successive Generations[a]

Lactation Day	Mean Body Weight at Each Dose Level (mg/kg/day) 0	0.5	1.5	3.5
F_0 Generation-F_1 litters				
0	287 ± 22	293 ± 29	293 ± 23	269 ± 20*
7	300 ± 17	311 ± 23	301 ± 22	279 ± 15**
14	311 ± 18	320 ± 22	308 ± 20	285 ± 17***
21	300 ± 19	311 ± 24	302 ± 18	290 ± 16
F_1 Generation-F_2 litters				
0	296 ± 27	297 ± 27	301 ± 30	272 ± 28**
7	311 ± 23	312 ± 23	305 ± 26	280 ± 24***
14	320 ± 23	327 ± 24	318 ± 27	293 ± 22***
21	308 ± 24	313 ± 22	304 ± 29	290 ± 20*

[a]Data were extracted from Study No. OLA/9/88, Tables 2 and 11.

*Significantly different from control ($p \leq 0.05$)

**Significantly different from control ($p \leq 0.01$)

***Significantly different from control ($p \leq 0.001$)

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or in F_0 males or F_0 females. Therefore, this decrease was not considered to be toxicologically important.

Gross pathology: Compound-related gross findings were observed in females that were sacrificed moribund during the study (one F_0 female and two F_1 females at 3.5 mg/kg/day). These animals exhibited wasting of the hindlimb muscles.

Histopathology: Compound-related histopathological findings were observed in both sexes and generations at 3.5 and 1.5 mg/kg/day. They were manifested as skeletal muscle atrophy in the upper hindlimb (reduction and variation in the diameter of muscle fibers, increase in the number of sarcolemmal nuclei, and fatty replacement of muscle fibers). At 3.5 mg/kg/day, 7 F_0 males, 19 F_0 females, 9 F_1 males, and 20 F_1 females exhibited this kind of atrophy. At 1.5 mg/kg/day, 3 F_1 females exhibited the same finding.

Reproductive Toxicity

Compound-related reproductive effects were observed in both generations at 3.5 mg/kg/day. Summaries of reproductive parameters are presented in Tables 4 and 5.

In the F_0 generation (Table 4) at 3.5 mg/kg/day, mating and fertility indices decreased below control in both sexes but attained statistical significance in males only. In addition, the number of estrous cycles per mating in females increased at this same dose level. The number of pups born per litter (including dead and alive pups) decreased nonsignificantly at 3.5 mg/kg/day (data not shown). Pup body weight decreased slightly by LD 21 at 3.5 mg/kg/day in both sexes. Selected developmental landmarks were affected in pups at 3.5 mg/kg/day (data not shown). The mean percentage of pups with ears open on LD 3 and eyes open on LD 15 decreased nonsignificantly by 19% and 7%, respectively, while the mean percentage of pups with startle response on LD 15 decreased significantly ($p<0.01$) by 10%.

In the F_1 generation (Table 5), the male mating indices in all dose groups were reported to be below normal for this laboratory, and the number of estrous cycles per mating was above normal. The number of pups born per litter (including dead and alive pups) decreased nonsignificantly at 3.5 mg/kg/day (data not shown). Pup body weight decreased slightly by LD 21 at 3.5 mg/kg/day in both sexes. Selected developmental landmarks were delayed in pups at 3.5 mg/kg/day (data not shown). The mean percentage of pups with startle response on LD 15 and eyes open on LD 15 decreased non-significantly by 13% and 14%, respectively.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses

Concentrations of the dosing solutions were within ±11% of nominal values. Homogeneity and stability analyses were not submitted.

Table 4. Effects of Oral Administration of Sodium Omadine on F_0 Reproductive Parameters and F_1 Offspring Survival and Body Weight[a]

Parameter	Dose level (mg/kg/day) 0	0.5	1.5	3.5
No. matings, males	23	25	25	24
females	25	25	25	24
Mating index (%), males[b]	96	96	84	71*
females	96	96	92	88
Fertility index (%), males[c]	96	92	95	71*
females	96	92	96	76
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	21.9	22.1	22.2	22.1
No. estrous cycles per mating	1.04	1.00	1.17	1.29
No. females with liveborn pups[e]	23	22	22	16
Total no. live pups[e]				
Day 0	253	273	239	159
Day 4	228	236	232	154
Day 21	166	156	169	116
Mean no. live pups/litter[e]				
Day 0	11.0	12.4	10.9	9.9
Day 4	9.9	10.7	10.5	9.6
Day 21	7.2	7.1	7.7	7.3
Live birth index (%)[f]	97	99	97	96
Viability index (%)[g]	90	88	97	97
Lactation index (%)[h]	95	99	99	94
Mean pup body weight (g), males				
Day 0	5.9	6.1	6.2	6.3
Day 7	14.7	15.2	14.9	14.9
Day 21	49.1	51.8	48.4	47.9
Mean pup body weight (g), females				
Day 0	5.6	5.8	5.9	5.8
Day 7	14.2	14.8	14.2	13.6
Day 21	47.4	49.8	46.3	44.8
Sex ratio (% males at birth)	49	48	54	58

[a]Data were extracted from Study No. OLA/9/88, Tables 5, 7, and 8 and Appendix 9.

[b]Mating index: Percentage of animals mating

[c]Fertility index: Percentage of matings resulting in pregnancy

[d]Gestation index: Percentage of pregnant females with live litters

[e]Calculated by the reviewers; not statistically analyzed

[f]Live birth index: Percentage of pups born alive based on no. of total pups born

[g]Viability index: Percentage of pups surviving 4 days based on no. of pups on day 1

[h]Lactation index: Percentage of pups surviving 21 days based on no. of pups on day 4 postcull

Table 5. Effects of Oral Administration of Sodium Omadine on F_1 Reproductive Parameters and F_2 Offspring Survival and Body Weight[a]

Parameter	Dose Level (mg/kg/day) 0	0.5	1.5	3.5
No. matings, males	25	25	25	24
females	25	25	25	23
Mating index (%), males[b]	76	60	72	58
females	100	84	96	96
Fertility index (%), males[c]	95	80	72	93
females	92	86	79	91
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.4	22.2	22.3	22.3
No. estrous cycles per mating	1.46	1.48	1.50	1.68
No. females with liveborn pups[e]	23	18	19	20
Total no. live pups[e]				
Day 0	244	205	205	194
Day 4	176	172	161	160
Day 21	126	123	113	130
Mean no. live pups/litter[e]				
Day 0	10.6	11.4	10.8	9.7
Day 4	7.7	9.6	8.5	8.0
Day 21	5.5	6.8	5.9	6.5
Live birth index (%)[f]	94	98	93	97
Viability index (%)[g]	68	84	82	83
Lactation index (%)[h]	99	94	94	99
Mean pup body weight (g), males				
Day 0	5.9	6.0	6.2	6.1
Day 7	14.1	14.7	13.7	13.9
Day 21	47.3	48.6	46.0	45.2
Mean pup body weight (g), females				
Day 0	5.6	5.6	5.6	5.8
Day 7	13.4	13.7	13.3	13.3
Day 21	46.4	45.3	44.0	42.1
Sex ratio (% males at birth)	53	53	50	48

[a]Data were extracted from Study No. OLA/9/88, Tables 14, 16, and 17 and Appendix 23.

[b]Mating index: Percentage of animals mating

[c]Fertility index: Percentage of matings resulting in pregnancy

[d]Gestation index: Percentage of pregnant females with live litters

[e]Calculated by the reviewers; not statistically analyzed

[f]Live birth index: Percentage of pups born alive based on no. of total pups born

[g]Viability index: Percentage of pups surviving 4 days based on no. of pups on day 1

[h]Lactation index: Percentage of pups surviving 21 days based on no. of pups on day 4 postcull

Parental Toxicity

Parental compound-related toxicity was observed in a dose-related manner in all dose groups. Although both sexes were affected, females appeared to be more sensitive to adverse effects than males as evidenced by affected females at 3.5 mg/kg/day that were sacrificed moribund. Toxicity was manifested as follows: increased clinical signs in both sexes at all dose levels in the first generation and at 3.5 and 1.5 mg/kg/day in the second generation; decreased body weight primarily in females of both generations at 3.5 mg/kg/day; increased gross pathology (wasting of hindlimb muscles) in females of both generations at 3.5 mg/kg/day; and increased histopathology (atrophy of hindlimb muscles) in both sexes and generations at 3.5 and 1.5 mg/kg/day. The decreased body weight in F_0 males was treatment related as well. However, when the dose was lowered after three weeks to 3.5 mg/kg/day from 4.5 mg/kg/day, this effect was no longer evident (i.e., in F_1 males).

Based on these results, the LOEL for parental toxicity was 0.5 mg/kg/day; the NOEL was not determined.

Reproductive Toxicity

Compound-related reproductive toxicity was observed at the highest dose level. Decreased pup body weights were observed in both generations on LD 21. Although the decreases were not significant and were <10%, they may have impacted negatively upon the development of the pups as evidenced by the selected developmental landmarks that were affected in males and females of both generations.

The significantly decreased mating and fertility indices in F_0 males were probably a result of the higher dose (4.5 mg/kg/day) given for the first three weeks. A similar effect was not noted at the highest dose level in the second generation (who consistently received 3.5 mg/kg/day). The mating indices among F_1 males though, should be compared to the laboratory's historical control data since they were unusually low in all dose groups including the control group.

The nonsignificant decrease in the number of pups born per litter (both generations at 3.5 mg/kg/day) should be compared to historical data for a determination of biolcgical significance.

Based on delayed pup development in both sexes and an equivocal effect on number of pups born per litter, the NOEL and LOEL for reproductive toxicity were 1.5 and 3.5 mg/kg/day, respectively.

Study/Reporting Deficiencies

Results from homogeneity and stability analyses were not reported. No historical control data were submitted (mating indices - males, number of pups born/litter).

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E. CORE CLASSIFICATION: Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats.

Parental NOEL = not determined
Parental LOEL = 0.5 mg/kg/day based on clinical signs (excessive salivaton)

Reproductive NOEL = 1.5 mg/kg/day
Reproductive LOEL = 3.5 mg/kg/day based on dolayed development in pups

F. RISK ASSESSMENT: Not applicable

Reviewed by: John E. Whalan JW 3-17-95
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 3/22/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 83-5; Chronic Oral Toxicity/Carcinogenicity in Rats

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.2% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 421009-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Toxicol Laboratories Limited, Ledbury, England

TITLE OF REPORT: 104-Week Oral (Gavage) Combined Carcinogenicity and Toxicity Study in the Rat

AUTHOR: R.F.A. Husband, A.J. Newman, and P.N. Lee

STUDY NUMBER: OLA-3-90

STUDY COMPLETED: May 28, 1991

EXECUTIVE SUMMARY: Sodium Omadine 40% Aqueous Solution (41.2% purity) was administered daily by oral gavage to groups of 70 Crl:CD(SD)BR Sprague-Dawley rats/sex at dosage levels of 0, 0.5, 1.5, or 5.0 mg/kg/day for 2 years. The highest dose was reduced to 3.5 mg/kg/day after 12 weeks because of excessive weight loss in females.

NOEL = 0.5 mg/kg/day
LOEL = 1.5 mg/kg/day based on significant increases in the incidence of degeneration of the skeletal muscle of the hindlimbs in both sexes.

At the highest dose tested (5.0/3.5 mg/kg/day) there was a significant decrease in mean body weight (as much as 10%) and body weight gain in females throughout the study; a marked increase in nerve fiber degeneration in the sciatic nerve and spinal cord in both sexes; and an increased incidence of retinal atrophy in both sexes. Under the conditions of the study, no increase in neoplasms was observed at any site. Dosing was considered adequate to assess carcinogenicity.

CORE CLASSIFICATION: **Core Guideline.** The study satisfies the requirements (Guideline Series 83-5) for a combined chronic/carcinogenicity study in rodents.

Comments: The DER lacked an executive summary, so the preceding summary was generated. The chemical structure on page 2 of the DER is incorrect.

TABLE 1. Representative Results of the Unscheduled DNA Synthesis (UDS) Rat Hepatocyte Assay with Sodium Omadine®

Treatment	Dose/mL	Number of Cells Scored/ Group	Net Nuclear Grains[a]	Percent of Cells in Repair (≥5 Net Nuclear Grains)
Negative Control				
Distilled water	--	150	-14.5±5.7	0
Positive Control				
2-Acetamido-flourene	$1x10^{-7}$ M	150	19.2±9.2[b]	100
Test Material				
Sodium Omadine®	22 (-)[c] ng[d]	150	-14.3±7.1	1
	71 (80) ng	150	-12.5±6.3	0
	220 (300) ng	150	-7.5±6.3	3

[a]Mean and standard deviations of net nuclear grain counts for 150 cells; 50 cells from each of three slides per group were analyzed.
[b]Fulfills the reporting laboratory's criteria for an acceptable positive control (i.e., mean net nuclear grain count ≥ 5 over the vehicle control)
[c]Doses in () are the analytically determined values and (-) corresponds to values that were below the limit of detection.
[d]The results from a lower dose [7.1 (-) ng/mL] did not suggest a genotoxic effect.

Note: Data were extracted from the report pp. 13, 28, 35, 42, 49, and 56.

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 85-1; Metabolism in Rats

CHEMICAL: ^{14}C-sodium omadine (>98% purity) and sodium omadine (41.4% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 412690-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Arthur D. Little, Inc., Acorn Park, Cambridge, MA 02140

TITLE OF REPORT: Sodium Omadine® Disposition and Metabolism in Rats after Oral and Intravenous Administration

AUTHOR: Marjory Chadwick, Denise M. Silveira, Madeline F. McComish, and Amin A. Nomeir

STUDY NUMBER: ADL 59798A

STUDY COMPLETED: August 25, 1989

EXECUTIVE SUMMARY: The absorption, distribution, metabolism, and excretion of sodium omadine were studied in groups of Sprague-Dawley rats administered a single oral dose of 0.5 or 25 mg/kg ^{14}C-sodium omadine, 0.5 mg/kg/day of sodium omadine for 14 days followed by a single oral dose of ^{14}C-sodium omadine (0.5 mg/kg), or a single (i.v.) dose of 0.5 mg/kg ^{14}C-sodium omadine.

Sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing levels. Total recovery of administered radioactivity was 85%-95% at 4 days postexposure. The urine is the major route of excretion of sodium omadine (73-85% of the dose); the feces are only a minor route of excretion (5-12% of the dose). Sodium omadine and its metabolites were not excreted in expired air.

In the single oral low-dose group and the i.v.-dose group, most of the administered radioactivity was excreted within the first 12 hours postdosing. In the repeated oral low-dose group and in the single oral high-dose group, the majority of the administered radioactivity

was excreted within 24 and 48 hours postdosing, respectively. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues.

The metabolic profiles in the urine were similar in all dose groups; 12 urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-S-glucuronide (Metabolite K) (41.4%-67.2% of the recovered radioactivity), while unchanged parent compound was not detected in the urine.

CORE CLASSIFICATION: **Supplementary** - upgradable. This study alone does not satisfy the minimum guideline requirements (85-1) for a general metabolism study. The study authors need to account for the unrecovered radioactivity, attempt to characterize the fecal metabolites, and propose a metabolic pathway for sodium omadine.

Comments: The penned corrections added by the secondary reviewer read as follows:

CORE CLASSIFICATION: **Supplementary** - upgradable.

011532

FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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Fairfax, VA 22031-1207

Primary Reviewer	Jessica Kidwell, M.S.	10/19/93 Date
Independent Reviewer	Karen Gan, M.S.	10/19/93 Date
QA/QC Manager	Sharon Segal, Ph.D.	10/19/93 Date

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Numbers: 407
Project Officer: Caroline Gordon

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GUIDELINE SERIES 85-1: Metabolism

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Date: 11/30/93

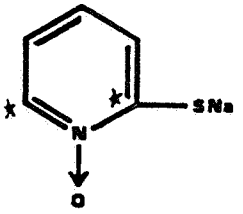
DATA EVALUATION REPORT

STUDY TYPE: Metabolism in rats (Guideline Series 85-1)

EPA IDENTIFICATION NUMBERS

Tox. Chem. No.: 790A
MRID No.: 412690-01
PC Code: 088004

TEST MATERIAL: Sodium omadine



* denotes the position of the ^{14}C label

SYNONYMS: Sodium pyrithione (pyridine-2-thiol-1-oxide, sodium salt)

AUTHORS: Marjory Chadwick, Ph.D., Denise M. Silveira, M.S., Madeline F. McComish, M.S., and Amin A. Nomeir, Ph.D.

SPONSOR: Olin Corporation, 91 Shelton Avenue, New Haven, CT 16511

TESTING FACILITY: Arthur D. Little, Inc., Acorn Park, Cambridge, MA 02140

REPORT TITLE: Sodium Omadine® Disposition and Metabolism in Rats after Oral and Intravenous Administration

STUDY NUMBER: ADL 59798A

STUDY COMPLETION DATES: August 25, 1989

CONCLUSIONS: The absorption, distribution, metabolism, and excretion of sodium omadine were studied in groups of Sprague-Dawley rats administered a single oral dose of 0.5 or 25 mg/kg ^{14}C-sodium omadine, 0.5 mg/kg/day of sodium omadine for 14 days followed by a single oral dose of ^{14}C-sodium omadine (0.5 mg/kg), or a single intravenous (i.v.) dose of 0.5 mg/kg ^{14}C-sodium omadine.

Sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing levels. Total recovery of administered radioactivity was 85%-95% at 4 days postexposure. The urine (73-85% of the dose) is the major route of excretion of sodium omadine; the feces (5-12% of the dose) are only a minor route of excretion. Sodium omadine and its metabolites were not excreted in expired air. In the single oral low-dose group and the i.v.-dose group, most

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of the administered radioactivity was excreted within the first 12 hours postdosing. In the repeated oral low-dose group and in the single oral high-dose group, the majority of the administered radioactivity was excreted within 24 and 48 hours postdosing, respectively. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues. The metabolic profiles in the urine were similar in all dose groups; 12 urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-*S*-glucuronide (Metabolite K) (41.4%-67.2% of the recovered radioactivity), while unchanged parent compound was not detected in the urine.

CORE CLASSIFICATION: Supplementary - upgradable [redacted]. This study alone does not satisfy the minimum guideline requirements (85-1) for a general metabolism study. The study authors need to account for the unrecovered radioactivity, attempt to characterize the fecal metabolites, and propose a metabolic pathway for sodium omadine.

A. MATERIALS

1. Test Substance

Unlabeled sodium omadine was supplied by the sponsor (41.41% w/w in aqueous solution; specific gravity 1.26; Olin Corporation Lot No. S08708, Sample No. F113B).

Labeled sodium omadine (2,6-^{14}C) had a specific activity of 12.6 mCi/mmol (New England Nuclear Research Products Lot No. 2332-038; Olin Corporation Sample No. F168A). The radiochemical purity was 99.1% by high performance liquid chromatography (HPLC).

2. Test Animals

Male and female (7-10-week-old) Sprague-Dawley rats were obtained from Taconic Farms, Germantown, NY. Males and females had body weights of 242-323 g and 176-232 g, respectively, at the time of randomization.

B. METHODS

1. Acclimation

Rats were acclimated to the laboratory environment for 1-2 weeks and then placed in individual stainless steel cages or Nalgene metabolism cages 48 hours prior to treatment. Rats were provided food (Purina Certified Rodent Chow #5002) and water (Poland Spring) *ad libitum*. The study authors did not indicate whether or not the rats were fasted prior to dosing. Contaminants that would have interfered with the study were not detected in the food or water.

2. Dose Preparation and Administration

Both preliminary and definitive tests were performed. The appropriate amounts of nonlabeled and labeled sodium omadine were dissolved in water for oral dosing and in 0.9% sodium chloride

solution for i.v. administration. ^{14}C-Sodium omadine was administered to 4 groups at single oral doses of 0.5 or 25 mg/kg and at 0.5 mg/kg following administration of unlabeled compound at 0.5 mg/kg for 14 days. ^{14}C-sodium omadine was also administered intravenously at 0.5 mg/kg. The final specific activities of the dose formulations were 68,900, 118,160, and 121,330 dpm/µg for the i.v.-, single oral low-dose, and repeated oral low-dose groups, respectively, and 8970 and 5630 dpm/µg for the preliminary and definitive high-dose groups, respectively. The formulations were stable for 5 days at room temperature. The radiochemical purity of the dose formulations was determined to be 99.5% by HPLC. According to the authors, the low dose corresponds to a no-effect level and the high dose produces toxic effects following oral administration

The dosage and treatment regimens for the preliminary and definitive studies are indicated below.

Dose Group	Route	Sex	No. of Animals
		Preliminary	
25 mg/kg[a]	oral	M	6
		F	6
		Definitive	
0.5 mg/kg[b] (single low)	oral	M	10
		F	10
0.5 mg/kg[c] (repeated low)	oral	M	10
		F	10
25 mg/kg[b] (single high)	oral	M	10
		F	10
0.5 mg/kg[d]	i.v.	M	10
		F	10

[a]Rats were given a single oral dose of 25 mg/kg ^{14}C-sodium omadine. Two rats of each sex were used for serial blood collection, for expired air, and for urine and feces collection.

[b]Rats were given a single oral low dose of 0.5 mg/kg or a single oral high dose of 25 mg/kg ^{14}C-sodium omadine. Five rats/sex were used for serial blood collection and 5 rats for urine, feces, and tissue collection.

[c]Rats were given 0.5 mg/kg/day of unlabeled sodium omadine for 14 days, followed by a single oral dose of ^{14}C-sodium omadine on day 15. Five rats/sex were used for serial blood collection and 5 rats for urine, feces, and tissue collection.

[d]Rats were given a single intravenous (i.v.) injection (0.5 mg/kg ^{14}C-sodium omadine) via the caudal vein. Five rats/sex were used for serial blood collection and 5 rats for urine and feces collection.

3. Sample Collection

In the preliminary study, expired $^{14}CO_2$ was collected in potassium hydroxide at 0-6, 6-12, 12-24, 24-32, and 32-48 hours postdosing. Urinary and fecal samples were collected at 0-6, 6-12, and 12-24 hours and then at 24-hour intervals for a total of 7 days postdosing. Blood samples were collected from the orbital sinus at 15 and 30 minutes, at 1, 2, 4, 6, 12, 16, 24, 36, 48, 72, and 96 hours, and at 7 days postdosing.

For each of the definitive test groups, urine and feces were collected at 0-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hours postdosing. Blood samples were collected at 15 and 30 minutes, at 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours, and at 7 days postdosing for all groups. Additional blood samples were collected at 2, 6, 15, and 30 minutes for the i.v. dose group. Tissues and carcass were collected on day 7 postdosing following euthanasia. The tissues removed included the liver, kidney, heart, brain, spinal cord, sciatic nerve, lung, skeletal muscle, fat, femur, reproductive organs, spleen, urinary bladder, and intestines. Radioactivity determinations of collected samples were made using liquid scintillation counting (LSC) in duplicate. Feces and some tissue samples were homogenized and combusted prior to radioanalysis. Statistical analysis was limited to means and standard deviations.

4. Metabolite Analyses

The 0-6-, 6-12-, and 12-24-hour urine samples were pooled according to sex for the single oral low-dose, repeated oral low-dose, and single oral high-dose groups to give a total of six 0-24-hour samples. For the i.v.-dose group, the 0-6-hour and the pooled 6-24-hour samples were used. For all dose groups, the 24-48-hour and 48-72-hour samples were pooled. The urine samples were analyzed in duplicate by HPLC. Three known urinary metabolites of sodium omadine were synthesized as standards.

5. Regulatory Compliance

A signed statement indicating that these studies were conducted according to EPA's Good Laboratory Practice (GLP) standards, was provided; however, this statement was not dated. A quality assurance statement, signed and dated 8/29/89, was provided.

C. REPORTED RESULTS

Preliminary Study

Analysis of expired air indicated no radiolabeled CO_2; therefore, expired air was not collected in the definitive study. The preliminary data indicated that most of the radioactivity (92-98%) was recovered in

the urine and feces within 96 hours of dosing; therefore, the definitive study was terminated at 4 days postdosing. The study authors indicated that the time intervals selected for blood collection gave a good description of the concentration-time curve for sodium omadine equivalents in the blood and were used, with minor modifications, in the definitive study.

Definitive Study

1. Pharmacokinetics: Following i.v. administration, blood radioactivity levels peaked within 2 minutes postexposure and then plateaued. Following oral administration, blood radioactivity peaked within 15 minutes to 1 hour, followed by broader peaks at 4-12 hours postexposure for the single and repeated oral low-dose groups and at 12-24 hours for the single oral high-dose group. Radioactivity for oral dose groups was eliminated from blood at three different rates: a rapid initial phase (1.3-5.5 hours), followed by an intermediate phase (3.8-5.9 days), and then a slower terminal phase (10.9-15.5 days). The estimated percentages of dose absorbed were 102%-105%, 90%-92%, and 88%-94% for the single oral low-dose, repeated oral low-dose, and single oral high-dose groups, respectively.

2. Elimination and Recovery: The mean total recoveries of radioactivity are shown in Table 1 (85.1%-95.1% for all dosing groups after 4 days). The urine is the major route of excretion; the feces were only a minor route of excretion. At 4 days postexposure, 73.3%-85.0% of the administered dose was excreted in the urine, while 3.2%-12.3% of the administered dose was excreted in the feces for all dose groups. In the single oral low-dose and i.v.-dose groups, most of the administered radioactivity (71%-77%) was excreted within the first 12 hours postdosing. In the repeated oral low-dose group, most of the radioactivity (81%) was excreted within the first 24 hours postdosing. In the single oral high-dose group, the majority of the administered radioactivity (90%-91%) was excreted within 48 hours postdosing.

   There were no sex-related differences in excretion; however, there were dose-related differences. In the single oral low-dose, repeated oral low-dose, and i.v.-dose groups, the majority of recovered radioactivity was excreted in the urine (73.6%-85.0%); lesser amounts were excreted in the feces (3.2%-8.0%). However, in the single oral high-dose group, males and females showed a shift in elimination towards increased fecal excretion (11.4%-12.3% of the recovered radioactivity) and decreased urinary excretion (73.3%-75.7% of the recovered radioactivity) compared to the other dose groups (Table 1).

3. Distribution: Recovery of radioactivity in the tissues was negligible at 4 days postdosing; ≤0.8% of the administered dose was retained in the tissues and 1.3%-2.1% was retained in the carcass (Table 1). There was no evidence of bioaccumulation of ^{14}C in tissues.

   In general, recovery of radioactivity in tissues was dose related, with greater radioactivity in the single oral high-dose group than

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in the single and repeated oral low-dose groups (Table 2). The highest amounts of radioactivity were found in the blood cells (0.23-12.26 nmol/g), liver (0.13-13.09 nmol/g), and kidneys (0.14-15.92 µg/g) for all dose groups.

4. Metabolism: The metabolic profiles in the urine were similar for all dose groups (Table 3). Twelve urinary metabolites (A-L) were characterized, of which three (Metabolites A, H, and K) were identified (Table 3). The study authors did not determine the identities of the other metabolites. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-*S*-glucuronide (Metabolite K) (41.4%-67.2% of the recovered radioactivity). Metabolite A, 2-(methylsulfonyl)pyridine, and Metabolite H, 2-pyridinethiol-S-glucuronide, accounted for 11.0%-21.3% and 1-6% of the radioactivity in the urine, respectively. Sex-related differences in the amount of metabolites excreted were noted for the single and repeated oral low-dose groups only. The males excreted approximately twofold greater amounts of Metabolite A than females, while females excreted slightly higher amounts of Metabolite K than males. The remaining metabolites each accounted for 0.1%-8.0% of the radioactivity for all dose groups. The parent compound was not detected in the urine of any of the dose groups.

D. REVIEWERS' DISCUSSION

The study described the absorption, distribution, metabolism, and elimination of sodium omadine in male and female rats following oral and i.v. exposures. Sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing regimens. Total recovery of radioactivity in all dose groups at 4 days postdosing was low (85.1%-95.1% of the administered dose). The urine is the major route of excretion for sodium omadine; the feces are only a minor route of excretion. Sodium omadine and its metabolites were not excreted in expired air. Most of the administered radioactivity was excreted within the first 12 hours postdosing in the single oral low-dose group and the i.v.-dose group, within the first 24 hours postdosing in the repeated oral low-dose group, and within 48 hours postdosing in the single oral high-dose group. Radioactivity was eliminated from blood in three different phases: a rapid initial phase, followed by an intermediate phase, and then a slower terminal phase for all dose groups. Comparisons of i.v. and oral dosing indicated that the compound was estimated to be well absorbed at all dose levels (88%-105% absorption from the gastrointestinal tract). Blood kinetic data further indicate that sodium omadine is rapidly absorbed following oral administration. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues after 4 days postdosing. Metabolism of sodium omadine was extensive since no parent compound was detected. The metabolic profiles in the urine were similar for all dose groups. Twelve urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-*S*-glucuronide (41.4%-67.2% of the recovered radioactivity). Fecal metabolites were not characterized.

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FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Title:
104 Week Oral (Gavage) Combined Carcinogenicity
and Toxicity Study in the Rat

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: William L. McLellan Date May 18, 1994
William McLellan, Ph.D.

Independent Reviewer: John J. Liccione Date 5/18/94
John Liccione, Ph.D.

QA/QC Manager: Carol Maczka Date 5/18/94
Carol Maczka, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 2-124/389
Project Officer: Caroline Gordon

Guideline Series 83-5: Chronic Oncogenicity-Rat

EPA Reviewer: William Greear, M.P.H.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: mc for WGreear
Date:

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Marion Copley
Date: 6/10/94

DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/oncogenicity in rats

TEST MATERIAL: Sodium omadine

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 421009-01

SYNONYMS: Sodium pyrithione; sodium 2-pyridinethiol-1-oxide; RD 8702

STUDY NUMBER: OLA-3-90

SPONSOR: Olin Corporation, Stamford, CT 06904

TESTING FACILITY: Toxicol Laboratories Ltd., Ledbury, Herefordshire, England

TITLE OF REPORT: 104-Week Oral (Gavage) Combined Carcinogenicity and Toxicity Study in the Rat

AUTHORS: Husband, R.F.A., Newman, A.J., and Lee, P.N.

REPORT ISSUED: May 28, 1991

CONCLUSIONS: Sodium omadine was administered daily by oral gavage to groups of 70 Crl:CD(SD)BR Sprague-Dawley rats/sex at dosage levels of 0, 0.5, 1.5, or 5.0 mg/kg/day for 2 years. The highest dose was reduced to 3.5 mg/kg/day after 12 weeks because of excessive weight loss in females.

NOEL = 0.5 mg/kg/day

LOEL = 1.5 mg/kg/day based on significant increases in the incidence of degeneration of the skeletal muscle of the hind limbs in both sexes.

In addition, at the highest dose tested (5.0/3.5 mg/kg/day) the following observations were made: a significant decrease in mean body weight (and body weight gain) in females throughout the study; a marked increase in nerve fiber degeneration in the sciatic nerve and in the spinal cord in both sexes; and an increased incidence of retinal atrophy in both sexes. Under the conditions of the study, no increase in neoplasms was observed at any site. Dosing was considered adequate to assess carcinogenicity.

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CORE CLASSIFICATION: Core Guideline. The study satisfies the requirements (Guideline Series 83-5) for a combined chronic/oncogenicity study in rodents.

A. MATERIALS AND METHODS

1. Test Article Description

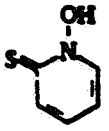
Name: Sodium omadine

Lot number: 8508-P-166H

Purity: Aqueous solution 41.2%

Physical property: Pale amber liquid

Chemical structure:



Storage: Room temperature in the dark in a plastic, screw-top drum

Stability: Reported to be covered in other submissions

2. Dose Formulation

Dosing solutions were prepared fresh weekly by dilution of the 40% aqueous solution of the test compound (as received) with distilled water. The dosing volume was 10 mL/kg body weight. The control rats received distilled water by gavage. After each daily dosing, the residual dosing solutions for that day were discarded. Dosing formulations were analyzed at week 1 and every third week thereafter. A spectrophotometric method using 305-nm wavelength was used; samples were diluted in distilled water to give a concentration of about 50 µg/mL and absorbance was compared with standards.

Results: With the exception of week 7 when dosing solutions were 85-87% of target and week 97 when solutions were 90-91% of target, all dosing solutions were 101-111% of target. The mean concentrations (±SD) were 104.7±4.7%, 105.2±4.8%, and 105.8±4.5% of target at dosage levels of 0.5, 1.5, and 5.0/3.5 mg/kg/day, respectively.

The stability of the formulations was tested in other concurrent studies and found adequate. Homogeneity was not checked since test material was completely soluble in water.

3. Animals

Species: Rat

Strain: Crl:CD(SD)BR® (VAF plus)

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Age: Approximately 25 days old on receipt and 36 days old at initiation of dosing

Weight at initiation: Males, 163-231 g; females, 128-172 g

Source: Charles River (UK) Limited, Margate, England.

Group assignment: Animals were found to be healthy on arrival. They were acclimated for 11 days to laboratory conditions, and prior to initiation five/sex were examined microscopically (liver, kidneys and lungs) and confirmed healthy. Two animals were eliminated because of ocular findings. Animals were allocated randomly to the following groups:

Test Group	Doses (mg/kg body weight)	Number of Animals			
		Oncogenicity Study		Chronic Toxicity Study	
		Males	Females	Males	Females
1,5 Control	0	50	50	20	20
2,6 Low-dose (LDT)	0.5	50	50	20	20
3,7 Mid-dose (MDT)	1.5	50	50	20	20
4,8 High-dose (HDT)	5.0[a]	50	50	20	20

[a]The high dose was reduced to 3.5 mg/kg/day from week 12.

Animals were individually caged and housed in an environmentally controlled room with a temperature range of 15-27°C (19-25°C in protocol), a humidity range of 18-76% (30-70% in protocol), and a 12-hour light/dark cycle. Food (SQC Rat and Mouse Maintainance Diet from Special Diet Services, Witham, England) and tap (mains) water were available *ad libitum*.

Rationale for dose selection: A 90-day gavage study in rats (MRID No. 407569-01) has been reviewed. In this study, gavage doses of 0.5, 2.0, or 8.0 mg/kg/day were administered to groups of 20 rats/sex. At the highest dose (8.0 mg/kg/day), 10 females were sacrificed *in extremis* because of severe hind-limb motor dysfunction. Hind-limb paralysis was observed in 16/20 high-dose females and 4/20 high-dose males. This was accompanied by emaciation, piloerection, and hunched posture; body weight gains and food consumption were also decreased.

4. Statistics

Body weight and absolute organ weight were analyzed for variance using Bartlett's test. If variance was homogeneous, data were further analyzed using ANOVA. If variances were heterogeneous, a log transformation was performed, and if data were still non-

parametric, the Wilcoxon rank sum test was used. Hematology and clinical chemistry data were analyzed using the Kruskal-Wallis one-way analysis of variance. Body weight data were analyzed at 8-week intervals, and body weight gain data were analyzed for the overall study.

Survival data and incidence data were analyzed by the method of Peto (IARC method) using a Microvax computer. Both trend and chi square analyses were performed. For histologic lesions of kidney, liver, lung, muscle, and other tissues examined in all animals in all groups, the number of tissues examined was the denominator. For tissues designed by protocol to be only examined in decedents in the low- and mid-dose groups or when an abnormality was present post-mortem, the number of animals (not tissues examined) was used as the denominator. In these cases, controls and high-dose animals were analyzed based on decedents plus terminals, and for low- and mid-dose groups, analysis was based on decedents only.

When incidences of histologic findings were low, age-adjusted exact tests were used instead of chi square tests. Statistics were performed separately by sex and also for the sexes combined.

5. Quality Assurance/Compliance

A Quality Assurance Statement, signed and dated May 28, 1991, was provided. A GLP Compliance Statement, a Flagging Statement, and a statement of No Data Confidentiality Claims were also present.

B. METHODS AND RESULTS

1. Clinical Observations

Mortality checks were performed twice daily, and all rats were examined once a day for changes in condition or behavior. Beginning at week 27, all animals were palpated weekly for masses, and details of their location, size, and consistency were recorded. Clinical observations were recorded weekly.

Results: Table 1 summarizes mortality and survival data at selected study intervals. No accidental deaths due to gavage errors were reported. No effect of dosing on survival was observed. In the oncogenicity study, survival at 104 weeks ranged between 34% and 50% in dosed males compared to 38% in controls and ranged from 50 to 56% in dosed females compared to 64% in controls. No statistically significant trends in survival were seen, even though survival was slightly greater in high-dose males and slightly decreased in dosed females when compared to controls (oncogenicity study). Survival was similar in the 20 rats/group in the chronic toxicity study.

The only treatment-related clinical sign was hind-limb muscle wastage observed in the majority of surviving high-dose males and females from week 89 onward. The incidence ranged from 9 to 21 in high-dose males and from 10 to 18 in high-dose females from week-89 to termination (oncogenicity study).

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Table 1. Cumulative Mortality (and Percent Survival) at Selected Intervals in Rats Orally Administered Sodium Omadine for 104 Weeks[a]

Dosage Level (mg/kg/day)	Mortality and Percent Survival						
	Oncogenicity Study Week				Chronic Study Week		
	52	76	104	terminal[b]	52	76	104
				Males			
0	5 (90)	14 (72)	31 (38)	32 (36)	1 (95)	6 (70)	11 (45)
0.5	5 (90)	16 (68)	32 (36)	33 (34)	2 (90)	5 (75)	11 (45)
1.5	3 (94)	12 (76)	33 (34)	33 (34)	0 (100)	1 (95)	8 (60)
5.0/3.5	5 (90)	10 (80)	25 (50)	26 (48)	1 (95)	2 (90)	11 (45)
				Females			
0	1 (98)	6 (88)	18 (64)	21 (58)	1 (95)	3 (85)	12 (40)
0.5	1 (98)	6 (88)	22 (56)	25 (50)	0 (100)	4 (80)	10 (50)
1.5	1 (98)	5 (90)	25 (50)	26 (48)	3 (85)	6 (70)	12 (40)
5.0/3.5	4 (92)	12 (76)	25 (50)	25 (50)	2 (90)	3 (85)	7 (65)

[a]Data extracted from Table 1B, pages 62-63, study no. OLA-3-90.
[b]In males, sacrifices were carried out between 105 and 107 weeks.

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The incidence of palpable masses was not increased in treated animals

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2. Body Weights and Food Consumption

Each animal was weighed on the first day of dosing, weekly for 16 weeks, and every month thereafter. Food consumption was recorded weekly for 16 weeks and every fourth week thereafter. Weight gain data were provided for the overall 104 weeks of the study only. Body weight data were statistically analyzed at 8-week intervals for the oncogenicity study.

Results: Table 2 summarizes mean body weights at selected intervals during the study (oncogenicity groups). The mean body weights in high-dose females at week 8 were decreased 7% from controls, and they remained about 10% lower than control body weights throughout the study. Mean body weights in high-dose males were decreased 3% below controls at 8 weeks. Because of the decreased weight gain in the high-dose females, the high dose was reduced from 5.0 mg/kg/day to 3.5 mg/kg/day at week 12. Mean body weights in high-dose males were significantly lower ($p<0.05-0.001$) than controls at all of the 8-week intervals up to week 80 with the exception of week 48.

Table 3 presents weight gain data for selected intervals. The overall weight gains were 13% depressed in high-dose males and 19% depressed in high-dose females when compared to controls. Body weight data for animals in the chronic toxicity segment of the study were essentially similar to those in the oncogenicity segment for the first 78 weeks of the study. They were more variable in the final weeks of the study.

Food consumption was similar in control and dosed groups of males and females in both the oncogenicity and chronic toxicity segments of the study. In high-dose males and females, the overall food consumption values were 101.5% and 98.9% of control, respectively.

3. Ophthalmoscopic Examination

Both eyes of all animals were examined at the start of the study. Prior to termination, the eyes of all control and high-dose animals were examined. The examinations used both direct and indirect ophthalmoscopes after instillation of a mydriatic agent (2% Homotropine hydrobromide).

Results: Two animals with ocular abnormalities were replaced at study initiation. No treatment-related ocular findings were observed prior to study termination.

4. Clinical Pathology

Blood samples were taken from 10 rats/sex/group from the chronic toxicity groups by retroorbital sinus puncture after overnight fasting in weeks 27, 53, 78, and 104. At week 104, some animals from the oncogenicity study supplemented the chronic toxicity group to have 10/sex/group.

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Table 2. Mean Body Weights and Percent Control at Selected Intervals in Rats Adminstered Sodium Omadine for 2 Years (Oncogenicity Study)[a]

Dosage Level	Mean Body Weights and Percent Control at Weeks[b]						
(mg/kg/day)	1	8	16	24	56	80	104
				Males			
0	194	386	475	528	642	666	654
0.5	195 (101)	382 (99)	479 (101)	524 (99)	642 (100)	696 (104)	660 (101)
1.5	189 (97)	389 (101)	482 (101)	526 (99)	641 (99)	703 (106)	737 (113)*
5.0/3.5	194 (100)	376 (97)	454 (96)*	510 (97)	612 (95)	652 (98)	656 (100)
				Females			
0	149	212	244	265	336	389	428
0.5	148 (99)	218 (103)	252 (103)	271 (102)	335 (99)	391 (100)	427 (99)
1.5	146 (98)	220 (104)	253 (104)	270 (102)	331 (98)	379 (97)	406 (95)
5.0/3.5	143 (96)	196 (93)***	225 (92)***	243 (92)***	299 (89)**	345 (87)**	368 (86)**

[a]Data extracted from Table 2, pages 64-73, study no. OLA-3-90.
[b]These intervals were chosen since data were statistically analyzed at 8-week intervals.

*Significantly different from control value, $p < 0.05$.
**Significantly different from control value, $p < 0.01$.
***Significantly different from control value, $p < 0.001$.

Table 3. Weight Gains (g) at Selected Intervals in Rats Orally Administered Sodium Omadine for 2 Years[a]

	Weight Gain (g) at Week[b]				
	Oncogenicity Study			Oncogenicity Study	Chronic Study
Dosage Level (ppm)	1–12	13–28	29–52	1–104	1–104
0	238	122	72	463	498
0.5	239 (100)	114 (93)	87 (121)	471 (102)	535 (107)
1.5	248 (104)	113 (93)	79 (110)	546* (118)	443 (89)
5.0/3.5	214 (90)	123 (100)	77 (107)	462 (100)	432 (87)
0	79	49	44	278	264
0.5	88 (111)	46 (94)	48 (109)	278 (100)	240 (91)
1.5	90 (114)	42 (100)	49 (111)	259 (93)	260 (98)
5.0/3.5	65 (82)	47 (106)	44 (100)	225 (81)	214 (81)

[a]The 1–104 week values are from Table 2, pages 64–70, study no. OLA-3-90. The values for weeks 1–12, 13–28, and 29–52 were derived by subtraction of mean values in the same table, so they are not statistically analyzed.

[b]The numbers in parentheses are percentages of control values.

*Significantly different from control value, $p<0.05$.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocyte count (RETIC)[a]
X Red cell morphology
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
X Prothrombin time (PT)
X Partial thromboplastin time (PTT)

*Recommended by Subdivision F (November 1984) Guidelines

Results: No adverse effects on hematology parameters were observed. Minor changes in RBC in mid- and high-dose females at week 27 (4% and 6% decrease) and at week 53 (10% and 9% decrease) reached a level of significance but were transient, and the values were within the normal range.

(b) Blood (Clinical) Chemistry

Electrolytes

X Calcium*
X Chloride*
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
X Creatine phosphokinase
Lactic acid dehydrogenase
X Serum alanine aminotransferase (ALAT)*
X Serum aspartate aminotransferase (ASAT)*
X Gammaglutamyl transpeptidase (GGT)

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol (total)*
X Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related effects on clinical chemistry parameters were observed.

(c) Urinalysis: Urine samples were collected at the same intervals as the blood samples (and from the same rats). Urine was collected overnight from rats deprived of water.

X Appearance*
X Volume*
X Specific gravity*
X pH*
X Sediment (microscopic)
X Protein*
X Glucose*
X Ketones*
X Bilirubin*
X Blood*
Nitrate
Urobilinogen

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related effects on urinary parameters were observed.

5. Sacrifice and Pathology

All animals that died or were sacrificed moribund and all animals sacrificed at termination received a complete necropsy. The tissues checked (X) below were preserved in formalin (except the eyes which were fixed in Davidson's fluid), and the double-checked (XX) organs were weighed from all rats in the toxicity groups. Histology was performed on the specified tissues from all control and high-dose animals and all decedents. The lungs, liver, kidneys, all gross lesions, and all masses suspected of being tumors were examined. The following additional tissues were examined from the low- and mid-dose groups of the toxicity study: hind-limb skeletal muscle, skin-subcutaneous panniculus muscle, spinal cord-paravertebral muscle, and eyes. Tissues not processed, stained, or examined were retained.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain* (four levels)
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes* (submandibular and mesenteric)	XX Pituitary*a
X Duodenum*	XX Spleen*	X Eyes* (optic nerve)
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	Glandular
X Colon*		
X Rectum*	XX Kidneys*	XX Adrenals*
XX Liver*	X Urinary bladder*	Lacrimal gland
Gallbladder*	XX Testes*	X Mammary gland (females only)
X Pancreas*	X Epididymides	XX Thyroids*2 with parathyroids
Respiratory	X Prostate*	X Harderian glands
X Trachea*	X Seminal vesicle	
XX Lungs*	XX Ovaries*	
	X Uterus*	

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin*
X All gross lesions and masses*

*Recommended by Subdivision F (November 1984) Guidelines
[a]Pituitaries and thyroids were weighed after fixation.

(a) Organ Weights

No effects of treatment on organ weights were observed. The relative weight of liver as a percentage of body weight in high-dose males was increased 3.07-3.53% over controls, and the relative lung weights (percentage of body weight) were increased slightly at 1.5 and 3.5 mg/kg/day; these increases were considered related to body weight decreases (chronic study) and not of toxicologic importance. No changes in relative organ weights were observed in females.

(b) Macroscopic Pathology

The only gross finding that was related to dosing was wasting of the hind-limb skeletal muscle. The incidence is shown in Table 4.

(c) Microscopic Pathology

Nonneoplastic:

Table 5 summarizes the incidence of important histologic findings. An increased incidence of skeletal muscle degeneration was observed in mid- and high-dose males. For the 50 animals/group in the carcinogenicity study, the increase was significant ($p<0.001$) in both sexes and there was a positive trend ($p<0.001$). The finding was marked in one high-dose male and four high-dose females; it was graded at least moderate in 18% and 26% of the high-dose males and females, respectively.

An increased incidence of nerve fiber degeneration was seen in high-dose groups. The increase was significant ($p<0.01$) for each sex at the high dose (carcinogenicity group), and there was a significant positive dose-trend ($p=0.01$ males, $p=0.001$ females). Three high-dose males had marked degeneration, and moderate degeneration was observed in eight males and eight females in the high-dose group.

Spinal cord nerve fiber degeneration was increased in the high-dose animals. The finding was marked in 3 males and 1 female in the high-dose group and moderate in 18 males and 8 females in the high-dose group. For "any grade" the increases were not significant.

The authors reported that muscle degeneration was also found in the paravertebral and panniculus (skin) muscle, but these sites were evaluated only for the toxicity segment (20/sex/group). Retinal atrophy may be compound related. The increase in high-dose females or in high-dose males and females combined was significant (carcinogenicity study).

Retinal atrophy was significantly increased in high-dose females ($p=0.001$) and slightly increased in high-dose males. The incidence in females at 0, 0.5, 1.5, and 3.5 mg/kg/day was 8/50 (16%), 3/25 (12%), 8/27 (30%), and 34/50 (68%), respectively. The incidence in high-dose males was

Table 4. Incidence of Muscle Wasting in Rats Administered Sodium Omadine for 2 Years[a,b]

	Incidence at Each Dosage Level (mg/kg/day)							
	Males				Females			
	0	0.5	1.5	5.0/3.5	0	0.5	1.5	5.0/3.5
Chronic	(20)	(20)	(20)	(20)	(20)	(20)	(20)	(20)
Study	0	0	4	5	0	0	0	8
Oncogenicity	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Study	1	2	1	10	1	3	2	16
Total	1	2	5	15	1	2	3	20
%	1	3	7	21	1	3	4	29

[a]Data extracted from Appendix 21, pages 832-839, and Appendix 24, pages 1397-1407, study no.OLA-3-90.
[b]The numbers in parentheses are the number of animals necropsied.

Table 5. Incidence of Selected Nonneoplastic Lesions in Rats Orally Administered Sodium Omadine for 2 Years[a,b]

		Incidence at Each Dosage Level (mg/kg/day)							
		Males				Females			
		0	0.5	1.5	5.0/3.5	0	0.5	1.5	5.0/3.5
Skeletal muscle degeneration	CA	10/50	9/50	13/50***	34/50***	1/50	5/50	8/50***	38/50***
	TX	2/20	4/20	11/20	12/20	2/20	1/20	1/20	19/20
	TOTAL	12/70	13/70	24/70	46/70	3/70	6/70	9/70	57/70
	%	17	19	34	66	4	9	13	81
Retinal atrophy	CA	8/50	2/34	4/32	13/50	8/50	3/25	8/27	34/50***
	TX	1/20	3/20	2/20	6/20	3/20	1/20	6/20	15/20
	TOTAL	9/70	5/54	6/52	19/70	11/70	4/45	14/47	49/70
	%	13	9	12	27	16	9	30	70
Sciatic nerve fiber degeneration	CA	15/49	6/33	6/32	30/49**	12/50	4/24	4/26	26/50**
	TX	9/20	7/19	8/20	13/20	7/20	6/20	6/19	13/20
	TOTAL	24/69	13/52	14/52	43/69	19/70	10/44	10/45	39/70
	%	35	25	27	62	27	23	22	56
Spinal cord degeneration	CA	28/50	16/33	7/33	35/50	23/50	6/25	5/26	28/49
	TX	14/19	15/20	16/20	16/20	13/20	11/20	9/20	17/20
	TOTAL	42/69	31/53	23/53	51/70	36/70	17/45	14/46	45/69
	%	61	59	43	73	51	38	30	65

[a]Data extracted from Appendices 21 and 24, Report OLA-3-90.
[b]CA = carcinogenicity study; TX = toxicity study

**Significantly different from control value, $p < 0.01$.
***Significantly different from control value, $p < 0.001$.

i to 16% for control males. The increase may be
iated. No other nonneoplastic lesions were
d treatment related.

Neoplastic Pathology

No treatment-related increases in tumors were found at any site. All incidences were within the range of historical control (Study report, Volume 12, p. 28.1).

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study appeared to be well conducted and adequately reported. However, a number of minor numerical errors were found when histologic data in the statistics report and some summary text tables were compared with the pathology report. These errors do not confound study interpretation. Statistical analysis was only performed for pathology findings in the carcinogenicity study and not for the toxicity groups or all animals combined. The statistical report gave additional information on grades of lesions that were not summarized elsewhere in the report. In addition, panniculus muscle and paravertebral muscles were examined in sections of skin and spinal cord from animals in the toxicity study but not in the oncogenicity study. Examination of muscle tissue at these sites is not required by guidelines. An increase in retinal atrophy in high-dose females may be related to compound administration. However, eye abnormalities were not reported at the ophthalmologic examination prior to the terminal sacrifice.

Under the conditions of the study, there was no increase in neoplasms at any site. The highest dose tested was adequate for assessment of carcinogenicity. The males might have been able to tolerate a slightly higher dose since there was no decrease in weight gain at 5 mg/kg/day at 12 weeks as in females at this dose. However, neurologic effects were observed at the 3.5-mg/kg/day dose level in both sexes.

Based on muscle wasting, which was probably secondary to neurological changes, and histologic evidence of neurotoxicity, the LOEL is 1.5 mg/kg/day and the NOEL is 0.5 mg/kg/day.

Table 6. Incidence of Selected Neoplastic Lesions in Rats Orally Administered Sodium Omadine for 2 Years[a,b]

		Incidence at Each Dosage Level (mg/kg/day)							
		Males				Females			
Observation		0	0.5	1.5	5.0/3.5	0	0.5	1.5	5.0/3.5
Hepatocellular adenoma	CA	-	-	-	3/50	-	-	1/50	1/50
	TX	-	1/20	-	-	-	-	-	-
	TOTAL	-	1/20	-	3/50	-	-	1/50	1/50
	%	-	5%	-	6%	-	-	2%	2%
Hepatocellular carcinoma	CA	-	-	-	-	-	-	-	-
	TX	-	-	-	2/20	-	-	-	1/20
	TOTAL	-	-	-	2/20	-	-	-	1/20
	%	-	-	-	10%	-	-	-	5%
Renal Adenocarcinoma	CA	-	-	-	-	-	-	-	1/50
	TX	-	-	1/20	-	-	-	-	-
	TOTAL	-	-	1/20	-	-	-	-	1/50
	%	-	-	5%	-	-	-	-	2%
Adrenocortical adenoma	CA	-	-	-	3/50	8/50	5/32	7/34	5/50
	TX	3/20	1/12	2/8	2/20	2/20	3/14	-	3/20
	TOTAL	3/20	1/12	2/8	5/70	10/70	8/46	7/34	8/70
	%	15%	8.3%	25%	7.1%	14.3%	17.4%	20.6%	11.4%
Pituitary adenoma	CA	29/49	27/39	24/40	31/47	39/50	37/41	35/41	35/48
	TX	10/18	11/16	10/14	13/20	14/20	16/17	10/16	11/20
	TOTAL	39/67	38/55	34/54	44/67	53/70	53/58	45/57	46/68
	%	58.2%	69.1%	63.0%	65.7%	75.7%	91.4%	78.9%	67.6%
Mammary adenocarcinoma[f]	CA	-	-	-	-	3/13	4/17	3/21	2/14
	TX	-	1/3	-	-	2/4	1/7	2/3	-
	TOTAL	-	1/3	-	-	5/17	5/24	5/24	2/14
	%	-	33.3%	-	-	29.4%	20.8%	20.8%	14.3%
Mammary fibroadenoma[f]	CA	-	-	1/6	-	9/13	9/17	15/21	8/14
	TX	-	-	-	-	2/4	6/7	1/3	2/4
	TOTAL	-	-	1/6	-	11/17	15/24	16/24	10/18
	%	-	-	16.7%	-	64.7%	62.5%	66.7%	55.6%

Table 6. Incidence of Selected Neoplastic Lesions in Rats Orally Administered Sodium Omadine for 2 Years[a,b]

		Incidence at Each Dosage Level (mg/kg/day)							
		Males				Females			
Observation		0	0.5	1.5	5.0/3.5	0	0.5	1.5	5.0/3.5
Thyroid follicular adenoma	CA	1/50	2/36[d]	1/34[e]	5/50[c]	-	-	-	-
	TX	1/20	-	2/9	1/20	1/20	-	-	-
	TOTAL	2/70	2/36	3/43	6/70	1/20	-	-	-
	%	2.9%	5.6%	7.0%	8.6%	5.0%	-	-	-
Islet cell adenoma	CA	2/49	2/35	1/34	3/49	1/50	-	1/27	-
	TX	2/20	-	3/10	1/20	-	-	-	-
	TOTAL	4/69	2/35	4/44	4/69	1/50	-	1/27	-
	%	5.8%	5.7%	9.1%	5.8%	2%	-	3.7%	-
Interstitial cell adenoma	CA	1/50	2/36	-	3/50	-	-	-	-
	TX	-	-	1/10	-	-	-	-	-
	TOTAL	1/50	2/36	1/10	3/50	-	-	-	-
	%	2%	5.5%	10%	6%	-	-	-	-
Keratoacanthoma of skin	CA	-	-	-	2/43	1/30	-	-	1/20
	TX	1/13	-	2/17	3/16	-	1/11	-	-
	TOTAL	1/13	-	2/17	5/59	1/30	1/11	-	1/20
	%	7.7%	-	11.8%	8.5%	3.3%	9.1%	-	5%

[a]Data extracted from Appendices 21 and 24, Report OLA-3-90.
[b]CA = carcinogenicity study; TX = toxicity study
[c]1/50 thyroid follicular cell adenocarcinoma at this dose level.
[d]1/36 thyroid follicular cell carcinoma at this dose level.
[e]1/34 thyroid follicular cell carcinoma at this dose level.
[f]These tumors were found in the subcutaneous tissue sections, not the mammary gland sections.
*Significantly different from control value, $p < 0.05$.
**Significantly different from control value, $p < 0.01$.
***Significantly different from control value, $p < 0.001$.

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 84-2a; Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT)

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.4% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 404115-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay

AUTHOR: L.F. Stankowski, Jr.

STUDY NUMBER: PH 314-OL-001-87

STUDY COMPLETED: May 20, 1987

EXECUTIVE SUMMARY (revised): Sodium Omadine 40% Aqueous Solution (41.4% purity) did not induce forward gene mutations at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells up to actual concentrations, based on analytical determinations, of 0.08 μg/ml -S9 or 11 μg/ml +S9. Actual doses ≥0.08 μg/ml -S9 or 27 μg/ml +S9 were severely cytotoxic (i.e., <10% cell survival).

CORE CLASSIFICATION: **Acceptable.** This study satisfies the requirements for FIFRA Test Guideline Series 84-2 for genetic effects Category I, Gene Mutations and is acceptable for regulatory purposes.

Comments: The test article is Sodium Omadine 40% Aqueous Solution (41.4% purity).

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE®

Study Type: Mutagenicity: Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Mary E. McCarroll for Date 10/7/93
Dean Walton, Ph.D.

Independent Reviewer Mary E. McCarroll Date 10/7/93
Nancy E. McCarroll, B.S.

QA/QC Manager Sharon Segal Date 10/7/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 404
Project Officer: Caroline Gordon

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011532

GUIDELINE § 84: MUTAGENICITY
MAMMALIAN CELLS IN CULTURE GENE MUTATION

EPA Reviewer: Irving Mauer, Ph.D. Signature: [signature] 10-14-93
Immediate Office/HED (H-7509C) Date:

EPA Section Head: Marion Copley, D.V.M., DABT Signature: [signature] 10/19/93
Review Section IV, Date:
Toxicology Branch I/HED (H-7509C)

DATA EVALUATION REPORT

STUDY TYPE: Gene mutation in cultured Chinese hamster ovary cells (CHO/HGPRT)

CHEMICAL: Sodium Omadine®

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 404115-01

SYNONYM(S)/CAS NUMBER: Sodium 2-pyridine thiol-1-oxide; Sodium pyrithione/ 3811-73-2

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® CHO/HPRT Mammalian Cell Forward Gene Mutation Assay

AUTHOR: L.F. Stankowski, Jr.

STUDY NUMBER: PH 314-OL-001-87

REPORT ISSUED: May 20, 1987

CONCLUSIONS--EXECUTIVE SUMMARY: Negative for inducing forward gene mutations at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells up to actual concentrations, based on analytical determinations, of 0.08 µg/mL -S9 or 11 µg/mL +S9. Actual doses ≥0.08 µg/mL -S9 or 27 µg/mL +S9 were severely cytotoxic (i.e., <10% cell survival).

STUDY CLASSIFICATION: Acceptable. This study satisfies the requirements for FIFRA Test Guideline Series 84-2 for genetic effects Category I, Gene Mutations and is acceptable for regulatory purposes.

A. MATERIALS:

1. Test Material: Sodium Omadine®

Description: Light amber liquid; specific gravity: 1.258 g/mL
Identifieation No.: Lot No. F113B
Purity: 41.4% active ingredient (a.i.)
Receipt date: January 5, 1987
Stability: Not reported
Contaminants: None listed
Solvent used: Sterile deionized water (dH_2O)
Other provided information: The test material was stored at room temperature. Test material dilutions were prepared the day of the test and used within one hour of preparation. Analytical determinations were performed by the sponsor on all dosing solutions (see Section C.--REPORTED RESULTS). Prepared dosing solutions were corrected for the 41.4% a.i.

2. Control Materials:

Negative: Ham's F12 complete medium supplemented with 5% fetal bovine serum (F12CM5)

Solvent/final concentration: dH_2O/50 µL/5 mL culture medium

Positive:

Nonactivation (concentrations, solvent): Ethyl methanesulfonate (EMS) was prepared in DMSO to yield a final concentration of 200 µg/mL.

Activation (concentrations, solvent): Dimethylnitrosamine (DMN) was mixed with dH_2O to yield a final concentration of 100 µg/mL.

3. Activation: S9 derived from a male Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other		_____ other	

The source of the S9 liver homogenate (Lot No. 12/17/86) was not reported and it was not indicated if the S9 homogenate was characterized prior to use.

The S9 mix contained the following components:

Component	Concentration
$MgCl_2$	10 mM
$CaCl_2$	10 mM
KCl	30 mM
Glucose-6-phosphate	5 mM
NADP	4 mM
Na_2HPO_4 (pH 7.4)	50 mM
S9 homogenate	10% (v/v)

4. Test Cells: Mammalian cells in culture

_____ mouse lymphoma L5178Y cells
__x__ Chinese hamster ovary (CHO K1 BH4) cells
_____ V79 cells (Chinese hamster lung fibroblasts)
_____ other (list):

Properly maintained? Yes.
Periodically checked for mycoplasma contamination? Yes.
Periodically checked for karyotype stability? Not reported.
Periodically "cleansed" against high spontaneous background?
Maintained in logarithmic growth phase to reduce the spontaneous mutation frequency.

5. Locus Examined:

_____ thymidine kinase (TK)
selection agent: _____ bromodeoxyuridine (BrdU)
(give concentration) _____ fluorodeoxyuridine (FdU)

__x__ hypoxanthine-guanine-phosphoribosyl transferase (HGPRT)
selection agent: _____ 8-azaguanine (8-AG)
(give concentration) 1.25×10^{-5}M 6-thioguanine (6-TG)

_____ Na^+/K^+ATPase
selection agent: _____ ouabain
(give concentration)

_____ other (locus and/or selection agent; give details):

6. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Nonactivated and S9-activated assays were performed with 10 doses (0.0691-2070 µg/mL a.i.) of the test material.

(b) Mutation assays: The original assays were performed with doses ranging from 0.0414 to 0.414 µg/mL -S9 and from 4.14 to 103.5 µg/ml +S9; however, these doses were severely cytotoxic and the assay was voided. Each assay was repeated with the following concentrations:

- Nonactivated: Nine doses (0.005-0.5 µg/mL) were evaluated and cells exposed to ≈0.005, ≈0.01, ≈0.02, 0.035, (0.052), 0.05 (0.06), or 0.1 (0.08) µg/mL were plated for mutant selection.

  Note: Doses in parentheses are the actual concentrations based on analytical determinations. Only calculated values (based on purity) were available for the lowest levels; the two lowest levels were below the detection limit of the procedure and the ≈0.02 µg/mL solution was lost.

- S9-activated: Nine doses (0.5-100 µg/mL) were evaluated and cells exposed to 0.5 (0.44), 1 (0.7), 2.5 (2.3), 5 (5), and 10 (11) µg/mL were plated for mutant selection.

B. TEST PERFORMANCE:

1. Cell Treatments:

(a) Cells exposed to test compound, solvent or positive controls for: 5 hours (nonactivated) 5 hours (activated)

(b) After washing, cells were cultured for 7 days (expression period) before cell selection.

(c) After expression, $2x10^5$ cells were added to each of 5 dishes and were cultured for 7 days in selection medium to determine numbers of mutants and 200 cells/dish (3 dishes) were cultured for 10 days without selection medium to determine cloning efficiency (CE).

2. Statistical Methods: The data were evaluated by least-squares methods of linear regression according to the methods of Snee and Irr.[1]

3. Evaluation Criteria:

(a) Assay validity: Not reported.

(b) Positive response: The test material was considered positive if (1) it caused a dose-related ($r \geq 0.80$ by least-squares analysis) increase in the mutation frequency (MF) compared to the solvent control, (2) at least one dose resulted in a ≥3-fold increase in the MF, and (3) the MF was ≥95% confidence interval of the pooled concurrent negative controls.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Assay: In the nonactivated dose groups, cells exposed to the lowest and second lowest test material concentrations (0.069 and 0.207 µg/mL a.i.) had relative survivals (RSs) of 83.3% and 31.8%, respectively, the remaining cultures treated with ≥1.67 µg/mL a.i. -S9 were discarded due to cytotoxicity. In the S9-activated system, ≤2.2% of the cells survived treatment with doses ≥207 µg/mL a.i. In addition, the report stated that cell densities of cultures treated with ≥6.91 µg/mL a.i. were reduced (primary data were submitted but were not legible). Based on these data, the study author selected dose ranges of 0.0414–0.414 µg/mL -S9 and 4.14–103.5 µg/mL +S9 (a.i.).

2. Mutation Assays: The initial results from the mutation assays indicated that the selected ranges produced unacceptable levels of cytotoxicity. Therefore, the assay was repeated with a.i. levels

[1]Snee, R.D. and J.D. Irr. 1981. Design of a statistical method for the analysis of mutagenesis at the hypoxanthine guanine phosphoribosyl transferase locus of cultured Chinese hamster ovary cells. Mutat. Res. 85:77-93

that ranged from 0.005 to 0.5 µg/mL -S9 and from 0.5 to 100 µg/mL +S9. Representative results from the nonactivated trials conducted with Sodium Omadine® are shown in Table 1. Severe cytotoxicity was observed at the three highest nonactivated doses; accordingly, cultures treated with these concentrations were not cloned. For the remaining treatment groups, RS decreased in a dose-related manner with increasing concentrations of the test material. At 0.10 µg/mL, the average RS was 4.7%. In general MFs for cultures treated with the test material were within the reported spontaneous MF range for CHO cells (0-20 TG^r mutants/10^6 cells) and did not suggest a mutagenic response. Although a MF of 42.5 mutants/10^6 cells was calculated for one of the replicate cultures exposed to 0.05 µg/mL, the finding was considered by our reviewers to be spurious. The average MF of CHO cultures exposed to 200 µg/mL EMS was 223.6 mutants/10^6 cells indicating that the test system was adequately sensitive to detect mutagenesis.

The data presented in Table 2 show that RS of CHO cells exposed to the S9-activated test material also decreased in a dose-related manner. At ≥25 µg/mL <1% of the cells survived and cultures treated with these doses were discarded because of extreme cytotoxicity. The MFs for cells exposed to the remaining doses (≈0.5-10 µg/mL) were ≤9.8 mutants/10^6 cells and within the spontaneous MF range for CHO cells. By contrast to negative results with the test material, the positive control (100 µg DMN) induced a powerful mutagenic effect.

3. Analytical Determinations: The analysis of dosing solutions used in both the nonactivated and S9-activated trials indicated that all of the doses in the nonactivated assay exceeded ±10% of the target values and the differences ranged from 12% to 49% of the nominal value. Three stock solutions in the S9-activated assay were also outside of the acceptable range with their differences ranging from 12% to 30% of the nominal dose. Actual concentrations for selected doses are shown in Tables 1 and 2.

Based on the overall findings, the study author concluded that Sodium Omadine® was not mutagenic in this mammalian cell gene mutation assay.

D. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS: We agree with the study author's conclusions that the data did not suggest that Sodium Omadine® was mutagenic in this assay. The test material was evaluated over appropriate nonactivated and S9-activated dose ranges that included cytotoxic levels. In addition, the sensitivity of the test system was adequately demonstrated by the results obtained with the positive controls. We further assess that the wide variations between actual and target concentrations, as indicated by the analytical data, did not compromise the study because there was clear evidence of test material interaction with the target cells.

TABLE 1. Representative Results from the Chinese Hamster Ovary (CHO) Cell Forward Gene Mutation Assays with Sodium Omadine® in the Absence of S9 Metabolic Activation

Substance	Dose/mL	Average Percent Relative Survival (posttreatment)[a]	Average Total Mutant Colonies	Average Absolute Cloning Efficiency (%)[a]	Average Mutation Frequency/ 10^6 survivors[b]
Negative Control					
Ham's F12 Medium	--	100.0	1.5	93.6	1.6
Solvent Control					
Water	10 µL	88.3	8	93.4	8.5
Positive Control					
Ethyl methane-sulfonate	200 µg	74.5	235.5	105.8	223.6[c]
Test Material					
Sodium Omadine®	0.020 (-)[d] µg[e]	87.2	2.5	93.6.	2.7
	0.035 (0.052) µg	42.0	4.5	89.9	5.0
	0.050 (0.06) µg	16.2	21.75[f]	83.2	24.4
	0.100 (0.08) µg[g]	4.7	0	78.5	<1.4

[a]Average values from duplicate cultures for all groups; calculated by our reviewers.

[b]Mutation Frequency (MF) = $\frac{\text{Average Total Mutant Colonies}}{\text{No. of Dishes (5) X No. of Cells Plated (2X10}^5\text{) X Absolute Cloning Efficiency}}$

[c]Exceeds 3 times the average MF of the negative control and, therefore, meets one of the requirements for a positive response

[d]This level of the test material was below the limit of detection of the analytical procedure. Other values in () are the actual concentrations, based on analytical determinations.

[e]Results for lower levels (0.005 or 0.01 µg/mL +S9) did not suggest a mutagenic response.

[f]Estimated MF based on a single mutant in one set of 5 dishes and 42.5 mutants in the second set (42.5 total mutants/4 dishes; one of 5 dishes was contaminated).

[g]Higher doses (≥0.170 µg/mL, actual concentration) were reported to be extremely cytotoxic

Note: Data were extracted from the study report, pp. 12-13.

TABLE 2. Representative Results from the Chinese Hamster Ovary (CHO) Cell Forward Gene Mutation Assay with Sodium Omadine® in the Presence of S9 Activation

Substance	Dose/mL	Average Percent Relative Survival (posttreatment)[a]	Average Total Mutant Colonies	Average Absolute Cloning Efficiency (%)[a]	Average Mutation Frequency/ 10^6 survivors[b]
Negative Control					
Ham's F12 Medium	--	101.2	5.5	97.9	5.7
Solvent Control					
Water	10 µL	87.6	1	91.0	1.2
Positive Control					
Dimethylnitrosamine	100 µg	36.3	112.5	84.5	132.3[c]
Test Material					
Sodium Omadine®	0.5 (0.44)[d] µg	55.6	12.5	118.4	9.8
	1.0 (0.7) µg	22.2	1.0	100.8	1.0
	2.5 (2.3) µg	12.6	2.5	103.2	2.6
	5.0 (5.0) µg	11.7	0.0	86.2	<1.2
	10.0 (11.0) µg	13.1	0.0	89.35	<1.2
	25.0 (27.0) µg[e]	0.4	--[f]	--[f]	--[f]

[a]Average values from duplicate cultures for all groups; calculated by our reviewers.

[b]Mutation Frequency (MF) = $\frac{\text{Average Total Mutant Colonies}}{\text{No. of Dishes (5) X No. of Cells Plated } (2X10^5) \text{ X Absolute Cloning Efficiency}}$

[c]Exceeds 3 times the average MF of the negative control and, therefore, meets one of the requirements for a positive response

[d]Values in ( ) are the actual concentrations, based on analytical determinations

[e]Higher levels (50.0, 75.0, or 100 µg/mL -S9) were not scored because of extreme cytotoxicity

[f]Not plated

Note: Data were extracted from the study report, pp. 12, 14, 36-38.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A quality assurance statement was signed and dated May 28, 1987.)

CORE CLASSIFICATION: Acceptable. This study satisfies the requirements for FIFRA Test Guideline Series 84-2 for genetic effects Category I, Gene Mutations and is acceptable for regulatory purposes.

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 84-2b; *In Vivo* Micronucleus Assay in Mice

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.4% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 403437-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® Micronucleus Test

AUTHOR: R.S. Sorg

STUDY NUMBER: PH 309-OL-001-87

STUDY COMPLETED: March 30, 1987

EXECUTIVE SUMMARY (revised): Sodium Omadine 40% Aqueous Solution (41.4% purity) did not cause micronucleus induction in the bone marrow cells of male or female CD-1 mice at 30, 48, or 72 hours after the intraperitoneal administration of 575 mg/kg (238 mg/kg/active ingredient). Clinical signs of toxicity (decreased body tone, body drop, and abnormal gait in all animals, ptosis in 9/10 animals, lacrimation in 6/10 animals, and tremors in two females) and target cell cytotoxicity [significantly decreased ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) at 72 hours] were observed at this level.

CORE CLASSIFICATION: **Acceptable.** The study satisfies the requirements for FIFRA Test Guideline Series 84-2 for genetic effects Category II, Structural Chromosome Aberrations, and is acceptable for regulatory purposes.

Comments: The test article is Sodium Omadine 40% Aqueous Solution (41.4% purity).

011532

FINAL

DATA EVALUATION REPORT

Sodium Omadine®

Study Type: Mutagenicity: In Vivo Micronucleus Assay in Mice

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer — Dean Walton, Ph.D. — Date 10/7/93

Independent Reviewer — Nancy E. McCarroll, B.S. — Date 10/7/93

QA/QC Manager — Sharon Segal, Ph.D. — Date 10/7/93

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 405
Project Officer: Caroline C. Gordon

GUIDELINE SERIES 84: MUTAGENICITY
MICRONUCLEUS

EPA Reviewer: Irving Mauer, Ph.D. Signature:
Immediate Office Date: 10-14-93
Toxicology Branch II/HED (H7509C)
EPA Section Head: Marion Copley, D.V.M., DABT Signature:
Review Section IV, Date: 10/19/93
Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: In vivo micronucleus assay in mice

CHEMICAL: Sodium Omadine®

TOX CHEM NUMBER: 790A

P.C. CODE: 088004

MRID Number: 403437-01

SYNONYM/CAS No.: Sodium 2-pyridine thiol-1-oxide; Sodium pyrithione/ 3811-73-2

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® Micronucleus Test

AUTHOR: R.S. Sorg

STUDY NUMBERS: PH 309-OL-001-87

REPORT ISSUED: March 30, 1987

CONCLUSIONS-EXECUTIVE SUMMARY: Negative for micronucleus induction in the bone marrow cells of male or female CD-1 mice at 30, 48, or 72 hours after the intraperitoneal administration of 575 mg/kg (238 mg/kg active ingredient) of Sodium Omadine®. Clinical signs of toxicity (decreased body tone, body drop, and abnormal gait in all animals, ptosis in 9/10 animals, lacrimation in 6/10 animals, and tremors in two females) and target cell cytotoxicity [significantly decreased ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) at 72 hours] were observed at this level.

CLASSIFICATION: Acceptable. The study satisfies the requirements for FIFRA Test Guideline Series 84-2 for genetic effects Category II, Structural Chromosome Aberrations, and is acceptable for regulatory purposes.

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A. MATERIALS:

1. Test Material: Sodium Omadine®

Description: Clear amber liquid; specific gravity = 1.258 g/mL
Identification number: Lot Number F113B
Purity: 41.4% Active ingredient (a.i.)
Storage: Room temperature
Receipt date: January 5, 1987
Stability: Not reported
Contaminants: None listed
Vehicle used: Distilled water (DH_2O)
Other provided information: The dosing solutions were adjusted to 100% purity and were prepared within two hours of use. Analytical determinations revealed that the dosing solution prepared for the micronucleus assay was within ±2.3% of the target concentration.

2. Control Materials:

Vehicle: DH_2O by intraperitoneal (ip) injection at a dosing volume of 10 ml/kg.

Positive: Triethylenemelamine (TEM) was prepared in 0.9% saline solution to yield a final dose of 0.5 mg/kg and was administered by ip injection at a dosing volume of 10 mL/kg.

3. Test Compound:

Route of administration: Single ip injection

Volume of test substance administered: 10 ml/kg

Dose levels used:

- Acute dose range-finding study: 41.4, 103.5, 155, 207, 269, 331, and 414 mg/kg a.i.
- Micronucleus assay: 238 mg/kg a.i.

4. Test Animals:

(a) Species: Mouse Strain: CD-1 Age (at dosing): 9 weeks Acute dose range-finding study; 7 weeks Micronucleus study

Weight Range:

- Acute dose range-finding study (at dosing): 32-40 g (males); 31-37 g (females)
- Micronucleus assay (at dosing): 28-34 g (males); 23-29 g (females)

Source: Charles River Laboratories, Wilmington, MA

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(b) Number of animals used per dose:

Acute study: 2 (males); 2 (females) /treatment group 011532

Micronucleus assay (dose groups/sacrifice time):

- Treatment groups: 5 males 5 females
- Positive control: 5 males 5 females
- Vehicle control: 5 males 5 females

Note: All animals were weighed immediately prior to dosing and dosing volumes were based on individual weights.

(c) Animals were properly maintained? Yes.

B. TEST PERFORMANCE:

1. Acute Dose Range-finding Study: Animals received the selected dose of the test compound or vehicle control by single ip injection. Clinical signs data were recorded immediately postdosing and at 4, 24, 48, and 72 hours.

2. Micronucleus Assay:

Treatment and sampling times:

(a) Test compound:
Dosing: x once _____ twice (24 hours apart)
Sampling (after last dose): _____ 6 hours _____ 12 hours
x 30 hours x 48 hours x 72 hours

(b) Vehicle control:
Dosing: x once _____ twice (24 hours apart)
Sampling (after last dose): _____ 30 hours x 48 hours
_____ 72 hours

(c) Positive control:
Dosing: x once _____ twice (24 hours apart)
Sampling (after last dose): x 30 hours _____ 48 hours
_____ 72 hours

3. Tissues and Cells Examined:

x bone marrow _____ other (list):
Number of polychromatic erythrocytes (PCEs) examined per animal: 1000
Number of normochromatic erythrocytes (NCEs, more mature RBCs) examined per animal: Number observed while scoring 1000 polychromatic erythrocytes

4. Details of Cell Harvest and Slide Preparation: At 30, 48, and 72 hours after administration of the test material, the appropriate groups of animals were sacrificed by cervical dislocation. Animals in the positive control group were sacrificed 30 hours postexposure and mice in the vehicle control group were sacrificed at 48 hours. Bone

marrow cells from both femurs of each animal were aspirated into fetal bovine serum, centrifuged, resuspended and spread onto glass slides. Prepared slides were dried at 56°C, fixed in methanol, stained with 5% Giemsa and mounted. After coding, slides were scored for total erythrocytes, PCEs, and micronucleated PCEs (MPEs).

5. Statistical Methods: The results were evaluated for statistical significance ($p \leq 0.05$ and 0.01) using a one-tailed t-test for comparison of treatment groups and using arcsin transformation followed by a pairwise t-test.

6. Evaluation Criteria:

   (a) Assay Validity: The assay was considered acceptable if the mean incidence of MPEs was ≤0.5% in the vehicle control, the incidence of MPEs in the positive control was significantly greater than the vehicle control, and at least seven animals per group survived treatment.

   (b) Positive Response: The test material was considered positive if a statistically significant ($p \leq 0.05$) increase in the incidence of MPEs as compared to the vehicle control was observed.

C. REPORTED RESULTS:

1. Acute Dose Range-finding Study: All mice exposed to 414 mg/kg died within 4 hours of treatment. One female administered 331 mg/kg died within 72 hours. Clinical signs observed in all treatment groups included decreased activity, decreased body tone, abnormal gait, and body drop. Lacrimation and/or ptosis were observed in animals administered ≥155 mg/kg. Additional clinical signs noted in animals receiving higher doses included tremors, hypothermia, and prostration at 269 mg/kg and rolling convulsions and straub tail at 414 mg/kg. Based on these results and after discussion with the sponsor, the study author determined that 238 mg/kg Sodium Omadine® a.i. was the maximum tolerated dose.

2. Micronucleus Assays:

   (a) Animal observations: Animals administered 238 mg/kg of the test material developed decreased body tone, body drop, tremors, abnormal gait, ptosis, and lacrimation immediately after dosing. At 4 hours postdosing, hypothermia was observed in one mouse. Decreased body tone and/or abnormal gait were observed in the mice at 24, 48 and 72 hours postdosing. No clinical sings were observed in animals from the vehicle or positive control groups.

   (b) Micronucleus assay: Representative results from the micronucleus assay are presented in Table 1. There were no increases in MPEs observed in bone marrow cells harvested from mice treated with 238 mg/kg Sodium Omadine® at 30, 48, or 72 hours. The PCE:NCE ratios for both males and females were ≈24% lower than the corresponding vehicle control at 72 hours, and the data combined

TABLE 1. Representative Results of the Micronucleus Assay in Mice Treated with Sodium Omadine

Substance	Dose/kg	Exposure Time[a] (hours)	Sex	Number of Animals Analyzed per Group	Number of PCEs Analyzed per Group	Number of MPEs per Group	Mean Percent MPEs ±S.D.	Mean PCE:NCE Ratio ±S.D.
Vehicle Control								
Distilled water	10 mL	48	M	5	5000	3	0.06±0.089	1.95±0.32
		48	F	5	5000	6 (9)[b]	0.12±0.084 (0.09±0.088)[c]	1.73±0.33(1.84±0.33)
Positive Control								
Triethylene-melamine	0.5 mg	30	M	5	5000	329	6.58±1.446	1.08±0.23
		30	F	5	5000	268 (195)	5.36±1.791 (5.97±1.66)*	1.30±0.25 (1.19±0.25)*
Test Material								
Sodium Omadine	238 mg	30	M	5	5000	4	0.08±0.045	1.58±0.33
		30	F	5	5000	5 (9)	0.10±0.071 (0.09±0.057)	2.20±0.54 (1.89±0.53)
		48	M	5	5000	6	0.12±0.084	1.50±0.53
		48	F	5	5000	4 (10)	0.08±0.089 (0.10±0.105)	2.20±0.38 (1.85±0.57)
		72	M	5	5000	7	0.14±0.055	1.50±0.15
		72	F	5	5000	5 (12)	0.10±0.089 (0.12±0.132)	1.32±0.35 (1.41±0.27)*

[a]Time after compound administration by intraperitoneal injection
[b]Values in () are the combined results for both sexes.

*Significantly higher ($p<0.01$) than the corresponding vehicle control

Abbreviations used:

PCE = Polychromatic erythrocytes
MPE = Micronucleated polychromatic erythrocytes
NCE = Normochromatic erythrocytes

Data were extracted from the study report; pp. 14-15.

for both sexes were significantly ($p \leq 0.01$) decreased. The positive control (0.5 mg/kg TEM) induced both a significant ($p \leq 0.01$) increase in the frequency of MPEs and a significant ($p \leq 0.01$) decrease in the PCE:NCE ratio.

Based on the overall results, the study author concluded that Sodium Omadine® was not genotoxic in this in vivo mouse micronucleus assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study was properly conducted and that the study author's interpretation of the data was correct. The test material was evaluated at a level (238 mg/kg) that produced clinical signs of toxicity. This dose also produce cytotoxic effects on the target organ resulting in a significant decrease in the PCE:NCE ratio at the 72-hour harvest time. However, there was no indication of a genotoxic response in bone marrow cells harvested 30, 48, or 72 hours posttreatment. In addition, the sensitivity of the test system to detect genotoxicity was demonstrated by the significant increase ($p \leq 0.01$) in MPEs from the combined results of male and female mice exposed to the positive control (0.5 mg/kg TEM).

We conclude, therefore, that the study provided acceptable evidence that Sodium Omadine® was negative in this in vivo micronucleus assay.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A Quality Assurance Statement was signed and dated April 14, 1987.)

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 84-2c; Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes

CHEMICAL: Sodium Omadine 40% Aqueous Solution (41.4% purity)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 403875-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® Rat Hepatocyte Primary Culture/DNA Repair Test

AUTHOR: T.R. Barfknecht

STUDY NUMBER: PH 311-OL-001-87

STUDY COMPLETED: March 16, 1987

EXECUTIVE SUMMARY (revised): Sodium Omadine 40% Aqueous Solution (41.4% purity) did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes treated with doses up to 220 ng/ml (300 ng/ml, based on analytical determinations). Concentrations ≥71 ng/ml (≥80 ng/ml) were cytotoxic.

CORE CLASSIFICATION: **Acceptable.** This study satisfies the requirements for FIFRA Test Guideline Series 84-4 for genetic effects Category III, Other Mutagenic Mechanisms, and is acceptable for regulatory purposes.

Comments: The test article is Sodium Omadine 40% Aqueous Solution (41.4% purity).

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE®

Study Type: Mutagenicity: Unscheduled DNA Synthesis (UDS) Assay in Primary Rat Hepatocytes

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer _____ Date 10/7/93
Dean Walton, Ph.D.

Independent Reviewer _____ Date 10/7/93
Nancy E. McCarroll, B.S.

QA/QC Manager _____ Date 10/7/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 406
Project Officer: Caroline Gordon

GUIDELINE SERIES 84: MUTAGENICITY
UDS

MUTAGENICITY STUDIES

EPA Reviewer: Irving Mauer, Ph.D.
Immediate Office,
Toxicology Branch I/HED (H7509C)
Signature: [signature]
Date: 10/14/93

EPA Section Head: Marion Copley, D.V.M., DABT
Review Section IV,
Toxicology Branch I/HED (H7509C)
Signature: [signature]
Date: 10/19/93

DATA EVALUATION REPORT

STUDY TYPE: Unscheduled DNA synthesis assay in primary rat hepatocytes.

CHEMICAL: Sodium Omadine®

Tox Chem Number: 790A

P.C. Code: 088004

MRID Number: 403875-01

SYNONYMS/CAS No.: Sodium 2-pyridine thiol-1-oxide; Sodium pyrithione/ 3811-73-2

SPONSOR: Olin Corporation, New Haven CT

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Sodium OMADINE® Rat Hepatocyte Primary Culture/DNA Repair Test

AUTHOR: T.R. Barfknecht

STUDY NUMBER: PH 311-OL-001-87

REPORT ISSUED: March 16, 1987

CONCLUSIONS-EXECUTIVE SUMMARY: Negative for inducing unscheduled DNA synthesis (UDS) in primary rat hepatocytes treated with doses of the test material up to 220 ng/mL (300 ng/mL, based on analytical determinations). Concentrations ≥71 ng/mL (≥80 ng/mL) were cytotoxic.

STUDY CLASSIFICATION: Acceptable. This study satisfies the requirements for FIFRA Test Guideline Series 84-4 for genetic effects Category III, Other Mutagenic Mechanisms and is acceptable for regulatory purposes.

A. MATERIALS:

1. Test Material: Sodium Omadine®

Description: Clear, amber liquid; Specific gravity: Initially reported by the sponsor to be 1.22 g/mL, subsequently revised to 1.258 g/mL.
Lot number: F113B
Purity: 41.4% Active ingredient (a.i.)
Receipt date: January 5, 1987
Stability: Not reported
Contaminants: Not reported
Solvent used: Deionized water (DH_2O)
Other provided information: The test material was stored at ambient temperature in its shipping container. Dosing solutions were prepared within 4 hours of use and the unused portion was returned to the sponsor for verification of the target dose. Prepared dosing solutions were corrected for the 41.4% a.i.

2. Indicator Cells: Rat hepatocytes, collected from adult male rats (Strain: Fischer-344, Charles River Laboratories; weight: 192-232 g).

3. Control Substances:

- The positive control was $1x10^{-7}$ M (≈0.025 µg/mL) 2-acetamido-fluorene (2AAF)

- Williams' Medium E (WME) served as the negative control

4. Medium: WME; WME+: WME plus 10% calf serum

5. Test Compound Concentrations Used: Ten doses from 0.069 to 2070 µg/mL were initially evaluated but were found to be severely cytotoxic. A second range of 10 doses (0.0071-220 ng/mL) were evaluated and cells exposed to ≈7.1, ≈22.0, 71.0 (80), or 220 (300) ng/mL were scored.

Note: Doses in () are the actual concentrations based on analytical determinations. Only calculated values (based on purity and revised specific gravity) are available for the lower levels because these doses were below the limit of detection of the test procedure.

B. STUDY DESIGN:

1. Cell Preparation:

(a) Perfusion technique: The liver was perfused with media A [0.5 mM ethylene-glycol-bis-(B-aminoethyl ether)-N-N'-2-tetraacetic acid (EGTA) in Ca^{++}-Mg^{++} free Hank's balanced salt solution buffered with 10 mM HEPES followed by media B

[collagenase 100 units/mL in WME buffered with 10 mM HEPES, pH 7.35]. After perfusion, the liver was excised, placed in WME, rinsed and transferred to fresh medium B; the hepatocytes were dispersed.

(b) Hepatocyte harvest/culture preparation: Cells were dispensed into tubes with WME+ and allowed to flocculate for 10 minutes. Cell viability was determined by trypan blue exclusion and $\approx 1 \times 10^5$ viable cells were inoculated into each well of replicate cluster culture dishes containing WME+ and plastic coverslips. Cells were incubated for a 2-hour attachment period.

2. UDS Assay:

(a) Treatment: The UDS assay was initiated by adding the selected dose of the test material or positive control, and [^{3}H]-thymidine (10 µCi/mL) to the prepared monolayers. The hepatocytes were incubated for 18-20 hours. Cells were washed three times with phosphate buffered saline. The cells were swollen with 1% sodium citrate and fixed in ethanol:acetic acid (3:1). The coverslips were rinsed and mounted onto slides. Each slide was dipped in NTB photographic emulsion in the dark and dried overnight.

(b) Preparation of autoradiographs/grain development: Slides were exposed for 7 days at 4°C in light-proof boxes containing desiccant, developed and stained with hematoxylin-eosin. Slides were coded prior to analysis.

(c) Grain counting: The nuclear and cytoplasmic grains of 150 cells (50/coverslip) per treatment were counted. The net nuclear grain counts were quantitated by subtracting the highest cytoplasmic grain count of three nuclear-sized areas adjacent to each nucleus from the nuclear grain count. Cells in S-phase were not scored.

3. Evaluation Criteria:

(a) Assay validity: The assay was considered valid if: (1) the solvent and/or the untreated controls had a net nuclear grain count of ≤1; (2) the mean net nuclear grain count for the solvent control did not exceed the upper 95% confidence limit of the mean historical data; (3) the positive control induced a mean net nuclear grain count that was within one standard deviation of its mean historical data.

(b) Positive response: The test material was considered to be positive if: (1) a mean net nuclear grain count of ≥5 grains/nucleus was consistently observed in triplicate wells; and (2) the response was dose related.

4. Statistical Methods: The data were not analyzed for statistical significance.

C. REPORTED RESULTS:

1. Parallel cytotoxicity/UDS assay: Initially 10 doses, ranging from 0.069 to 2070 µg/mL were examined but were found to be severely cytotoxic. Therefore, a second assay using lower doses (≈7.1, ≈22, 71, and 220 ng/mL) was performed. Cytotoxicity was apparent in cultures exposed to the two highest doses; however, sufficient cells were available for analysis. Accordingly, hepatocytes exposed to the four selected levels of the test material were scored for the incorporation of tritiated thymidine. Representative findings presented in Table 1 show that the selected doses of Sodium Omadine® did not induce a genotoxic effect. By contrast, marked increases in the net nuclear grain counts and the percentage of cells in repair were observed in hepatocytes exposed to the positive control (10^{-7} M 2AAF).

2. Analytical Determinations: Initially, doses were calculated using 1.22 g/mL as the specific gravity for the test material; however, the value was subsequently revised by the sponsor to 1.258 g/mL. The study author indicated that the detection limit of Sodium Omadine® in aqueous solutions was 50 ng/mL; therefore, actual levels of the test material in the two lowest dosing solutions could not be verified. However, analysis of the two highest dosing solutions indicated that detectable concentrations for the 220- and 71-ng/mL dosing solutions were 135% and 113% of target, respectively; therefore, the actual concentrations of the test material in these solutions were 300 and 80 ng/mL, respectively.

Based on the overall results, the study author concluded that Sodium Omadine® was not genotoxic in this test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: Our assessment of the UDS test results agrees with the study author's conclusions that Sodium Omadine® did not induce a genotoxic effect in this rat hepatocyte DNA repair assay; there was also sufficient evidence that the two highest applied concentrations (80 or 300 ng/ml) entered the hepatocytes and caused cytotoxic effects. In addition, the sensitivity of the test system to detect UDS was adequately demonstrated by the results obtained with the positive control (10^{-7} M 2AAF).

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement was signed and dated April 20, 1987.)

CORE CLASSIFICATION: Acceptable. This study satisfies the requirements for FIFRA Test Guideline Series 84-4 for genetic effects Category III, Other Mutagenic Mechanisms and is acceptable for regulatory purposes.

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E. STUDY DEFICIENCIES

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The following study deficiencies were noted:

(1) The total recovery of radioactivity was low for all dose groups (85.1%-95.1% of the administered dose); approximately 5-15% of the radioactivity was unaccounted for. It is suggested that the study authors account for the missing radioactivity.

(2) Since 3.2%-12.3% of the radioactivity was recovered in the feces, fecal metabolite characterization should be performed, at least for the high-dose group (11%-12%).

(3) Since metabolism of sodium omadine was extensive, the study authors should propose a metabolic pathway for sodium omadine.

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TABLE 1. Mean Percent Recovery of Radioactivity 4 Days After Oral and Intravenous Administration of ^{14}C-Sodium Omadine to Rats (Definitive Study)[a]

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Dose Group	Sex[b]	Percentage of Radioactive Dose Recovered					
		Urine	Feces	Cage Rinse	Tissues	Carcass	Total Recovery[c]
0.5 mg/kg (single oral low)	Male	85.0	7.0	1.0	0.6	1.5	95.1
	Female	84.2	6.0	0.5	0.4	1.3	92.4
0.5 mg/kg[d] (repeated oral low)	Male	75.1	5.3	2.2	0.7	1.7	85.1
	Female	73.6	8.0	2.2	0.4	1.3	85.5
25 mg/kg (single oral high)	Male	73.3	12.3	0.9	0.8	2.1	89.4
	Female	75.7	11.4	2.8	0.6	1.3	91.2
0.5 mg/kg (i.v.)	Male	83.4	3.2	1.8	N.D.	N.D.	88.5
	Female	80.2	3.2	4.8	N.D.	N.D.	88.2

[a]Source: Tables IV-8-11 pp. 68-71 of the study report
[b]Five animals/sex
[c]Percent of administered dose
[d]Animals were given 0.5 mg/kg/day sodium omadine for 14 days followed by a single dose of 0.5 mg/kg ^{14}C-sodium omadine

N.D. = not determined

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TABLE 2. Distribution of Radioactivity in Tissues of Rats 4 Days After Oral Administration of ^{14}C-Sodium Omadine (Definitive Study)[a]

	Radioactivity (nmol/g) in Tissues of Rats[b] (% of dose in tissues)					
	0.5 mg/kg (single low)		25 mg/kg (single high)		0.5 mg/kg (repeated low)	
Tissue/Organ	Males	Females	Males	Females	Males	Females
Plasma	0.06 (0.02)	0.04 (0.01)	5.72 (0.03)	2.98 (0.02)	0.09 (0.02)	0.04 (0.01)
Blood cells	0.23 (0.07)	0.25 (0.08)	12.26 (0.07)	11.13 (0.07)	0.27 (0.06)	0.24 (0.07)
Liver	0.18 (0.23)	0.13 (0.14)	13.09 (0.29)	7.82 (0.19)	0.22 (0.27)	0.13 (0.16)
Kidney	0.17 (0.04)	0.14 (0.03)	15.92 (0.08)	8.15 (0.03)	0.30 (0.06)	0.16 (0.04)
Heart	0.08 (0.01)	0.06 (0.01)	5.91 (0.01)	3.78 (0.01)	0.11 (0.01)	0.08 (0.01)
Lung	0.09 (0.01)	0.08 (0.01)	6.86 (0.02)	4.34 (0.01)	0.12 (0.02)	0.08 (0.01)
Brain	0.06 (0.01)	0.02 (0.00)	4.64 (0.02)	2.39 (0.01)	0.08 (0.01)	0.02 (0.01)
Fat	0.01 (0.00)	N.D. (0.00)	1.57 (0.00)	0.88 (<0.01)	0.06 (0.01)	0.07 (0.00)
Skeletal muscle	0.06 (0.01)	0.03 (0.01)	4.23 (0.01)	2.35 (0.66)	0.08 (0.01)	0.04 (0.01)
Spleen	0.08 (0.01)	0.08 (0.01)	6.58 (0.01)	4.45 (0.01)	0.15 (0.01)	0.10 (0.01)
Reproductive organs	0.07 (0.02)	0.04 (0.00)	4.97 (0.03)	2.62 (0.00)	0.09 (0.02)	0.04 (0.00)
Bone marrow	0.24 (<0.01)	N.D --	3.69 (<0.01)	N.D. --	0.03 (<0.01)	0.02 (<0.01)
Sciatic nerve	0.04 (<0.01)	N.D. --	4.40 (<0.01)	2.28 (<0.01)	0.04 (<0.01)	N.D. --
Spinal cord	0.03 (<0.01)	N.D. --	3.50 (<0.01)	0.80 (<0.01)	0.05 (<0.01)	0.01 (<0.01)
Intestines	0.06 (0.07)	0.03 (0.03)	5.80 (0.09)	3.12 (0.07)	0.10 (0.09)	0.06 (0.06)
Intestinal contents	0.02 (0.08)	0.01 (0.05)	1.72 (0.14)	1.30 (0.13)	0.03 (0.11)	N.D. --
Urinary bladder	0.07 (0.01)	0.04 (0.01)	5.11 (<0.01)	2.66 (<0.01)	0.08 (<0.01)	0.02 (<0.01)
Total	(0.6)	(0.39)	(0.8)	(0.55)	(0.7)	(0.39)

[a]Source: Tables IV-2-7, pp. 59-62, 64 and 66 of the study report
[b]Each value represents the mean of five rats.

N.D. = Not detectable

TABLE 3. Distribution of Metabolites in Urine 72 Hours After Oral and Intravenous Administration of ^{14}C-Sodium Omadine[a]

	Percentage of Dose Found							
	0.5 mg/kg (i.v.)		0.5 mg/kg (single oral low)		0.5 mg/kg (repeated oral low)		25 mg/kg (single oral high)	
Metabolites[b]	Male	Female	Male	Female	Male	Female	Male	Female
A	16.2	17.0	14.7	7.7	21.3	11.0	14.0	14.3
D	3.6	2.8	2.0	3.9	4.5	8.0	5.1	7.3
G	0.8	3.0	2.8	0.4	0.1	0.5	0.2	1.2
H	8.0	4.1	2.6	1.4	2.7	1.4	6.1	1.0
K	50.2	49.6	59.0	67.2	41.4	49.3	43.3	46.8
Others	2.3	1.4	2.8	2.5	3.1	1.7	2.8	2.9
Total	81.6	78.2	83.5	83.1	73.1	72.0	70.8	73.5

[a]Source: Tables IV-12-15, pp. 73-76 of the study report
[b]Identification of metabolites
A = 2-(Methylsulfonyl)pyridine
H = 2-Pyridinethiol-S-glucuronide
K = 2-Pyridinethiol-1-oxide-S-glucuronide
Metabolites D and G were not identified.
Others = Metabolites B, C, E, F, I, J, L

JW 1-20-95

011532

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-1; Acute oral Toxicity

CHEMICAL: Sodium omadine (10% solution)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-01

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution — Single Dose Oral Toxicity in Rats/LD_{50} in Rats

AUTHOR: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122A

STUDY COMPLETED: June 22, 1988

EXECUTIVE SUMMARY: The acute gavage LD_{50} for sodium omadine (10% solution) was reported to be >5000 mg/kg (limit test) for male and female Wistar rats. Clinical signs observed were limited to wet anogenital areas and brown staining on the body. No unusual findings were reported upon necropsy of the test animals.

CORE CLASSIFICATION: **Unacceptable.** This study does not satisfy the guideline data requirements (81-1) for acute toxic effects, and is not acceptable for regulatory purposes. This report can be upgraded if the appropriate information is submitted and meets the guideline requirements (see Section D, REVIEWERS' COMMENTS).

TOXICITY CATEGORY: IV — Caution

Comments: The DER did not mention that dosing was by gavage. In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable." This study can be upgraded provided several reporting deficiencies are addressed. The DER lacked an executive summary, so the preceding summary was generated.

The penned corrections added by the secondary reviewer read as follows:

Core Classification: **Supplementary.** This study does not satisfy the guideline data requirements (81-1) for acute toxic effects on the 10% formulation and is not acceptable for regulatory purposes.

Dosing: Once __x__ by gavage

Page numbers have been corrected.

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Acute Oral Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer _____ Date 9/20/93
Dean Walton, Ph.D.

Independent Reviewer _____ Date 9/20/93
Carolyn Rabe, Ph.D.

QA/QC Manager _____ Date 9/20/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 408
Project Officer: Caroline Gordon

ACUTE TOXICITY STUDIES

011532

EPA Reviewer and
Section Head: Marion Copley, DVM, DABT
Review Section IV,
Toxicology Branch I/HED H7509C

Signature: Marion Copley
Date: 9/29/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-1; acute oral toxicity - rats

CHEMICAL: Sodium omadine (10% solution)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID Number: 410275-01

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE(R) 10% Solution - Single Dose Oral Toxicity in Rats/LD_{50} in Rats

AUTHORS: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122A

STUDY COMPLETED: June 22, 1988

CONCLUSIONS: The acute oral LD_{50} for sodium omadine (10% solution) was reported to be >5000 mg/kg (limit test) for male and female Wistar rats. Clinical signs observed were limited to wet anogenital areas and brown staining on the body. No unusual findings were reported upon necropsy of the test animals.

CORE CLASSIFICATION: Supplementary This study does not satisfy the guideline data requirements (81-1) for acute toxic effects on the 10% formulation and is not acceptable for regulatory purposes. This report can be upgraded if the appropriate information is submitted and meets the guideline requirements (see Section D, REVIEWERS' COMMENTS).

TOXICITY CATEGORY: IV--Caution

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A. MATERIALS

1. Test Compound

Test material: sodium omadine, 10% solution
Identification number: Not reported
Active ingredient: sodium omadine
Formulation: Not indicated
Purity: 10% solution
Physical description: Clear liquid; specific gravity = 1.04
Storage condition: Ambient room temperature and humidity
Stability: Not reported
Dose level: 5 g/kg (5000 mg/kg)
Dosing volume: ≤1 mL/100 g (actual volumes, 0.96-1.1 mL)

2. Controls:

None

3. Test Animals

Species: Rat
Strain: Wistar Albino
Source: Ace Animals
Sex: Males and females
Age: ~8 weeks old
Weight: Males, 228-239 g; females, 200-217 g; test day
No. animals/dose: 10 (five/sex)
Identification: Cage cards and indelible body marks
Housing: five/sex/cage
Assignment: Random
Diet: Purina Rat Chow #5012 ad libitum
Water: Ad libitum
Environmental conditions: Temperature: Not reported; Humidity: Not reported; Number of air changes per hour: Not reported; Photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

Animals fasted: Not reported

Dosing: Once __x__ by gavage JMC 9/30/93; Other _____ (describe)

Observation period: 14 days

Observation frequency: 1, 2, and 4 hours postdosing and twice daily thereafter

Body weight interval: Pretest and at 7 and 14 days

Gross pathology: YES __x__; NO _____

Histopathology: YES _____; NO __x__

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C. RESULTS

1. Mortality: No mortalities were observed.

2. Clinical Observations: Female rats were observed with wet anogenital areas during week 1 and were normal during week 2. One male rat was observed with a wet anogenital area on day 1; the remaining males were normal. Brown staining of the body was also observed during week 1 in females.

3. Body Weights: All animals experienced normal body weight gains during the study. The mean increases in body weight for males and females were 54% and 36%, respectively.

4. Gross Necropsy: All observations of necropsied animals were reported to be normal.

5. LD_{50} Determination: The estimated acute oral LD_{50} for males, females, and the sexes combined was >5000 mg/kg (limit test).

The study author concluded that under the conditions of this study the acute oral LD_{50} for sodium omadine (10% solution) was >5000 mg/kg.

D. REVIEWERS' COMMENTS

Although the reviewers are in agreement with the study author's reported findings that the acute oral LD_{50} for a 10% sodium omadine solution was >5000 mg/kg, the following reporting deficiencies compromised the study:

- It was not indicated if the test animals were fasted prior to dosing.
- An identification or lot number for the test material was not included in the report
- The solvent for the test material was not reported.
- It was not indicated if the test material solution was formulated on a weight/volume or volume/volume basis.
- Environmental conditions were not reported.

E. QUALITY ASSURANCE MEASURES

Was the test performed under GLPs? YES X ; NO ___
A Quality Assurance Statement, signed and dated July 7, 1988, was submitted.

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-2; Acute Dermal Toxicity in Rabbits

CHEMICAL: Sodium omadine (10% solution)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-02

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution — Acute Dermal Toxicity in Rabbits/LD_{50} in Rabbits

AUTHOR: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122B

STUDY COMPLETED: June 23, 1988

EXECUTIVE SUMMARY: The estimated acute dermal LD_{50} for a 10% solution of sodium omadine in male and female rabbits was not determined. During a limit test (2000 mg/kg), 4/5 males and 2/5 females died. Clinical signs included lethargy, ataxia, yellow nasal discharge, tachypnea, tremors, diarrhea, emaciation, few feces, rales, soiling of the anogenital area, and wet area around the mouth and nose. Necropsy revealed abnormalities of the treated skin, intestines (distended containing mucus, red or black discoloration), ears (purple), lungs (hemorrhages, brown areas and/or congestion), conjunctiva (redness), liver (pale, mottled brown), stomach (pale, distended), spleen (pale, grey), kidneys (pitted), and the pleural cavity (excess fluid). Yellow staining of the mouth and/or nose was also observed.

CORE CLASSIFICATION (revised): Unacceptable - upgradable. This study does not satisfy guideline data requirements (81-2) for acute dermal toxicity on the 10% formulation, and is not acceptable for regulatory purposes. Although an LD_{50} was not calculated, it is apparent from the mortality pattern that the Toxicity Category is II. The identification numbers for the female rabbits did not correspond throughout the study. An identification

number for the test material was not provided, and the type of vehicle used was not identified. Rather than wasting additional life, this study can be upgraded provided these reporting deficiencies are addressed.

TOXICITY CATEGORY: II - Warning

Comments: In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable." Although an LD_{50} was not calculated, it is apparent from the mortality pattern that the Toxicity Category is II. Rather than wasting additional life, this study can be upgraded provided several reporting deficiencies are addressed.

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Acute Dermal Toxicity in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 394
Project Officer: Caroline Gordon

GUIDELINE SERIES 81-2: Acute dermal toxicity

EPA Reviewer and Section Head: Marion Copley, DVM Signature:
Review Section IV, Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-2; acute dermal toxicity - rabbits

CHEMICAL: Sodium omadine, 10% solution

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-02

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution - Acute Dermal Toxicity in Rabbits/LD_{50} in Rabbits

AUTHORS: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122B

STUDY COMPLETED: June 23, 1988

CONCLUSIONS: The estimated acute dermal LD_{50} for a 10% solution of sodium omadine in male and female rabbits was not determined. During a limit test, 4/5 males and 2/5 females died. Clinical signs included lethargy, ataxia, yellow nasal discharge, tachypnea, tremors, diarrhea, emaciation, few feces, rales, soiling of the anogenital area, and wet area around the mouth and nose. Necropsy revealed abnormalities of the treated skin, intestines (distended, containing mucus, red or black discoloration), ears (purple), lungs (hemorrhages, brown areas and/or congestion), conjunctiva (redness), liver (pale, mottled brown), stomach (pale, distended), spleen (pale, grey), kidneys (pitted), and the pleural cavity (excess fluid). Yellow staining of the mouth and/or nose was also observed.

CORE CLASSIFICATION: Supplementary. This study does not satisfy guideline data requirements (81-2) for acute dermal toxicity on the 10% formulation and is not acceptable for regulatory purposes because LD_{50} values were not determined. The study was also compromised for the following reasons: (1) the identification numbers for the female rabbits did not correspond throughout the study; (2) an identification number for the test material was not provided; and (3) the type of vehicle used was not identified.

TOXICITY CATEGORY: Not determined

A. MATERIALS

1. Test Compound

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Test material: Sodium omadine, 10% solution
Identification number: Not reported
Active ingredient: Sodium omadine
Formulation: 10% solution
Purity: 10%
Physical description: Clear liquid; specific gravity = 1.04
Storage condition: Ambient room temperature and humidity
Stability: Not reported
Dose levels: The limit dose, 2 g/kg (2000 mg/kg), was evaluated.
Dosing volume: 1.92 mL/kg based on a specific gravity of 1.04

2. Controls

None

3. Test Animals

Species: Rabbit
Strain: New Zealand white
Source: Ace Animals
Sex: Males and females
Age: ~8 weeks old
Weight: Males, 2.3 kg; females, 2.1-2.5 kg; test day
Number of animals/dose: 10 (five/sex)
Identification: Cage cards and ear tags
Housing: Individually
Acclimation period: At least 1 week
Diet: Purina Rabbit Chow #5321 ad libitum
Water: Ad libitum
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

Animals fasted: Not reported
Dosing: Once __x__; Other _____ (describe)
Skin preparation: Twenty-four hours prior to the application of the test material, a dorsal area of each rabbit's trunk, covering at least 10% of the body surface, was clipped free of hair. The test material was applied with a syringe type applicator and covered by a gauze patch. The patch was secured with non-irritating tape, and each animal's torso was wrapped in plastic. After 24 hours, the wrappings were removed and the material was washed away.
Observation period: 14 days
Observation frequency: 1, 2, and 4 hours postdosing and twice daily thereafter.
Body weight interval: Pretest, 7 days, and 14 days
Gross pathology: YES __x__; NO _____

Histopathology: YES _____; NO __x__

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C. RESULTS

1. Mortality: At the dose tested (2.00 g/kg), 4/5 males and 2/5 females died. All deaths occurred on day 1.

2. Clinical Observations: Clinical signs included lethargy, ataxia, yellow nasal discharge, tachypnea, tremors, diarrhea, emaciation, few feces, rales, soiling of the anogenital area, and wet area around the mouth and nose. Several clinical signs were still evident at the end of the 14-day observation period and included yellow nasal discharge, few feces, diarrhea, emaciation, and anogenital soiling

   Note: The identification numbers for the female rabbits did not correspond between the section on clinical signs (C2224-F, C2141-F, C2127-F, C2143-F, and C2122-F) and the sections on dermal reactions or necropsies (C4047/F, C4041/F, C4048/F, C4055/F, and C4044/F).

3. Dermal Irritation: The test material produced mild erythema and edema, paleness, and discoloration of the skin (brown) all lasting <7 days; flaking of the skin was observed at 14 days. Discoloration and flaking of the skin were observed in only 1 animal each.

4. Body Weights: Body weights were decreased at one or more observation periods in all surviving animals.

5. Gross Necropsy: Necropsy revealed abnormalities of the treated skin, yellow staining of the nose/mouth, abnormalities of the intestines (distended, containing mucus, red or black discoloration) each in 7/10 rabbits; purple ears were observed in 6/10 rabbits. Abnormalities of the lungs (hemorrhages, brown areas and/or congestion) and of the conjunctiva (redness) were observed in half of the test animals. Abnormalities of the liver (pale, mottled brown), stomach (pale, distended), spleen (pale, grey), kidneys (pitted), as well as fluid in the pleural cavity were observed in ≤4 rabbits.

6. LD_{50} Determination: A dermal LD_{50} was not determined.

   The study authors concluded that the dermal LD_{50} of a 10% sodium omadine solution was <2000 mg/kg.

D. REVIEWERS' COMMENTS

Although the reviewers are in agreement with the study authors' reported findings that the acute dermal LD_{50} was <2000 mg/kg for 10% sodium omadine solution in male rabbits, the study was compromised because LD_{50}s were not determined for either sex. The study was also compromised for the following reasons: (1) the identification numbers for the female rabbits did not correspond throughout the study; (2) an identification number for the test material was not provided; and (3) the type of vehicle used was not identified.

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E. QUALITY ASSURANCE MEASURES

Was the test performed under GLPs? YES _X_; NO ___
A Quality Assurance Statement, signed and dated July 8, 1988, was submitted.

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-4; Primary Eye Irritation in Rabbits

CHEMICAL: Sodium omadine (10% solution)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-03

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution — Primary Eye Irritation/Corrosion in Rabbits

AUTHOR: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122D

STUDY COMPLETED: June 10, 1988

EXECUTIVE SUMMARY: Reported to be a slight ocular irritant when 0.1 ml of a 10% sodium omadine solution was instilled into the eyes of New Zealand Albino rabbits. A positive response (grade 2 conjunctival redness) lasting <48 hours was observed in 1/6 animals.

CORE CLASSIFICATION: **Unacceptable** - upgradable. This study does not satisfy guideline data requirements (81-4) for a primary eye irritation study for the 10% formulation, and is not acceptable for regulatory purposes. A manufacturing number for the test material, the purity of the test material, and the identification of other components of the solution should be included in the study. The study can be upgraded if information fulfilling these requirements is provided.

TOXICITY CATEGORY: III — Caution

Comments: In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable."

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Primary Eye Irritation in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Sara Lundgaard (for) Date 10/19/93
Dean Walton, Ph.D.

Independent Reviewer Carolyn D. Rabe Date 10/19/93
Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 399
Project Officer: Caroline Gordon

GUIDELINE SERIES 81-4: Primary eye irritation

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV Date: 10/25/93
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-4; primary eye irritation - rabbits

CHEMICAL: Sodium omadine, 10% solution

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-03

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution - Primary Eye Irritation/Corrosion in Rabbits

AUTHORS: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122D

STUDY COMPLETED. June 10, 1988

CONCLUSIONS: Reported to be a slight ocular irritant when 0.1 mL of a 10% sodium omadine solution was instilled into the eyes of New Zealand Albino rabbits. A positive response (grade 2 conjunctival redness) lasting <48 hours was observed in 1/6 animals.

CORE CLASSIFICATION: Supplementary. This study does not satisfy guideline data requirements (81-4) for a primary eye irritation study for the 10% formulation and is not acceptable for regulatory purposes. A manufacturing number for the test material, the purity of the test material, and the identification of other components of the solution should be included in the study. The study can be upgraded provided information fulfilling these requirements is provided.

TOXICITY CATEGORY: III--Caution

A. MATERIALS

1. Test Compound

Test material: Sodium omadine
Identification number: Not reported
Active ingredient: Sodium omadine
Formulation: 10% solution; other components not reported
Purity: Not reported
Physical description: Clear liquid
Storage condition: Ambient room temperature and humidity
Stability: Not reported

2. Dose level

0.1 mL liquid administered as received

3. Test Animals

Species: Rabbits
Strain: New Zealand albino
Source: Ace Animals
Number of animals: 6
Sex: 4 males, 2 females
Age: Not reported
Mean body weight: Not reported
Housing: Individual
Identification: Cage cards and ear tags
Feed: Purina Rabbit Chow #5321, ad libitum
Water: Ad libitum
Selection: Animals free of ocular irritation
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

1. Test Material Application: The test substance was placed in the lower conjunctival sac of one eye of each animal. Eyelids were gently held together for 1 second. The other eye of each animal served as the untreated control.

2. Eye Examination: Twenty-four hours after instillation of the test material, the treated eyes were examined with sodium fluorescein.

3. Observation Period: X 1 hr X 24 hrs X 48 hrs X 72 hrs
___ 4 days ___ 7 days ___ 10 days ___ 14 days
___ 17 days ___ 21 days

4. Scoring System: Eyes were examined and scored for ocular lesions using the Draize scoring system.

C. REPORTED RESULTS: A summary of ocular effects is presented below:

Summary of Incidence of Positive Ocular Effects for Each Observation Interval (hour)

	1	24	48	72
Cornea				
Opacity	0	0	0	0
Iris				
Iritis	0	0	0	0
Conjunctivae				
Redness	1/6	1/6	0	0
Chemosis	0	0	0	0

[a]The following grades for each tissue are considered positive:

Opacity (Density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (Redness) - Grades 2 and 3
(Chemosis) - Grades 2, 3, and 4

One animal was observed with diffuse crimson red conjunctival irritation (Grade 2) up to 24 hours after the instillation of the test material. All other observations for redness and chemosis were scored as grade 1 or less. At the 1-hour observation, discharge with moistening of the lids and adjacent hairs (grade 2) occurred in 3 rabbits, and greater-than-normal discharge (grade 1) occurred in the other 3. Only 1 rabbit had greater-than-normal discharge 24 hours after instillation of the test material. No signs of irritation were noted at the 48- and 72-hour observation periods. One animal died (potentially treatment related) during the course of the study and was replaced with an additional rabbit. Data shown above reflect the scores of the replaced rabbit.

The study authors concluded that sodium omadine (10% solution) was a slight ocular irritant.

Toxicity Category: III--Caution

D. REVIEWERS' COMMENTS: Although the reviewers agree with the study authors' reported conclusion that sodium omadine instilled in the eyes of test rabbits produces slight irritation lasting <48 hours, the following reporting deficiencies were noted:

- The test material purity and other components of the solution were not identified.
- It was not reported if the eyes of the test animals were examined with sodium fluorescein prior to the instillation of the test material.

- Environmental conditions under which the test animals were maintained were not reported.
- A manufacturing identification number for the test material was not provided.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement was signed and dated July 11, 1988.)

JW 1-20-95

Reviewed by: John E. Whalan
Section I, Tox. Branch I (7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/20/95
Section I, Tox. Branch I (7509C)

STUDY TYPE: Guideline 81-5; Primary Dermal Irritation in Rabbits

CHEMICAL: Sodium omadine (10% solution)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-04

SYNONYM(S): Sodium 2-pyridinethiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution — Primary Dermal Irritation in Rabbits

AUTHOR: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122C

STUDY COMPLETED: June 10, 1988

EXECUTIVE SUMMARY: Application of 0.5 ml sodium omadine (10% solution) to the skin of rabbits for 4 hours resulted in very slight erythema and slight edema lasting <48 hours.

CORE CLASSIFICATION: **Unacceptable** - upgradable. This study does not satisfy the guideline series data requirements (81-5) for a primary dermal irritation study on the 10% formulation, and is not acceptable for regulatory purposes. This study can be upgraded if the appropriate information on the test material purity, manufacturing identification number, and the percent of inerts in the test solution are provided.

TOXICITY CATEGORY: IV — Caution

Comments: In keeping with HED procedures, the core classification is changed from "Supplementary" to "Unacceptable."

011532

FINAL

DATA EVALUATION REPORT

SODIUM OMADINE

Study Type: Primary Dermal Irritation in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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Carolyn Rabe, Ph.D.

QA/QC Manager Sharon A. Segal Date 10/19/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-124
Clement Number: 395
Project Officer: Caroline Gordon

GUIDELINE SERIES 81-5: Primary dermal irritation

EPA Reviewer and Section Head: Marion Copley, DVM Signature: Marion Copley
Review Section IV Date: 10/25/88
Toxicology Branch I/HED H7509C

DATA EVALUATION REPORT

STUDY TYPE: Guideline 81-5; primary dermal irritation - rabbits

CHEMICAL: Sodium omadine (10% soln)

TOX CHEM. NUMBER: 790A

PC CODE: 088004

MRID NUMBER: 410275-04

SYNONYM(S): Sodium 2-pyridine thiol-1-oxide, sodium pyrithione

SPONSOR: Olin Corporation, New Haven, CT

TESTING FACILITY: MB Research Laboratories, Inc., Spinnerstown, PA

TITLE OF REPORT: Sodium OMADINE® 10% Solution - Primary Dermal Irritation in Rabbits

AUTHORS: O.M. Moreno and D.R. Cerven

STUDY NUMBER: MB 88-9122C

STUDY COMPLETED: June 10, 1988

CONCLUSIONS: Application of 0.5 mL sodium omadine (10% solution) to the skin of rabbits for 4 hours resulted in very slight erythema and slight edema lasting <48 hours.

CORE CLASSIFICATION: Supplemental. This study does not satisfy the guideline series data requirements (81-5) for a primary dermal irritation study on the 10% formulation and is not acceptable for regulatory purposes. This study can be upgraded if the appropriate information the test material purity, manufacturing identification number, and the percent of inerts in the test solution are provided.

TOXICITY CATEGORY: IV--Caution

A. MATERIALS

1. Test Compound

Test material: Sodium omadine, 10% solution
Identification number: Not reported
Active ingredient: Sodium omadine
Formulation: 10% Solution
Purity: Not reported
Physical description: Clear liquid
Storage condition: Ambient room temperature and humidity
Stability: Not reported

2. Dose levels

0.5 mL liquid

3. Test Animals

Species: Rabbits
Strain: New Zealand white
Source: Ace Animals
Number of animals: 6
Sex: Not reported
Age: ~8 weeks
Mean body weight: 2.0-3.0 kg; individual weights not reported
Identification: Cage cards and ear tags
Housing: Individual
Diet: Purina Rabbit Chow #5321, ad libitum
Water: Ad libitum
Environmental conditions: Temperature: not reported; humidity: not reported; number of air changes per hour: not reported; photoperiod: 12 hours light/12 hours dark

B. TEST PERFORMANCE

1. Skin Preparation: Approximately 24 hours prior to testing, the dorsal area of the trunk of each animal was clipped, and one test site (reported to be 6 cm and assumed to be 6 cm^2) was selected.

2. Test Material Application: The test substance was applied to a gauze patch which was then applied to the test site. The patch was secured by tape, and the animal's body was wrapped in a semi-occlusive dressing. After 4 hours of exposure, the wrappings and the patch were removed and residual test material was removed with an appropriate solvent.

3. Observation Period: __x__ 0.5-1 hr __x__ 24 hr __x__ 48 hr __x__ 72 hr _____ 7 days _____ 10 days _____ 14 days

4. Scoring System: Dermal readings were based on the Draize scoring system.

C. REPORTED RESULTS: The incidence of dermal reactions (Grade 2 and Grade 1) compared to the total number of animals is presented below:

Parameter	Incidence at Each Observation Interval (hours) 5.0	24	48	72
Erythema				
Grade 1	3/6	4/6	2/6	0/6
Edema				
Grade 2	2/6	0/6	0/6	0/6
Grade 1	2/6	3/6	0/6	0/6

Very slight erythema was observed in 3 rabbits during the first observation period and was also evident in 4 and 2 rabbits during the 24- and 48-hour observation periods, respectively. Two rabbits had slight edema and 2 others had very slight edema at the first observation period. Three animals were observed with very slight edema 24 hours postexposure. The incidence and severity of the irritation observed in the animals decreased after the 24-hour observation period, and no signs of irritation were evident at the 72-hour observation period.

The study author concluded that sodium omadine produced slight erythema and edema.

Toxicity Category: IV--Caution

D. REVIEWERS' COMMENTS: Although the reviewers agree with the study authors' conclusion that, under the conditions of this study, sodium omadine produced slight dermal irritation, the following reporting deficiencies were noted in the study:

- The purity of the test material and the components of the test material solution were not identified.
- A manufacturing identification number for the test material was not provided.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A Quality Assurance Statement was signed and dated July 8, 1988.)