004282

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

12/20/1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Submission of the Toxicology Branch Chapter of the Registration Standard for Sodium Omadine®

Tox. Chem. No. 790A

TO: John H. Lee
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THRU: Edwin R. Budd, Section Head
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Budd 12/20/84

WLB 12-20-84

Enclosed is the Toxicology Branch chapter for the Registration Standard for Sodium Omadine®. The following three subparts are included:

1. Sodium Omadine® Policy Discussion
2. Generic Data Requirements for Sodium Omadine®
3. Summaries of the Evaluated Data ("One-liners" and detailed reviews)

John E. Whalan 12-13-84

John E. Whalan, Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769c)

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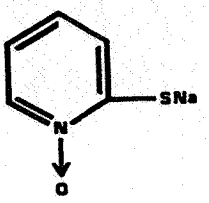
Sodium Omadine® Policy Discussion

A. Physical Properties:

Structure:



Names:
Sodium Omadine®
Sodium pyrithione
Sodium 2-pyridinethiol 1-oxide

Molecular weight: 149.2
Melting range (powder): 252-257°C
Density (bulk powder): 0.5 g/ml

Sodium Omadine® is a pale yellow powder with a mild odor. In aqueous solution, it has a clear amber color. It is a strong sternutator (induces sneezing). It is mildly basic with pH values of 8.6 and 9.4 for 2 and 10% solutions respectively. It is relatively unaffected by alkali, but can be converted by acid to 1-hydroxypyridine-2-thione. Degradation occurs in the combined presence of ultraviolet light and water. It is more soluble in polar solvents:

Solvent (@ 25°C)	Solubility (by weight)
Water (pH 7)	45.4%
Methanol	28.6%
Ethylene glycol	19.1%
Ethanol	5.4%
Acetone	0.13%
Benzene	0.0%

B. Use Summary

The potential uses and expected quantities (1984) for Sodium Omadine® are as follows:

	Pounds A.I.		
	Low	Expected	High
INDOOR DOMESTIC HOUSEHOLD USES (I)			
Bacteriostat for household laundry rinse and spray starch	0	0	0
INDUSTRIAL PRESERVATIVE (IP)			
Industrial processing chemicals (spin finishing lubricant preservatives)	0	12	25
Preservation of latex and resin emulsions	0	18,000	53,000
Preservation of metalworking cutting fluids	6000	24,000	60,000
Preservation of paints	0	12	25
Preservation of floor finishes, styrene acrylic polymers, polyethylene emulsion polymers, and acrylic emulsion polymers	0	0	0
Specialty products (e.g. preservation of jet-printer inks)	0	10,000	53,000
Preservation of casein aqueous dispersion solutions	-	-	-
	6000	52,024	166,050

Related compounds such as Zinc Omadine® and tertiary-butylamine Omadine® (TBAO) are not included in this registration standard, per RCB's recommendation (October 1, 1984 memorandum; William J. Hazel). This decision was based, in part, on the Registrant's cancellation of registrations for those uses that would result in residues of these compounds in food or feed (i.e. cottonseed treatment). The registrant has also cancelled all registrations for the use of Sodium Omadine® as a cooling water biocide (see Olin letter of August 9, 1984 to John Lee).

C. Data Summary:

1. One-Liners

Attached

2. Toxicological Assessment

a. The toxicological data base for Sodium Omadine® is scanty and largely inadequate. Nearly all available studies were deficient in numerous respects. See below under "Deficiencies Affecting This Registration Standard." Therefore, data gaps exist for nearly all studies required to support the registered uses of Sodium Omadine®. See Table A and Table B for a listing of these data gaps.

b. In a recently conducted rabbit teratology study, Sodium Omadine® was found to have a potential teratogenic effects at all dosage levels tested. In this study (a Core-Minimum study), Sodium Omadine® was applied dermally to the backs of pregnant rabbits at dosage levels of 0 (control), 0.5, 2.0, and 8.0 mg/kg/day on gestation days 6 through 18 inclusive. Each daily exposure was for 6 hours. Dose-related maternal toxicity was observed at all dosage levels. Since a NOEL could not be defined for either maternal toxicity or teratogenic effects, an additional rabbit teratology study (using the dermal route of administration) must be performed using lower doses. The results of this study should be submitted as soon as possible.

c. Human exposure studies have been requested.

d. Sodium Omadine® has also been shown in a subchronic feeding study in rats to produce hindlimb paralysis and/or weakness at the lowest dosage level tested (3 mg/kg/day). Hindlimb paralysis was also observed in an acute inhalation LC_{50} study in rats, in an 8-day repeated dermal study in rabbits, and possibly in a metabolism study in swine. Although all these studies were categorized as Core-Invalid or Core-Supplementary, considerable concern nevertheless exists regarding the potential toxicological significance of these observations.

e. Sodium Omadine® has also been shown to produce reproductive effects (consisting of decreased pregnancy rate, decreased fetal weights, decreased numbers of live fetuses, and increased resorptions) in a reproduction study categorized as Core-Supplementary. Concern also exists regarding the potential toxicological significance of these findings.

f. In conclusion, Sodium Omadine® appears to be a potent chemical which may affect several body systems and/or processes at low dosage levels. Some of its registered uses are likely to result in significant dermal and/or inhalation exposure to persons using products containing Sodium Omadine®. Of particular concern are household uses in laundry rinses and spray starches and workplace uses including its use as a preservative in metal cutting fluids and other industrial processes and/or products. The potential human exposure due to household uses is obvious. With respect to workplace uses, metal machinists can potentially have long-term exposure by the dermal route, and by inhalation of vaporized and aerosolized fluids. Textile workers may receive long-term dermal exposure by handling textiles and equipment using spin processing lubricants. Furthermore, if Sodium Omadine® is retained in cloth, the general public may also receive long-term exposure through contact with clothing.

Deficiencies Affecting This Registration Standard:

There are numerous inadequacies in the submitted reports. In some cases, data evaluation was hampered by the lack of data. The majority of studies are graded as Core-Supplementary. The major inadequacies seen in many studies include the following:

1. Inadequate protocol description including:
   a. Length of the study.
   b. Animal data (strain, supplier, age, sex, body weight, and number used).
   c. Doses used, dosing regimen and procedures, and rationale for dose selection.
   d. Method of dose formulation including vehicles used.
   e. Necropsy procedures.
   f. Tissues examined.
2. Failure to give the name of the performing laboratory, the report number, and the date of the Final Report.
3. Several studies were too short to assess reversibility of toxicity.
4. An insufficient number of animals were dosed.
5. Insufficient dose levels were used.
6. Failure to present clinical observations, body weights, and times of death.
7. Failure to report probit analyses.
8. Failure to use a control group and measure mean particle size data during an inhalation study.
9. Failure to perform clinical pathology, urinalysis, and gross and microscopic pathology evaluations when necessary.
10. Failure to grade dermal and ocular irritation by the Method of Draize or failure to present scores in a meaningful way.
11. Failure to measure the radioactivity levels of tissues in absorption and excretion studies.
12. A reproduction study was performed for only one generation.
13. Failure to present the nature and extent of skeletal anomalies.
14. Failure to perform dose concentration analyses during a GLP study.
15. Inconsistencies and arithmetic errors in some of the reports.

D. Tolerance Reassessment:

Since Sodium Omadine® will not be used on food or feed items, there are no tolerances, and a tolerance reassessment is unnecessary.

E. Use Classification

There is insufficient toxicological data available at this time on which to base a determination of use classification. Appropriate studies, for this purpose, have been required in this Registration Standard.

Table A
Generic Data Requirements for Sodium Omadine®

§158.135 Toxicology Data Requirement	Composition	Use Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	MRID No.	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
Acute Testing:					
81-1 Oral LD_{50}-Rat	TGAI	I, IP	No	00054704, 00070762	Yes
81-2 Dermal LD_{50}	TGAI	I, IP	No	00042376, 00056677	Yes
81-3 Inhalation LC_{50}-Rat	TGAI	I, IP	No		Yes
81-4 Primary Eye Irritation -Rabbit	TGAI	I, IP	Yes	00092174, 00042376	No
81-5 Primary Dermal Irritation - Rabbit	TGAI	I, IP	No		Yes
81-6 Dermal Sensitization -Guinea pig	TGAI	I, IP	No	00068980	Yes
Subchronic Testing:					
82-1 90-Day Feeding -rodent	TGAI	I	No	00070762	Yes
-nonrodent	TGAI	I	No		Yes
82-3 90-Day Dermal	TGAI	I, IP	No		Yes
82-4 90-Day Inhalation	TGAI	IP	No		Yes(1)
82-5 90-Day Neurotoxicity -mammal	TGAI	I, IP	No		Yes(2)
Chronic Testing:					
83-1 Chronic Toxicity -rodent	TGAI	I	No		Yes(2)
	TGAI	I	No		

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Table A
Generic Data Requirements for Sodium Omadine®

Data Requirement	Composition	Use Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	MRID No.	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
83-2 Oncogenicity-Rat	TGAI	I	No		Yes(2)
-Mouse	TGAI	I(3), IP(3)	No		Yes(2)
83-3 Teratology -Rat	TGAI	I, IP	Yes	00056708, 00056701 00077157	No
-Rabbit	TGAI	I, IP	Partially	00077156	Yes(5,6)
83-4 Reproduction - 2 generations	TGAI	I, IP	No		Yes(1,2)
Mutagenicity Testing:					
84-2 Gene Mutation	TGAI	I, IP	Yes	00058358	No
84-2 Chromosome Aberration	TGAI	I, IP	No		Yes
84-2 Other Mechanism of Mutagenesis	TGAI	I, IP	No		Yes
Special Testing:					
85-1 General Metabolism	TGAI or PAIRA	I, IP	No	00056662	Yes(2)
- Human Exposure Studies	As Appropriate	I, IP	No		Yes(4)

Composition: TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radio-labelled.

Use Patterns: A = Terrestrial, food crop; B = Terrestrial, non-food; C = Aquatic, food crop; D = Aquatic, non-food; E = Greenhouse, food crop; F = Greenhouse, non-food; H = Domestic, outdoor; I = Indoor (domestic, household laundry and spray starch) ; IP = Industrial Preservative (including use in metal cutting fluids)

Footnotes: See next page

Footnotes for Table A:

(1) Contingent upon results of other subchronic and/or chronic studies.
(2) Contingent upon results of human exposure studies.
(3) Mouse skin painting oncogenicity study.
(4) For each registered use (testing material and design of study will depend on particular use.
(5) Route of administration to be dermal.
(6) To be submitted by December 31, 1985.

Table B

Product Specific Data Requirements for Manufacturing-Use Products Containing Sodium Omadine®

§158.135 Toxicology Data Requirement	Composition	Use Patterns	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	MRID No.	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?
Acute Testing:					
81-1 Oral LD_{50}-Rat	MP	I, IP	No		Yes
81-2 Dermal LD_{50}	MP	I, IP	Partially	00042376, 00056679 00056677	Yes
81-3 Inhalation LC_{50}-Rat	MP	I, IP	No	00056709	Yes
81-4 Primary Eye Irritation -Rabbit	MP	I(1), IP(1)	Partially	00042376	Yes
81-5 Primary Dermal Irritation - Rabbit	MP	I(1), IP(1)	No		Yes
81-6 Dermal Sensitization -Guinea pig	MP	I, IP	No		Yes

Composition: MP = Manufacturing-Use Product (including 40% Sodium Omadine®, Omacide™-24, Omacide™-6, Omacide™-50, etc.)

Use Patterns: A = Terrestrial, food crop; B = Terrestrial, non-food; C = Aquatic, food crop; D = Aquatic, non-food; E = Greenhouse, food crop; F = Greenhouse, non-food; H = Domestic, outdoor; I = Indoor (domestic, household laundry and spray starch); IP = Industrial Preservative (including use in metal cutting fluids)

(1) In addition, a second study at two times the final end-use dilution is required (in an appropriate vehicle, depending on the particular use)

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral Toxicity-Rats [laboratory name, report no., and date are unknown] MRID # 00054704	Pure and Technical		LD50 (mg/kg) Male Female Pure 900 ± 70 660 ± 60 Technical 900 ± 20 770 ± 60 No other data available	III	Supplementary
Acute Oral Toxicity-Rats (X1 and X5) Institute of Experimental Pathology and Toxicology Report No. 2402-128-15 April 14, 1969 MRID # 00070762	Technical		LD50 (mg/kg) Male Female Single Dose 1120 ± 66 980 ± 53 Five Daily Doses 900 ± 20 910 ± 23 Increased motor activity, salivation, lacrimation, dyspnea, prostration, increased muscle tone, tonic/clonic convulsions, respiratory depression, and respiratory failure. Lung congestion, hemorrhagic foci in the gastric glandular mucosa.	III	Supplementary
Acute Dermal Toxicity-Rabbits Food & Drug Research Laboratories Report No. 88494c November 30, 1967 MRID # 00042376	Technical		Emaciation, moderate to severe erythema, mild edema, severe body weight loss. Lethal at 100 mg/kg to 1 of 2 rabbits (this death may or may not have been due to treatment).	I (?)	Supplementary
Acute Dermal Toxicity-Rabbits Food & Drug Research Laboratories Report No. 88494d1 April 3, 1968 MRID # 00042376 00056679	40% (aqueous solution)		LD50 about 6400 mg/kg. Erythema and edema, CNS depression, prostration, erratic breathing. Abdominal fluid, cystic and pitted kidneys, reddened abscessed lungs, subcutaneous vascular dilatation, pale liver.	III	Minimum

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Dermal Toxicity-Rabbits Food & Drug Research Laboratories Report No. 88494 July 10, 1968 MRID # 00056677	100% (pure) Omacide™-24 (24% powder) Omacide™-6 (6% aqueous solution) Omacide™-50 (2% powder)		LD50's not calculable. Tremors, convulsions, death. Sporadic deaths over an extremely broad range made results uninterpretable.		Supplementary
Acute Inhalation Toxicity-Rats Biometric Testing Inc. Report No. A-1927 March 28, 1976 MRID # 00056709	40% (aqueous solution)		Toxic signs included death, ocular damage (unspecified) hind limb paralysis, lacrimation, diarrhea, diminished renal function, reduced body weight gain. Lung hemorrhage, darkened livers, distended intestines.		Invalid
Acute Intravenous Infusion-Rabbits [no laboratory name, report No., or date] MRID # 00056706	Pure and Technical		Lethargy, prostration, injection site edema, restlessness, urination, defecatyion, tachycardia, head drdooping, irregular breathing, anoxia, imbalance between diaphragmatic and intercostal muscles, excitement, convulsions, cyanosis, death. Pure compound had a slightly higher threshold for causing respiratory toxicity.		Supplementary
Acute Mucous Membrane (Eye) Irritation - Rabbits Food & Drug Research Laboratories Report No. 88496c December 14, 1967 MRID # 00092174 00042376	Technical		Lid redness, eye discharge	III	Minimum

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Mucous Membrane (Eye) Irritation - Rabbits Food & Drug Research Laboratories Report No. 88496d December 14, 1967 MRID # 00042376	40% (aqueous solution)		Slight corneal opacity, lid redness eye discharge	III	Minimum
Acute Mucous Membrane (Eye) Irritation - Rabbits Food & Drug Research Laboratories Report No. 88496e November 9, 1967 MRID # 00042376	Omacide™-24 (24% powder)		Slight lid redness, chemosis, eye discharge.	III	Minimum
Acute Mucous Membrane (Eye) Irritation - Rabbits Food & Drug Research Laboratories Report No. 88496f December 14, 1967 MRID # 00042376	Omacide™-6 (6% aqueous solution)		Very slight lid redness, eye discharge.	III	Minimum
Acute Mucous Membrane (Eye) Irritation - Rabbits Food & Drug Research Laboratories Report No. 88496g November 9, 1967 MRID # 00042376	Omacide™-50 (2% powder)		Very slight lid redness, eye discharge.	III	Minimum

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Absorption & Excretion Following Topical Application on the Skin of Monkeys and Rats; American Chemical Co. [report No. is unknown] 1967 MRID # 00042375	Sodium Omadine-S^{35}		Monkey: Not readily absorbed through monkey skin; less than 1.5% of dose found in urine. Rats: Some radioactivity was measured in urine, bladder, muscle, and liver.		Not Acceptable
Metabolism Study - Swine Medical College of Va. [Report No. and date are unknown] MRID # 00056662	^{14}C-Sodium Omadine		Salivation, emesis, urination, defecation, vasodilatation, altered skeletal function, hyperactivity, enhanced motor activity, ataxia, muscle weakness, increased SGOT and CPK, rapid serum clearance during distributive phase (0-2 hr). Clearance was via urine. Radioactivity in liver, kidney, and pancreas. Swine convert Sodium Omadine into Omadine disulfide.		Supplementary
Acute Dermal Absorption and Excretion Study - Mice Biometric Testing, Inc. Report No. A-1099 June 22, 1976 MRID # 00098014	^{14}C-Sodium Omadine		< 1% of dose found in the urine & feces. The distribution of the remainder of the dose is unknown.		Not Acceptable
In Vitro Microbial Mutagenicity Study in Salmonella Typhimurium Haskell Laboratory for Toxicology and Industrial Medicine Report No. 552-76 July 27, 1976	Technical		Not mutagenic at HDT: 25 ug/petri plate (activated) 3 ug/petri plate (nonactivated)		Acceptable

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subchronic Oral Toxicity -Rats Institute of Experimental Pathology and Toxicology Report 2402-128-15 April 14, 1969 MRID # 00070762	Technical		Hyperactivity, salivation followed by inactivity, slight respiratory depression, reddened conjunctiva, lacrimation, weight loss, and death at 100 and 200 mg/kg/day. Decreased body weight at 50, 100, and 200 mg/kg/day. Marked inhibition in electron transfer activity (succinate substrate). Normal clinical pathology and gross pathology, and no limb weakness or paralysis seen. A NOEL was not defined. Levels tested: 50, 100, 200 mg/kg/day X 15 weeks (oral) in Charles River CD®		Supplementary
Subacute Oral Toxicity-Fasted and Nonfasted Rats Food and Drug Research Laboratories Report No. 6030 October 10, 1979 MRID # 00098024	Technical		Salivation, increased liver and pancreas weights, and decreased ovary weights at 100 mg/kg/day. Arched backs at 30 mg/kg/day. Patchy hair loss and hindlimb weakness at 3, 30, and 100 mg/kg/day. A NOEL was not defined. Levels tested: 3, 30, 100 mg/kg/d X 30 or 31 days (oral) in Charles River CD®		Supplementary
Subacute Oral Toxicity-Vitamin-Deficient Rats [Laboratory name and Report No. are unknown] July 8, 1955 MRID # 00057612	Technical		Photophobia, conjunctiva reddening, lacrimation, salivation, hyperactivity, alopecia, excess urination, body weight loss, alopecia, and stomatitis. The vitamin-deficient diet caused marked weight loss which reversed when a hypervitaminized diet was given. Level tested: 76 mg/kg/day; 5d/w; X 4 weeks; strain unknown		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Dermal and Ocular Irritation-Monkeys Institute of Experimental Pathology and Toxicology Report No. 2402-128-15 April 14, 1969 MRID # 00070762	Technical in 1% soap sol.		Dermal exposure caused slight irritation (probably due to the vehicle). Levels tested: 1.875, 18.75, 187.5 mg/kg/day X 5d/w for 5 weeks in Rhesus. Ocular administration as a lather caused immediate discomfort, but no lesions. No other clinical signs were seen (probably because exposures were only 3 minutes long) Levels tested: One drop of 0.0625, 0.625, and 6.25% lathered solutions (regimen unknown) in Rhesus.		Supplementary
Subacute Dermal Irritation-Rats [Laboratory Name is unknown] Report No. Ph.0101 SL:G3/R June 19, 1962 MRID # 00056687	Technical		Slight erythema caused by the vehicle may have masked any compound effects. No other clinical signs were reported. Levels tested: 250 mg/rat X 5 days Strain unknown.		Supplementary
Subacute Dermal Irritation-Rabbits [Laboratory Name is unknown] Report No. Ph.0101 SL:G3/R June 19, 1962 MRID # 00056687	Technical		Slight reversible erythema may have been a compound effect. No other clinical signs were reported. Levels tested: 250 mg/rat X 2 days Strain unknown.		Supplementary

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Dermal Irritation-Rabbits Institute of Experimental Pathology and Toxicology Report No. 2402-128-15 April 14, 1969 MRID # 00070762	Technical		100 mg/kg/day - diarrhea, weakness, depressed respiration, drooping ears, decreased body temperature, hind limb paralysis, weight loss, marked erythema, edema, and necrosis. Microscopic findings of necrotic epidermis and outer-most portion of dermis; hemorrhage, edema, and diffuse inflammation in the innerlayers of the dermis and subcutaneous tissues. 300 mg/kg/day - death, marked erythema, edema, skin discoloration and necrosis, diarrhea, weakness, labored breathing, weight loss. Levels tested: 100 mg/kg/d X 8 days 300 mg/kg/d X 4 days in New Zealand white strain.		Supplementary
Subacute Dermal Irritation - Monkeys Food and Drug Research Laboratories Report No. 0725 February 2, 1972 MRID # 00056704	Technical		Dose-related erythema with macropapular rash extending from dosing site on back to the axillae and groin areas. Decreased activity and gross findings of dry, rough, scaly, and irritated skin were seen at 18.8 mg/kg/day. Dose-related microscopic findings of chronic dermal inflammation, hyperkeratosis, parakeratosis, & acanthosis. Levels tested: 3.8 and 18.8 mg/kg twice daily, 5 d/w (19 doses) in Rhesus.		Supplementary
Skin Sensitivity - Guinea Pig [Laboratory name and Report No. are unknown] October 22, 1957 MRID # 00068980	Pure and Technical		Non-sensitizing Levels tested: 0.05 ml, 5 times weekly X 3 weeks. Strain unknown.		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Eye Irritation-Rabbits [Laboratory name is unknown] Report Ph.0101 SL:G3/R June 19, 1962 MRID # 00056687	Technical		Rinsed eyes were not irritated. Unrinsed eyes were slightly irritated, but all signs reversed quickly. Levels tested: 50 mg/rabbit X 3 days. Strain unknown.		Supplementary
Reproduction and Teratology - Rats Institute of Experimental Pathology and Toxicology [Report No. is unknown] February 5, 1970 MRID # 00056708 00056701	Technical		Clinical signs - "Groveling," salivation, reddish brown eye discharge, alopecia, excessive drinking and urination, reduced weight gain. Maternal effects - Normal estrus cycling and mating behavior; reduced pregnancy rate, maternal and fetal weights, and number of live fetuses. Resorption rate increased if dosing occurred during the second half of gestation. Male fertility - No effect on ability to inseminate or on sex organ weights. Reduced number of resultant pregnancies and implantations. Teratogenic effects - None Levels tested: A variety of dosing regimens were used at doses of 50 and/or 150 mg/kg/day. Strain unknown.		Supplementary
Teratology - Rats (Dermal Application) International Research and Development Corp. Report No. 397-017 January 21, 1980 MRID # 00077157	Technical		Not teratogenic at 7 mg/kg/day (HDT) when dermally applied as a 1% w/w Aquaphor® cream formulation (this dose was lethal to some dams) Levels tested: 0.5, 1.5, 3.0, 7.0 mg/kg/day on gestation days 6-15 in Charles River CORS® CD® strain,		Minimum

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - Rabbits (Dermal Application) Huntingdon Research Centre Report No. SR305 October 30, 1980 MRID # 00077156	Technical (in 5% shampoo)		A teratogenic NOEL could not be established since defective or missing vertebrae, ribs, and sternebrae of unspecified severity were observed at all dose levels, including the lowest dose tested, 0.5 mg/kg/day. Dose-related maternal toxicity was also observed at all dose levels tested. Levels tested: 0.5, 2.0, 8.0 mg/kg/day on gestation days 6-18 in New Zealand White strain.		Minimum
Dermal Absorption and Excretion - Monkeys and Rats Institute of Experimental Pathology and Toxicology June 18, 1969 MRID # 00056670	Technical (S^{35}-labelled) in 1% soap solution		Skin retention was low in monkeys and rats, and increased slightly with multiple dosings. Elimination was by the urine at a rate determined by the rate of dermal absorption, and was greater in the rat because of greater skin permeability. Pretreatment of rat skin with 2% aqueous sodium lauryl sulfate, and the abrading of monkey skin increased absorption and skin retention. Levels tested: A variety of doses and dosing regimens used (some dosing data was not provided) in Macaca mulatta and Sprague Dawley		Supplementary
Teratology - Rats (Oral administration) Industrial BIO-TEST Laboratories, Inc. Report No. B 1242 June 19, 1972	Pure				Invalid

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - Rats (Oral administration) Industrial BIO-TEST Laboratories, Inc. Report No. 622-03088 June 6, 1973	"Commercial Grade" [unspecified]				Invalid
Teratology - Pigs (Dermal application) Industrial BIO-TEST Laboratories, Inc. Report No.651-04101C October 21, 1974	[unspecified]				Invalid
Photosensitization - Human Industrial BIO-TEST Laboratories, Inc. Report No. F 7817 January 29, 1970	40%				

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Acute ORAL TOXICITY of Pure and Technical Sodium Omadine® in Rats

MRID # 00054704

Protocol: Groups of ten fasted male and female albino rats ($\bar{x}$ 175 g) were dosed by gavage with 5% (w/v) aqueous solutions of either pure or technical Sodium Omadine® at doses ranging from 550 to 1000 mg/kg.

Results: The pure and technical formulations caused similar toxicity with all but one death occurring during the night of day 1. The following table summarizes the LD_{50} values

		LD_{50} (mg/kg)
Pure	Male	900 ± 70
	Female	660 ± 60
Technical	Male	900 ± 20
	Female	770 ± 60

This study is CORE SUPPLEMENTARY. Toxicity Category III. The study protocol was lacking specifics on the length of the study, observations made, and animal data (strain, supplier, and age). There was no presentation of observations except for the time of death. There was no mention of which laboratory performed the study, and the report lacked signatures and a date.

Acute ORAL TOXICITY (x1 and x5 Regimens) of Sodium Omadine® in Rats

Institute of Experimental Pathology and Toxicology; Report 2402-128-15; April 14, 1969; MRID # 00070762

Protocol: An unspecified number of male and female albino rats were orally dosed by gavage with an aqueous solution of Sodium Omadine®. The doses administered for the single dose study (x1) were 650, 850, 1050, and 1250 mg/kg. The five daily dose study (x5) doses were 725, 910, 1150, and 1450 mg/kg/day. LD_{50} values were calculated by the method of Miller and Tainter, 1944. The rats were observed for clinical signs and gross lesions.

Results: The LD_{50} values were as follows:

	Males	Females
Single dose (x1)	1120 ± 66 mg/kg	980 ± 53 mg/kg
Five daily doses (x5)	900 ± 20 mg/kg/day	910 ± 23 mg/kg/day

Within 1-2 minutes of dosing, the rats had increased motor activity, salivation, and lacrimation. These signs persisted for 5-10 minutes and were followed by respiratory depression and dyspnea. One to three hours after dosing, the rats were prostrate and had increased muscle tone and deep respiratory depression. Terminal signs included tonic-clonic convulsions and respiratory failure. Gross lesions included slight lung congestion and hemorrhagic foci in the gastric glandular mucosa.

This study is CORE SUPPLEMENTARY. The Toxicity Category for single dose administration is Category III. There were inadequate data regarding the animals (age, weight, strain, supplier, number used), body weight changes, and the times of death.

Acute DERMAL TOXICITY of Pure and 40% Sodium Omadine® in Rabbits - Food and Drug Research Laboratories, Inc.

Sodium Omadine® - Report No. 88494c; November 30, 1967; MRID # 00042376

Protocol: A male and a female albino rabbit (2.5-3.6 kg) were assigned to each of three dose groups. They were depilated over the trunk and dosed with 25, 50, and 100 mg/kg of Sodium Omadine® over 24 hours by continuous skin contact. Dosing formulations were prepared as a 40% paste in 0.5% CMC. Observations including appearance, behavior, body weight, skin irritation, and mortality. Surviving rabbits were sacrificed on study day 14.

Results: A male rabbit dosed at 100 mg/kg died on day 2 with hemorrhagic congested lungs. A female rabbit dosed at 50 mg was observed grossly to be emaciated and having necrotic pancreatitis on day 14. All other rabbits appeared normal. Over the course of the study, body weights were essentially unchanged except for a 50 mg/kg female which lost 24% of its day 0 body weight. Erythema was observed to be moderate to marked in the 25 and 50 mg/kg dose groups and marked to severe in the 100 mg/kg dose group on day 1. On day 3, erythema was more severe in the 25 and 100 mg/kg rabbits. Erythema had nearly reversed by day 14. Mild edema was observed in a 50 mg/kg rabbit on day 1 only.

This study is CORE SUPPLEMENTARY. An insufficient number of animals was used. At the 100 mg/kg dose, one of two rabbits died. Assuming that this rabbit died as a result of treatment, the Toxicity Category for Sodium Omadine® by the dermal route is Category I. This is somewhat questionable, however, when the results of other acute studies are considered. There was no information on the strain or supplier of rabbits.

40% Sodium Omadine® - Report No. 88494d_1; April 3, 1968; MRID # 00042376, 00056679

Protocol: Eighteen male and eighteen female albino rabbits were depilated over the trunk and assigned to nine dose groups (four rabbits per dose group). They were dosed with 40% Sodium Omadine® by 24 hour continuous skin contact at doses ranging from 0.133 to 12.8 ml/kg. Dermal irritation was evaluated by the method of Draize on days 1 and 3 only, and all surviving animals were sacrificed on day 14.

Results: Deaths occurred on the day of dosing in the groups dosed at 3.2 ml/kg (2 females) and 12.8 ml/kg (1 male, 2 females). On day 2, a 6.4 ml/kg male died. A male rabbit in the low dose group died on day 1 after experiencing convulsions and diarrhea. It had subcutaneous vascular dilatation and multiple renal cysts. This death was probably due to the oversensitivity of an unhealthy animal. The surviving rabbits at the two highest doses had moderate to severe weight loss over the course of the study. Dermal irritation scores ranged from 0 to 4 and were not clearly dose-related. Sporadic findings of skin edema were seen in 2 rabbits on day 1. Skin irritation had reversed in most of the surviving rabbits on day 3. Prostration, CNS depression, and erratic breathing occurred mostly at doses $\geq$ 3.2 ml/kg. Gross pathological findings included abdominal fluid, cystic and pitted kidneys, reddened and abscessed lungs, subcutaneous vascular dilatation, skin edema, and pale liver.

This study is CORE MINIMUM. Inadequacies in this study include the lack of data on the strain and supplier of rabbits. "The acute dermal toxicity" is reported to be 6.40 ml/kg with confidence intervals of 2.34 to 10.46 ml/kg. Assuming 1 ml weighs approximately 1 g, this is roughly equivalent to an LD_{50} of 6400 mg/kg (Toxicity Category III). Four rabbits constituted a dose group as opposed to the

recommended 10 rabbits/dose group. There were, however, nine closely spaced dose groups which compensated for the small dose groups.

Acute DERMAL TOXICITY of Sodium Omadine®, Omacide™-24, Omacide™-6, and Omacide™-50 in Rabbits

Food and Drug Research Laboratories; Report No. 88494; July 10, 1968; MRID #00056677

Protocol: Groups of four albino rabbits were depilated over the trunk and dosed with either a solution or a paste and encased in a polyethylene sleeve. Omadine-6 was supplied as a 6% solution; the other formulations were prepared as aqueous pastes. After 24 hours of dermal exposure, the skin was thoroughly rinsed and dried. They were observed for changes in appearance, behavior, and body weights. Survivors were sacrificed after 14 study days.

Results: The mortality patterns for each formulation were as follows:

Compound	Dose (mg or ml of formulation/kg)	Dead/Dosed
Sodium Omadine® [100% powder]	25 mg	0/2
	50	0/2
	100	1/2
	700	2/4
	1400	3/4
	2800	1/4
	5600	2/4
Omacide™-50 [2% powder]	800 mg	1/4
	1600	1/4
	3200	3/4
	6400	4/4
Omacide™-24 [24% powder]	267 mg	1/4
	400	2/4
	600	1/4
	900	1/4
	6400	0/4
Omacide™-6 [6% aqueous solution]	1.0 ml	1/4
	3.2	2/4
	6.4	4/4
	12.8	3/4

It was not possible to calculate LD_{50} values because of the sporadic incidences of death over a broad range of doses. There was a great deal of variability in Sodium Omadine® concentrations in the formulations used. The majority of deaths occurred on day 1 especially at the higher dose levels. Those rabbits which survived past day 1 had central nervous system toxicity including tremors and convulsions.

This study is CORE SUPPLEMENTARY. There is no information provided regarding the strain, sex, age, and weight of the rabbits. Inadequate supporting data were presented. The results are not interpretable.

Acute INHALATION TOXICITY of 40% Sodium Omadine® in Rats

Biometric Testing, Inc.; Report No. A-1927; March 28, 1976; MRID # 00056709

Protocol: Adult Wistar derived albino rats (225 g mean body weight) were divided into four groups of 5 males and 5 females each (10 rats per group). They were dynamically exposed for one hour in a 3 cubic foot glass chamber to nominal Sodium Omadine® aerosol concentrations of 200, 500, 1000, or 2000 mg/l. Aerosols were generated with a glass nebulizer. To prevent compound ingestion, warm soap and water were used at the end of the exposure to remove the compound from the rats' fur. They were observed for 14 days, and then terminally sacrificed.

Results: One animal each died at 500, 1000, and 2000 mg/l. During exposure, rats dosed at 1000 and 2000 mg/l had severe ocular damage (of unspecified nature) and paralysis of the hind limbs. Severe lacrimation, diarrhea, hind leg paralysis and diminished renal function were observed in many of these rats during the post-exposure period. Significant compound-related decreases in weight gain were observed in the 1000 mg/l females and the 2000 mg/l males and females. Many of the rats had slight to moderate lung hemorrhage, and many dosed at 1000 and 2000 mg/l had darkened livers and distended intestines. The LC_{50}, which was not calculable, was reported to be >2000 mg/l.

This study is CORE INVALID. Nominal calculations of concentrations are unacceptable. No supporting data whatsoever were presented on animals (other than initial and terminal body weights).

Acute INTRAVENOUS TOXICITY in Rabbits Dosed With Pure and Commercial Sodium Omadine®

MRID # 00056706

Protocol: An unspecified number of female Dutch rabbits (1-2 kg) were divided into groups of five rabbits each. Conscious rabbits were intravenously dosed via the marginal ear vein (20 mg/min) with either the pure or commercial formulation. Presumably, they were given a single dose. They were dosed at 200, 250, 300, 450, and 800 mg/kg, and at unspecified doses below 200 mg/kg and at "lethal doses" greater than 800 mg/kg (a complete list of the doses used was not presented). Isotonic 2% dosing solutions were formulated by dissolving purified and commercial Sodium Omadine® in distilled water.

Results: As presented in the report, many clinical observations were seen at only certain dose levels. For example, lethargy, prostration, and injection site edema (especially with the pure compound) were seen only at $\leq$200 mg/kg. Restlessness, urination, defecation, and tachycardia were seen only at doses of 300-450 mg/kg. All of the rabbits had drooping of the head. The most significant observation was dose-related irregular breathing at doses greater than 200 mg/kg. Anoxia resulted from an apparent imbalance of diaphragmatic and intercostal muscle contractions and caused excitement, convulsions, impaired ventilation, cyanosis, and death at 800 mg/kg and the undefined lethal doses. The threshold for causing respiratory toxicity was higher for the pure compound than for the commercial compound. At the 300-450 mg/kg doses, the pure compound caused irregular breathing until the time of death, but the commercial compound caused oscillations between periods of normal and irregular breathing.

This study is CORE SUPPLEMENTARY. There was a failure to define the study protocol, including all the doses used, rationale for dose selection, dosing regimen, animal grouping, animal supplier, observations, necropsy procedures, and the length of the study. There were contradictions in the text, missing portions of the text, and inconsistencies in the reporting of observations. Days of death were not reported. Probit analyses were not performed; rather, "mean lethal doses" were discussed but not presented or defined. The title of the report is incomplete, there is no mention of which laboratory performed this study, and the report lacks a date and signatures.

Acute MUCOUS MEMBRANE (EYE) IRRITATION of Sodium Omadine®, 40% Sodium Omadine®, Omacide™-24, Omacide™-6, and Omacide™-50 in Rabbits - Food and Drug Research Laboratories

Sodium Omadine® (technical powder) - Report No. 88496c; December 14, 1967; MRID # 00092174, 00042376

Protocol: Three male and three female albino rabbits were dosed with 10 mg of powdered Sodium Omadine® in the right eye without washout. Their eyes were evaluated at 24, 48, and 72 hours after exposure by the method of Draize.

Results: Lid redness was slight in two rabbits and marked in four rabbits on day 1, and slight in four rabbits on day 3. One rabbit had slight discharge on day 2 only. No effect was observed in the corneas or irides of any rabbits.

This study is CORE MINIMUM. Toxicity is Category III for eye irritation. Insufficient time was allowed for complete reversal of eye irritation, but partial reversal was evident on days 2 and 3. The report was a synopsis of the study, and was lacking in elaboration of the protocol and observations for individual animals.

40% Sodium Omadine® (liquid) - Report No. 88496d; December 14, 1967; MRID # 00042376

Protocol: Three male and three female albino rabbits were dosed with 0.1 ml aliquots of undiluted 40% Sodium Omadine® in the right eye without washout. Their eyes were evaluated at 24, 48, and 72 hours after exposure by the method of Draize.

Results: Slight corneal opacity was reported in two rabbits on day 1. Unspecified occurrences of slight lid redness and discharge were reported in all rabbits during the three days of study. No iridic lesions were observed.

This study is CORE MINIMUM. Forty percent Sodium Omadine® is classified as a Category III eye irritant. Draize scores decreased rapidly between days 1 and 3, but complete reversal was not seen due to the short duration of this study. Only total Draize scores for each rabbit were presented.

Omacide™-24 (powder) - Report No. 88496e; November 9, 1967; MRID # 00042376

Protocol: Three male and three female albino rabbits were dosed with 10 mg of powdered Omacide™-24 in the right eye without washout. Their eyes were evaluated at 24, 48, and 72 hours after exposure by the method of Draize.

Results: Slight lid redness, chemosis, and discharge were observed on days 1, 2, and 3. These signs were seen in all of the rabbits in an unspecified sequence.

Scores on days 2 and 3 were slightly lower than those on day 1, but low enough to represent a reversal in irritation. No effect was observed in the corneas or irides of any rabbits.

This study is CORE MINIMUM. Omacide™-24 is a Category III eye irritant.

Omacide™-6 (liquid) - Report No. 88496f; December 14, 1967; MRID # 00042376

Protocol: Three male and three female albino rabbits were dosed with 0.1 ml aliquots of undiluted Omacide™-6 in the right eye without washout. Their eyes were evaluated at 24, 48, and 72 hours after exposure by the method of Draize.

Results: Lid redness was reported to be very slight in six rabbits on day 1, and in four rabbits on day 3. Very slight discharge was reported for three rabbits each on days 1 and 3. No effect was observed in the corneas or irides of any rabbits.

This study is CORE MINIMUM. Omacide™-6 is a Category III eye irritant.

Sodium Omacide™-50 (powder) - Report No. 88496g; November 9, 1967; MRID # 00042376

Protocol: Three male and three female albino rabbits were dosed with 10 mg of powdered Sodium Omacide™-50 in the right eye without washout. Their eyes were evaluated at 24, 48, and 72 hours after exposure by the method of Draize.

Results: Slight lid redness and discharge were observed sporadically in four rabbits on days 1-3. The severity of these signs decreased after day 1. No effect was observed in the corneas or irides of any rabbits.

This study is CORE MINIMUM. Omacide™-50 is a Category III eye irritant.

ABSORPTION AND EXCRETION of Sodium Omadine-S^{35} Following Topical Application on the Skin of Monkeys and Rats

American Chemical Company; 1967; MRID # 00042375

Monkeys

Protocol: Four monkeys were dosed by applying bandages containing 1 ml aliquots of 4.5 mg of Sodium Omadine-S^{35}/ml of 1% soap solution to abdominal skin. Other monkeys were similarly dosed with non-radiolabelled Sodium Omadine® in a soap solution. The bandages were removed after 1 or 1.5 hours and the abdomens wiped clean with wet gauze. Urine samples were collected over a 24 hour period for the two monkeys dosed for 1.5 hours and over a 72 hour period for the monkeys dosed for 1 hour. The monkeys were sacrificed and the S^{35} activity measured in the urine, abdominal muscle and skin, bladder, blood, kidneys, heart, liver, and brain. Two more monkeys were dosed by applying the dosing formulations directly to the skin. The dose was contained by a polypropylene ring for one hour. They were sacrificed 24 hours later and measured for S^{35} activity in the abdominal skin and muscle, kidneys, bladder, blood, heart, and urine.

Results: The two monkeys dosed via bandages for 1.5 hours retained 10.2 and 14.2% of the dose respectively on their skin after 24 hours. Label activity in the urine of these monkeys was not above background levels. Label activity in the urine of the two monkeys similarly dosed for one hour was slight (maximum of

1.5% in one monkey at 24 hours) and may be artefactual. The two monkeys dosed by direct skin application retained only 1.5% of the dose on their skin after 24 hours and had no evidence of activity in the urine. No S^{35} activity was found in any of the tissues measured.

Rats

Protocol: Three rats were dosed with an unspecified volume of 4.5 mg of Sodium Omadine-S^{35}/ml of 1% soap solution on their shaved abdominal skin. The doses were contained by a glass or polypropylene ring. After 15 minutes of exposure, the abdomen was washed with wet gauze. They were sacrificed at an unspecified time and measured for S^{35} activity in the abdominal skin and muscle, urine, kidneys, and liver.

Results: The three rats tested had slight skin retention (3.9%, 2.2%, and 1.4%) of Sodium Omadine-S^{35} after an unspecified time. One rat had no label activity in any of the other measured tissues, and slight activity was observed in the muscle and liver tissues of the other two rats. One rat had slight activity in the bladder and urine.

This study is NOT ACCEPTABLE. There is no rationale for the design of the study and little mention of the protocol design. There are many inconsistencies and numerical errors. The report lacks the name of the testing facility, report date, and signatures. Information lacking includes all animal specifications (age, sex, weight, strain, supplier, number used), length of some studies, means of sacrifice, and control data. An insufficient number of animals were used. Sodium Omadine-S^{35} in a 1% soap solution is not readily absorbed through the abdominal skin of the monkey and only slightly absorbed through the skin of the rat.

METABOLISM STUDY of Intravenously Administered Sodium Omadine® in Swine

Medical College of Virginia; MRID # 00056662

Protocol: Silicone rubber catheters were permanently implanted into the left external jugular veins of two sexually mature female Yorkshire pigs (80-130 kg). These catheters were used for dosing the animals and drawing blood samples. The swine were housed in metabolism cages. Unlabelled and radiolabelled Sodium Omadine® (^{14}C-Sodium Omadine®) were dissolved in isotonic saline and administered at a rate of 50 mg/kg (0.5 mc/100 kg) via the jugular catheter. Behavior, urine, stools, plasma, and serum were evaluated before and during the study at regular intervals. The pigs were stunned with a stunning pistol after 96 hours on study. They were sacrificed by exsanguination, and liver, kidney, and pancreas samples were taken for radioactivity measurements. Radioactivity was also measured in urine and plasma. The serum of one pig was measured for glucose, creatinine, BUN, alkaline phosphatase, CPK, LDH, SGOT, and SGPT (SGPT was measured only at 48 hours).

Results: Following dosing, the pigs had signs of cholinergic stimulation including salivation, emesis, urination, defecation, vasodilation (flushing), and altered skeletal muscle function. Initial signs of hyperactivity and enhanced motor activity were followed by ataxia and muscle weakness. These signs reversed within an hour of dosing. SGOT levels were moderately elevated at 8, 24, and 48 hours, and the CPK level was mildly elevated at 48 hours. These signs suggest skeletal muscle insult. Serum clearance was rapid during the distributive phase (0-2 hours),

then slow during the postdistribution phase (4-72 hours), suggesting the presence of a second compartment. Mean radioactivity recovered in the urine was 86.5% after 24 hours and 94.9% after 96 hours. The maximum urinary concentration occurred at 24 hours (mean = 68.6%). Clearly, the compound was being eliminated chiefly in the urine. Significant radioactivity was found in the liver, kidney and pancreas samples from both swine. Based on thin layer chromatography, it appears that swine enzymatically convert Sodium Omadine® into Omadine disulfide, the major metabolite, which is removed in the urine.

This study is CORE SUPPLEMENTARY. Insufficient swine were tested, and no males were included. At least two dose levels should have been used instead of one, and single and multiple dose regimens should have been used. All dosing was by the intravenous route; perhaps several groups should have been dosed orally. Only three tissue types were measured for radioactivity. In contrast, Zinc Omadine® was evaluated in 36 tissue types, and significant activity was measured in all tissues measured. No fecal radioactivity measurements were made. Clinical chemistry measurements were made in only one animal. The final report has no date or report number.

Acute DERMAL ABSORPTION AND EXCRETION Study of Sodium Omadine® in Mice

Biometric Testing, Inc.; Report No. A-1099; June 22, 1976; MRID # 00098014

Protocol: Three DBA mice were dosed on the shaved skin of their backs with 0.1 ml aliquots of an oil/water emulsion of radiolabelled Sodium Omadine® (^{14}C-Sodium Omadine®). A total dose of approximately 10 millicuries was applied by inunction to 24 mm^2 of skin on each animal. After eight hours, the dose was removed by washing with distilled water. The mice were individually housed in metabolism cages. Blood, urine, and feces were collected at regular intervals and evaluated for radioactivity. After 72 hours on study, the mice were sacrificed and frozen. No tissues were examined.

Results: Minute quantities of radiolabelled Sodium Omadine® were found in the mice's urine, feces, and blood, with the greatest concentrations being measured during the first 24 hours. Less than 1% of the dose was recovered in the urine and feces. Approximately 9-17% of the applied dose was recovered during washing after 72 hours. Presuming that the study was performed properly, the majority of the compound was either deposited throughout the body, or retained on the skin in spite of the washing procedure. The former hypothesis cannot be confirmed since no tissues were measured for radioactivity.

This study is NOT ACCEPTABLE. An insufficient number of mice were used, and only one dose level was used. The dose in mg/kg was never presented, and formulation information was lacking. There were no animal data (strain, source, sex, age, and weight). No toxic signs were reported except for slight weight loss; the significance of the weight loss is unknown in the absence of dosage information. In view of the inability to account for the distribution of the compound, the laboratory should have measured the tissues for radioactivity. They could have at least measured the dosing sites to support their hypothesis that Sodium Omadine® is retained in the skin.

IN VITRO MICROBIAL MUTAGENICITY Study of Sodium Omadine®

Haskell Laboratory for Toxicology and Industrial Medicine; Report No. 552-76; July 27, 1976; MRID # 00058358

Protocol: This study was performed using five histidine-requiring strains of Salmonella Typhimurium. Base-pair substitutions were tested for with strains TA 1535 and TA 100, and frame-shift mutations were tested for with strains TA 1538, and TA 98. Assays were performed with and without rat liver homogenate activation (S-9). Controls for each strain consisted of a positive control (2-aminoanthracene) and two negative controls (distilled water; w/o S-9) for the activated systems, and three positive controls (N-methyl-N'-nitro-N-nitroso-guanidine; 9-aminoacridine; 2-nitrofluorene) and one negative control (distilled water) for the nonactivated systems. Based on preliminary toxicity studies for each tester strain, the maximum doses used during the mutagenicity assays were limited to 25 ug/petri plate for the activated systems, and 3 ug/petri plate for the nonactivated systems.

Results: Sodium Omadine® was not mutagenic at the doses used in this study.

This study is ACCEPTABLE.

Subchronic ORAL TOXICITY Study of Sodium Omadine® in Rats

Institute of Experimental Pathology and Toxicology; Report 2402-128-15; April 14, 1969; MRID # 00070762

Protocol: Groups of male and female Charles River CD® rats were orally dosed daily with an aqueous solution of Sodium Omadine® by stomach tube for 15 weeks at doses of 50, 100, and 200 mg/kg/day. A vehicle control group was presumably dosed with water. The rats were fasted for 6 hours prior to each dosing as a means of avoiding potential chelation in the chow. Some of the rats were sacrificed at 7 weeks, and the remaining rats were sacrificed at 15 weeks. Body weights were measured regularly during the study. Blood was drawn and analyzed for clinical pathology effects. Liver enzyme studies (electron transfer activities, oxidative phosphorylation, isocitrate dehydrogenase, and hexobarbital metabolism) were performed using liver samples from control and high dose female rats. Liver and kidney weights were recorded. Unspecified organs were taken for light microscopic examination. Additional 50 and 200 mg/kg/day and vehicle control groups were dosed daily for 4 months. At the end of the dosing regimen, they were sacrificed and samples of liver, kidney, and jejunum examined with an electron microscope.

Results: Hyperactivity and salivation were observed shortly after dosing at all doses and was followed by inactivity and slight respiratory depression at the mid- and high-dose levels. Some reddening of the conjunctiva and lacrimation were seen in the early weeks of the study. During most of the study, very few signs other than occasional salivation were seen. There were no signs of paralysis or limb weakness. An unspecified number of rats dosed at the mid- and high-dose levels died during the second and third weeks. Body weights among the dosed animals lagged slightly behind those of the control rats for the first and second weeks. By the end of the study, the dosed males weighed slightly more than the control males, while the female groups were equivalent. The clinical pathology

profiles were normal. In the liver enzyme studies, there was a marked inhibition in electron transfer activity using succinate as substrate. There was no inhibition when DPNH was used as a substrate. No effect was observed on oxidative phosphorylation, isocitrate dehydrogenase activity, and hexobarbital metabolism. Liver weights were low in all dosed and control groups, probably due to the restrictive feeding regimen.

There were no significant gross lesions found in any rats. The high-dose and control rats were the only groups examined for light microscopic lesions. Lesions seen at 7 and 15 weeks included slight to moderate fatty accumulation in hepatic cells, vacuolation in the proximal convoluted tubular epithelium. Considering the minor severity of these lesions, and the rates of incidence in the control and dosed groups, these lesions are of little consequence. Electron microscopic examination of liver, jejunum, and kidney tissues was performed for the 50 and 200 mg/kg/day and vehicle control rats dosed for 4 months. Lesions were similar for both groups. The dosed groups had abnormally large mitochondria in their hepatic cells in which the internal cristae seemed to occupy the matrix. In the jejunal cells, supra and paranuclear mitochondria of the absorptive columnar cells were often grossly distended and rarefied. Also, vesicles and cisternae in and near the Golgi and the paranuclear and basal intercellular spaces were distended. Renal tissue had a slight increase in the number of autophagic vacuoles or cytolysosomes in the tubular epithelial cells, and lipid inclusions appeared increased in number and size. Dilatations of the ER were seen in some of the tubular epithelial cells. None of these ultrastructural changes were dose-related. The lesions observed by light microscopy were probably due to altered lipid metabolism, but this hypothesis was not supported by electron microscopy.

This study is CORE SUPPLEMENTARY. The Methods section was lacking specifics on the size of the groups, the length of the study, the biochemical studies performed, and tissues examined. Data from the hexobarbital metabolism study were not presented. The light microscopic findings should have been presented in a table, and all animals should have been examined. All dose levels elicited toxicity, so a NOEL was not established. Ophthalmologic examinations were not performed.

Subacute ORAL TOXICITY Study of Sodium Omadine® in Fasted and Nonfasted Rats

Food and Drug Research Laboratories, Inc.; Report No. 6030; October 10, 1979;
MRID # 00098024

Protocol: Groups of 10 male and 10 female Charles River CD® rats (140-160g) were dosed by oral intubation with aqueous solutions of Sodium Omadine® at 0, 3, 30, and 100 mg/kg/day. Groups of fasted and nonfasted rats were used at each dose level. The fasted animals were not fed 6 hours before and 3 hours after dosing. The fasted rats were dosed for 30 consecutive days and the nonfasted rats were dosed for 31 consecutive days. The studies terminated on the last day of dosing. Clinical signs of toxicity were recorded daily and body weights were recorded weekly. To determine whether Sodium Omadine® is a microsome inducer, 5 fasted and 5 nonfasted males from each dose level were dosed I.P. with 60 mg/kg of hexobarbital and measured for sleeping time. All rats were necropsied. Samples of pancreas, liver, gonads, and any gross lesions were retained, and weights were recorded for the pancreas, liver, and gonads.

Results: A nonfasted high dose female rat that was sacrificed moribund on day 7 had an abcessed duodenal wall, and a fasted high dose male that died on day 11

had an esophageal perforation. An increase in salivation was observed at the highest dose. Animals dosed at the mid-dose level had arching of the back, and some animals at each dose level had patchy hair loss. The most significant clinical sign was dose-related hindlimb weakness which began as early as the first week of study. This weakness was most frequently observed in the mid- and high-dose males and females, and the nonfasted low-dose males. Hindlimb paralysis was seen in a small percentage of fasted and nonfasted mid-dose males and females. The nonfasted females were the most sensitive group. The nonfasted mid-dose females had a moderate reduction in body weight gain. There was no significant change in mean sleeping times in any males tested; therefore, there was no evidence of microsome induction. Moderate increases in relative and absolute liver weights were observed in the high-dose fasted males and nonfasted males and females. The high-dose fasted and nonfasted females had moderate increases in relative and absolute pancreas weights. Decreased relative and absolute ovary weights were seen in the fasted and nonfasted mid- and high-dose females. Microscopic examinations were unsuccessful and inconclusive.

This study is CORE SUPPLEMENTARY. The dose concentration analyses were conducted as much as three months after the study termination. The data suggest that the dose formulations decomposed by as much as 27%. Thus, the delay in performing these analyses made the dose concentration data invalid. Further, the fact that there is great variability in the data casts doubts on the accuracy of the dose formulation and the analytical technique. An insufficient selection of tissues were preserved, and microscopic examination was limited almost entirely to the pancreas for unspecified reasons. Unfortunately, the performing laboratory (F&DRL) and two other histopathology laboratories could not satisfactorily stain the pancreas tissues. The kidney weights were not taken. The study ran for 31 days rather than the recommended 90 days. The dose selection did not allow for a nontoxic dose level. There were no clinical pathology measurements made. A NOEL was not defined.

Subacute ORAL TOXICITY of Sodium Omadine® in Vitamin Deficient Rats

July 8, 1955; MRID # 00057612

Protocol: Two groups of 5 males and 5 female rats were dosed 5 days per week for 4 weeks by stomach tube with 76 mg/kg/day of Sodium Omadine®. Both groups were fed a synthetic diet beginning 4 weeks pretest. One group's diet was vitamin deficient, while the other group had a standard diet. The rats were observed daily and body weights were measured weekly. One day after the twentieth dose, 3 males and 1 female from each group were sacrificed and grossly examined. Of the remaining 2 males and 4 females in each group, 1 male and 2 females were placed on a hypervitaminized diet. The other rats continued their standard or vitamin deficient diets. The dosing regimen was repeated after a 4 day interval. These rats were also observed and their body weights taken. Two control groups were treated with agar by the same regimen as the two dosed groups.

Results: Clinical signs seen 0.1 - 2 hours after dosing included photophobia, conjunctival reddening, lacrimation, salivation, and general hyperactivity. Over the course of a month, the rats were observed to have slight alopecia, excessive urination, and occasional stomatitis. Body weight gain was markedly reduced in the dosed and control rats fed the vitamin deficient diet, and moderately reduced in the dosed males fed the standard diet. A male rat that had been fed a standard

diet was found dead after receiving 6 doses of Sodium Omadine®. It had intestinal intussuscaption and acute gastritis. Alopecia and stomatitis were the only lesions observed during the interim necropsy.

During the second monthly regimen, no affect on body weight gain was seen in the dosed and control rats that had been on a standard diet versus those on a hypervitaminized diet. Those dosed and control rats that had been fed a vitamin deficient diet had little change in body weight if continued on the diet, whereas those fed a hypervitaminized diet had a significant increase in body weight, irregardless of dosing.

This study is CORE SUPPLEMENTARY. Information lacking in the final report include the name of the performing laboratory, the report number, animal data (strain, supplier, and age), the method of formulation, and final necropsy data (assuming there was a final necropsy). The ocular effects reported seen in dogs (Moe to Linegar, Py 354/14, October 20, 1954) were not seen in the rats when fed with low, normal, or high levels of vitamins.

Subacute DERMAL AND OCULAR IRRITATION Study of Sodium Omadine® in Monkeys

Institute of Experimental Pathology and Toxicology; Report 2402-128-15; April 14, 1969; MRID # 00070762

Protocol: Twenty rhesus monkeys (2-3 kg) were assigned to four groups of 4 males and 1 female each. Aqueous 1% soap solutions of Sodium Omadine® were formulated at compound concentrations of 0.0625, 0.625, and 6.25%. The monkeys were dosed with a volume of 3 ml/kg/day for doses of 1.875, 18.75, and 187.5 mg/kg/day. One of the groups served as a vehicle control and was dosed with 3.0 ml/kg/day of the 1% soap solution. Doses were applied to shaved skin for 30 seconds, lathered for 2 minutes, then rinsed with warm water for 30 seconds. They were dosed once daily five days a week for 5 consecutive weeks. Dose formulations were prepared weekly. Each monkey was observed daily and weighed weekly. In addition, one drop of lather was instilled "biweekly" into the right eye of each monkey and then rinsed with warm water after an unspecified exposure time. Ophthalmologic examinations were performed pretest, and at the end of the second and fifth weeks. A clinical pathology profile was made for each monkey pretest and after the fifth week.

Results: The pH of the formulations ranged from 9.6 to 10.1. The low- and mid-dose formulations were uniform and lathered well, but the high-dose formulation was extremely turbid, would not lather, and settled on standing. A single control monkey had slight dosing site irritation between weeks 3 and 5. None of the low-dose monkeys had any signs of skin irritation. In the mid-dose group, minor skin irritation was seen in one monkey during weeks 1 and 2, and in another during weeks 1 through 5. In the high-dose group, slight skin irritation was seen in one monkey during week 5, and in another during weeks 1 through 5. These instances of skin irritation are attributed mostly to the vehicle used. Ocular exposure caused immediate discomfort as evidenced by rapid blinking, lacrimation, and movement of the entire body. Presumably, these signs were observed in all groups and were caused by the soap vehicle. On examination, no changes were seen in the eyes. No other clinical signs were observed, and body weight gain was normal. Clinical pathology profiles were normal.

This study is CORE SUPPLEMENTARY. Ocular exposure was performed "biweekly"; it was impossible to determine whether this meant 2 doses per week, or one dose every 2 weeks. The dosing procedure for ocular exposure was not well described. Draize scores were not used to rate skin irritation. The exposure periods of less than 3 minutes were probably too brief for significant irritation to occur.

Subacute DERMAL IRRITATION of Sodium Omadine® in Rats

Report Ph.0101 SL:G[illegible]R; June 19, 1962; MRID # 00056687

Protocol: Six rats were dosed daily for 5 days on shaved skin with 250 mg of 0.25% Sodium Omadine®. The skin of four rats was abraded, while the remaining two rats were unabraded. Some rats (perhaps the same rats) were dosed with an unspecified cream base on abraded and unabraded skin, or with 1% Quinolor® cream on abraded skin. All dosing sites were bandaged after treatment. The rats were observed daily for 20 days.

Results: Slight erythema was seen in rats dosed with Sodium Omadine® for 8 days (1 of 4) or 15 days (3 of 4) in abraded skin, and for 5 days (1 of 2) on unabraded skin. The cream base also caused slight erythema in one rat each for 6 or 8 days on abraded skin only (no irritation on unabraded skin), and 1% Quinolor® cream caused slight erythema in one rat each for 4, 6, or 8 days. Subsequent healing in all rats was described as normal.

This study is CORE SUPPLEMENTARY. The Methods section was deficient in details regarding the sites of dosing, the number of rats used, animal data (age, sex, weight, strain, and supplier), the method for dosing the control materials, and the length of each daily exposure (probably 24 hours). Draize scores were not used. The length of the healing period for each compound was not specified. The time of erythema onset was not presented, and must be assumed to be day 1. The composition of the cream base was not given, making any findings meaningless. No toxicity other than slight skin erythema was mentioned.

Subacute DERMAL IRRITATION of Sodium Omadine® in Rabbits

Report Ph.0101 SL:G3/R; June 19, 1962; MRID # 00056687

Protocol: Three rabbits were dosed daily for 2 days with 250 mg of 0.25% Sodium Omadine® on shaved abraded skin. They were also dosed on similar sites with 1% Quinolor® cream and Mycolog® cream.

Results: Two Sodium Omadine® dosing sites had evidence of slight erythema for 7 days. Healing was complete 10 days later. The 1% Quinolor® cream caused very slight erythema for 3 days in one dosing site, with complete reversal 7 days later. The Mycolog® cream was nonirritating.

This study is CORE SUPPLEMENTARY. The Methods section was deficient in details regarding the sites of dosing, animal data (age, sex, weight, strain, and supplier), the method for dosing the control materials, and the length of each daily exposure (probably 24 hours). An insufficient number of rabbits were used. Draize scores were not used. The time of erythema onset was not presented, and must be assumed

to be day 1. No toxicity other than slight skin erythema was mentioned. The length of the observation period was not given. The name of the laboratory that performed this study was not given.

Subacute DERMAL IRRITATION of Sodium Omadine® in Rabbits

Institute of Experimental Pathology and Toxicology; Report 2402-128-15; April 14, 1969; MRID # 00070762

Protocol: Six female New Zealand rabbits were dosed with either a 10 or 30% aqueous solution of Sodium Omadine®. They were dosed on the depilated skin of the back by the application of dose-containing gauze squares. Two rabbits were dosed with 1.0 ml/kg of distilled water on study day 1, and with 100 mg/kg/day (1.0 ml/kg/day) of the 10% solution on 8 of the subsequent 9 days. The other four rabbits were dosed with 300 mg/kg/day (1.0 ml/kg/day) of the 30% solution for four days. The rabbits' skin and eyes were observed and body weights recorded pretest and daily during the study. All surviving rabbits (low-dose only) were sacrificed on day 10. Eyes and unspecified thoracic and abdominal visceral organs were examined histopathologically.

Results: The low-dose rabbits had clinical signs of diarrhea, weakness, depressed respiration, drooping ears, decreased body temperature, and hindlimb paralysis. Except for diarrhea, these signs were seen on days 9 and 10. Signs of skin irritation began during the first half of the study, and included marked erythema, edema, and necrosis. Three rabbits in the high-dose group died the night after dosing. They had marked erythema, edema, and skin discoloration, but no other toxic signs. The fourth high-dose rabbit died on day 4. It had diarrhea on day 3, and weakness, labored breathing, and marked erythema, edema, and necrosis on day 4. Mild to moderate weight loss was seen in all animals that survived beyond day 1; the low-dose rabbits had the greatest weight loss.

When the low-dose rabbits were examined microscopically, the epidermis and outermost portion of the dermis were necrotic, and edema, hemorrhage, and diffuse inflammation were seen in the inner layers of the dermis and subcutaneous tissues. One of the two rabbits at this dose had several focal gastric hemorrhages (these animals had not been eating), and slightly swollen epithelial cells of the bladder. The other rabbit had congested liver sinusoids with diffuse heterophilic infiltration, and dilated renal tubules with occasional hyaline droplets. Neither animal had any eye lesions.

This study is CORE SUPPLEMENTARY. The age, weight, and supplier of the rabbits was not reported. The duration of each dose was not specified, but it appears that each daily dose was kept in place for 24 hours. The organs examined microscopically were not specified, and there was no explanation for histopathologic examinations not being performed for any of the high-dose animals. Dermal irritation was not rated with Draize scores. No clinical pathology parameters were measured. No time was allowed for reversal of the toxic signs. It is unlikely that this study followed a protocol.

Subacute DERMAL IRRITATION Study in Monkeys

Food and Drug Research Laboratories; Report No. 0725; February 2, 1972; MRID # 00056704

Protocol: Twelve healthy rhesus monkeys were individually dosed in metabolism cages. They were divided into three groups of two males and two females each. Each monkey was dosed twice daily, 5 days per week for a total of 19 applications. One group served as the vehicle control and was topically dosed with the vehicle, polyethylene glycol 300 in water. The other two groups were dosed with 0.75 ml/kg aliquots of 0.5 or 2.5% Sodium Omadine® in polyethylene glycol 300/water (3.8 and 18.8 mg/kg, respectively). All dosing was done on the skin of the back between the scapulae. The dosing sites were washed once daily before dosing to remove the vehicle. The monkeys were observed daily for clinical signs of toxicity. Urine samples were collected and measured for volume once pretest, and during and after the dosing interval for a period of 28 days. The monkeys were sacrificed and grossly necropsied on study day 28. Samples of skin, kidney, liver, spinal cord, and brain were evaluated histopathologically.

Results: Dose-related erythema with macropapular rash was seen at the dosing sites and extended to the axillae and groin areas in the dosed and control groups. The irritation began during the first week and increased in severity. The irritation was so severe in several monkeys that the full regimen of 20 doses was reduced to 19. There was no mention of discomfort in any of the monkeys. The high dose males showed some decrease in physical activity, however. No other toxic signs were observed. Gross findings of dry, rough, scaly, and irritated skin at the dosing site and irritated nondosed skin were reported only in the high dose group. Microscopic skin lesions were seen in two low dose monkeys and four high dose monkeys, and included minimal to mild chronic dermal inflammation and hyperkeratosis, and focal areas of parakeratosis and acanthosis. Based on the need to abort the dosing regimen due to severe irritation, and the mildness of the skin lesions on day 28, it appears that dermal irritation was reversible, (although reversibility was not discussed in the report).

This study is CORE SUPPLEMENTARY. Draize skin irritation scores were not assigned, making it difficult to assess the degree and reversibility of skin irritation. There was inadequate detail regarding the time of onset of skin irritation and the number of monkeys affected. There was no mention of the protocol for dosing site preparation or of means for covering the site after dosing, and no justification for using monkeys.

SKIN SENSITIZATION Study of Sodium Omadine® in Guinea Pigs

October 22, 1957; MRID # 00068980

Protocol: Two groups of guinea pigs were injected intracutaneously three times weekly for three weeks into the dorso-lumbar skin with 0.05 ml of either 100% (6 animals), or 95% (8 animals) Sodium Omadine®. The test formulations were prepared as 0.1% solutions in saline. The guinea pigs were examined regularly for induction skin lesions. Thirteen days after the final induction doses, 0.05 ml challenge injections were given to each animal and the dosing sites observed for lesions.

Results: No skin irritation was observed as a result of sensitizing or challenge injections of Sodium Omadine®.

This study is CORE SUPPLEMENTARY. Information lacking from the report includes the name of the performing laboratory, report number, animal data (including age, sex, weight, strain, and supplier), the doses used (in mg/kg/day), and dosing site preparation procedures. Also, no controls were used, and the days of dosing were not given.

Subacute EYE IRRITATION of Sodium Omadine® in Rabbits

Report Ph.0101 SL:G3/R; June 19, 1962; MRID # 00056687

Protocol: Four rabbits were dosed once daily for 3 days by instilling an unspecified formulation of 50 mg of 0.25% Sodium Omadine® into the conjunctival sac of one eye for one minute. The other eye was similarly dosed with an unspecified amount of 1% Quinolor® cream. The eyes of two rabbits were rinsed while the other two were not rinsed. The eyes were examined 1, 3, 6, and 24 hours after the initial dose, and 3 and 24 hours after the subsequent doses.

Results: The eyes dosed with Sodium Omadine® had slight irritation only if the eyes were unrinsed on day 1. The irritation on days 2 and 3 was seen again in the unrinsed eyes 3 hours after dosing but reversed 24 hours after dosing. The rabbits dosed with 1% Quinolor® cream had slight irritation on days 1 through 3 whether the eyes were rinsed or not. This irritation did reverse 24 hours after dosing on days 2 and 3 in the rinsed eyes. All irritation had reversed 48 hours after the third dose.

This study is CORE SUPPLEMENTARY. Information lacking in this report includes the name of the performing laboratory, information on the formulations used, individual animal data, Draize scores, the nature of the eye irritation, and animal data (age, sex, weight, and supplier). The description of the methods used is scimpy. The volume of 1% Quinolor® cream used and the physical nature of the test article formulation were not reported.

REPRODUCTION AND TERATOLOGY Study of Sodium Omadine® in Rats

Institute of Experimental Pathology and Toxicology; February 5, 1970;
MRID # 00056708, 00056701

This study has four different phases. Each is discussed in turn:

Phase I - Effects on Estrus, Mating Behavior, and Pregnancy

Protocol: Sexually mature female rats (200-250 g) were placed into three groups (7-10 rats/group), one of which was a control group. Two groups were dosed by stomach tube with an aqueous solution of Sodium Omadine® six days per week for three weeks at either 50 or 150 mg/kg/day. They were mated with non-medicated males at the first estrus after the third week of dosing. The presence of sperm in the vaginal smears defined day 0 of gestation. Dosing continued until gestation day 20. The females were weighed twice weekly. The number, size, and distribution

of the embryos were determined by laparotomy on gestation day 9 while the rats were under ether anesthesia. On day 20, the rats were sacrificed and the viscera grosely examined, the corpora lutea counted and the uteri examined for the presence, number, and distribution of resorption sites. The fetuses were examined for death, sex, individual weight, and malformations. The viscera of approximately one third of the fetuses were examined using the method of Wilson. The remaining fetuses were examined for skeletal malformations by clarifying the tissues and staining the skeletal components.

Results: There was no observed effect on estrus cycling or mating behavior. Dose-related signs of maternal toxicity included "groveling," salivation, reddish-brown eye discharge, alopecia, and excessive drinking and urination. All of the females were inseminated. The pregnancy rate on day 10 was 100% for the controls, and 60% and 71% for the 50 and 150 mg/kg/day groups, respectively. The average litter size was moderately reduced for the pregnant dosed rats. Thus, the dosed groups each had half the number of embryos compared to the controls. The following data represent the day 20 findings:

Dose (mg/kg/day)	Conceptus/ No. Inseminated	Resorptions	Live Fetuses			Dead
			Total	$\bar{x}$/Litter	$\bar{x}$ weight (g)	
0	9/9 (100%)	5	99	11.0	3.5	0
50	3/10 (33%)	16	8	2.7	2.9	0
150	0/7 (0%)	-	-	-	-	-

All of the high dose fetuses were resorbed by day 20 and very few of the low dose fetuses survived. There was a moderate decrease in fetal weight in the few surviving low dose fetuses. The control rats were considerably heavier than the dosed rats because of the high survival rate of their fetuses.

Phase II - Teratogenesis

Protocol: Sexually mature female rats (200-250g) were assigned to two dosed groups and one control group (24 rats/group). The dose groups were dosed during organogenesis (gestation days 6-15) by stomach tube with aqueous solutions of either 50 or 150 mg/kg/day of Sodium Omadine®. They were mated with non-medicated males. The presence of sperm in the vaginal smear defined day 0 of pregnancy. The study terminated on day 20 and the dams and fetuses were examined as in the Phase I study.
Results: The following data represent the day 20 findings:

Dose (mg/kg/day)	Conceptus/ No. Inseminated	Resorptions	Live Fetuses			Dead
			Total	$\bar{x}$/Litter	$\bar{x}$ weight (g)	
0	21/24 (88%)	10	196	9.3	3.4	2
50	17/21 (81%)	50	119	7.0	3.2	1
150	11/24 (46%)	79	38	3.2	3.0	1

These data indicate that embryotoxicity was similar to, but slightly less severe, than that in the Phase I study. The lessened severity is probaly due to the shorter time of exposure. Mean maternal weight gain decreased as the dose increased due to resorptions. There were no skeletal or visceral malformations.

Phase III - Effects on Male Fertility

Protocol: Groups of ten male rats (250-300g) were dosed by stomach tube with

50 mg/kg/day of an aqueous solution of Sodium Omadine®. They were dosed six days a week for either 2, 4, 6, or 8 weeks. For each dosed group, there was also a control group of equal size. At the end of each dosing regimen, 5 dosed and 5 control rats were sacrificed and their viscera examined grossly. The testes, seminal vesicles (full and empty), prostate, epididymides, thymus, and kidneys for those dosed for 2 or 4 weeks were weighed and examined microscopically. The remaining rats were mated with non-medicated females. For this study, fertility was defined as the ability to inseminate and impregnate a female. The males were sacrificed after mating and their viscera examined grossly. The females were sacrificed on gestation day 20 and examined as described in the Phase I study.

Results: The dosed and control males had similar rates of insemination. Decreased male fertility was, however, evident as presented in the following data:

Dose (mg/kg/day)	Regimen (weeks)	Conceptus/ Inseminated	Implantations	Mean Litter Size	Resorptions	Fetuses Live	Dead	Weight
0	2	5/5	63	12.0	2	61	0	3.4
50	2	4/5	28	7.0	0	28	0	3.8
0	4	4/5	46	10.5	4	42	0	3.1
50	4	2/4	13	6.5	0	13	0	4.7
0	6	2/4	13	7.5	3	15	0	2.7
50	6	3/4	13	5.0	2	16	0	2.5
0	8	5/5	61	11.0	6	55	0	3.7
50	8	4/5	27	7.0	0	27	0	3.3

The occurrence of pregnancies was decreased slightly, and the mean litter size and rate of implantations were markedly reduced in the dosed groups. There was a corresponding marked decrease in the number of live fetuses in the dosed groups. Total resorptions were greatest in the control groups. There was no clear pattern of fetal body weight effects. No skeletal or visceral malformations were observed in the fetuses. Body weight gains for the dosed male rats were markedly lower than those of the control groups. Organ weights for the males were similar for all groups, and no compound-related microscopic lesions were found.

Phase IV - Detailed Study of Embryopathology

Protocol: Non-medicated males and females were mated. Eight groups of eight females each were dosed with 50 mg/kg/day of an aqueous solution of Sodium Omadine® at one of the following intervals: days 0-3, 4-7, 6-9, 8-11, 9-12, 11-15, 15-20, and 0-20. Sixteen females served as controls. Five dosed rats from each regimen and 10 control rats were sacrificed on day 20, and the fetuses examined as described in Phase I. The remaining rats were examined by laparotomy (see Phase I) on day 10, then allowed to delivered their litters. The pups were observed for postnatal development for 21 days, at which time they were sacrificed and grossly examined.

Results: The following table summarizes the data for the rats sacrificed on day 20:

Days of Dosing	Pregnant: Day 10	Day 20	Implantations	Resorptions	Fetuses --- Live	Dead	% weight	Pups --- Total	% litter
0-3	3	3	34	2	32	0	3.0	27	13.5
4-7	5	5	60	7	53	0	2.9	24	8.0
6-9	5	3	40	0	40	0	3.8	31	10.3
8-11	4	3	39	1	38	0	3.7	22	11.0
9-12	3	4	33	2	31	0	2.8	31	10.3
11-15	ND	5	62	22	40	0	2.9	14	4.7
15-20	ND	5	51	30	20	1	2.4	15	7.5
0-20	ND	4	48	18	28	2	2.4	26	8.7
Control	7	9	106	6	100	0	3.4	64	10.6

ND - Not determined

Two rats dosed on days 6-9 and one rat dosed on days 8-11 lost their conceptus between days 10 and 20. Total resorptions were more frequent in rats dosed during the last half of the gestational period, resulting in fewer live fetuses and lower maternal body weights. These dams also had lighter fetuses. A notable exception is the group dosed on days 4-7 which had low maternal and fetal body weights and moderately frequent resorptions. No skeletal or visceral malformations were found in the fetuses. The dams dosed between days 11 and 20 which delivered spontaneously had approximately half the number of viable pups as the controls. There were no regimen-related body weight effects in the pups. Very few pups survived to day 21 in the groups dosed on days 0-3, 9-12, 11-15, and 0-20, possibly due to cannibalism.

Summary (Phases I - IV):

1. Dose-related clinical signs in the adults included "groveling," salivation, reddish-brown e discharge, alopecia, and excessive drinking and urination.
2. There was no effect on estrus cycling or mating behavior in the dosed females, but the preg. ..cy rate, the number of live fetuses, and fetal weights were considerably less than for the controls. Maternal body weights were less for the dosed rats due to the smaller number of fetuses.
3. There was no effect on the ability of males to inseminate. There was, however, a decrease in the number of pregnancies and implantations. Male sex organ weights were normal and no microscopic lesions were found. Body weight gain for the dosed males was markedly reduced.
4. When females were dosed during the last half of the gestation period, the resorption rate increased.
5. No skeletal or visceral malformations were observed.

These studies (Phases I - IV) are CORE SUPPLEMENTARY. There was no mention of the strain, supplier, or age of the rats used. Ideally, three dose levels should have been used (only 1 or 2 doses were used in these studies) and one of these should have had no evidence of toxicity. The Phase IV study was a single generation study; an F_2 generation should have been used. There were insufficient supporting data presented in the study to permit an independent evaluation of results.

TERATOLOGY STUDY of Dermally Applied Sodium Omadine® in Rats

International Research and Development Corporation; Report No. 397-017; January 21, 1980; MRID # 00077157

Protocol: One hundred-fifty pregnant female Charles River COBS® CD® rats (approximately 3.5 months old) were assigned to six groups of 25 rats each. There were four dosed groups, a positive control group, and a negative control group. Sodium Omadine® (93.6%, technical product) was formulated with Aquaphor® cream to yield a 1% w/w cream. Rats were treated at dosage levels of 0.5, 1.5, 3.0, and 7.0 mg/kg/day (0.053, 0.159, 0.317, and 0.740 ml/kg, respectively). The positive controls were treated with 0.03 ml/day of Aristocort® (Triamcinolone Acetonide Cream 0.1%). The vehicle controls were treated with a volume of Aquaphor Cream equivalent to the dose volume given to the high dose group. All females were dosed on the shaved skin of their backs and the doses spread evenly with a glass rod. They were given single daily doses on gestation days 6-15. Prior to dosing, the rats were fitted with Agar® collars to prevent oral ingestion of the test articles. The collars were removed 24 hours after the final dose and the dosing sites were washed with tap water and dried. The dams were observed daily for clinical signs on days 6-20, and body weights were measured regularly. Any rats that died before day 20 were necropsied and grossly evaluated for the cause of death. All surviving dams were sacrificed by carbon dioxide asphyxiation on day 20. Their thoracic and abdominal organs were grossly evaluated, and samples of skin, subcutaneous tissue and muscle from the dosing site and adjacent areas were preserved. A record was made of the sex, weight and number of live and dead fetuses, implantations, resorptions, and corpora lutea. The fetuses were examined for external malformations and variations. One-third of the fetuses were prepared for visceral examination by the method of Wilson. The remaining two-thirds were prepared for skeletal examination by the method of Dawson.

Results: Maternal signs of toxicity included clear ocular discharge and soft stools in some of the rats dosed with Sodium Omadine®. Alopecia, scabbing at the neck, dry red matter around the eyes and nose, swelling of the head were noted in the dosed and control groups and were attributed to the Agar® collars. No skin erythema was seen in the vehicle controls but it was seen in the positive controls (12%) and in the dosed groups (16-100%, dose-related). Some of the rats in each dosed group had dosing site desquamatization. Many of the high dose rats had arched backs, an inability to move forelimbs and/or hindlimbs, breathing rales, and stained, matted anogenital fur. Seven high dose rats and 4 positive control rats had reductions in the size of their thymus glands. Five of this group died of unknown causes between gestation days 17 and 20. Maternal body weights in the vehicle controls and the 0.5, 1.5, and 3.0 mg/kg/day groups increased at a normal rate (45-49%) . Body weight gains were markedly reduced in the positive controls (27%) and the 7.0 mg/kg/day group (7.6%). These reductions became apparent on gestation day 9 and became significant by gestation day 16. The following are mean litter data for the dosed and control groups:

Dose (mg/kg/day)	Nongravid/ Gravid	Corpora Lutea	Implant.	Live Fetuses	Resorptions	Body Weight	Total Malformations
Veh. Cont.	2/23	16.7	14.4	13.2	1.2	3.8	7
Pos. Cont.	3/22	16.6	14.4	13.2	1.1	3.0	153
0.5	3/22	17.7	15.4	14.5	0.9	3.7	8
1.5	6/19	16.6	13.5	12.8	0.7	3.7	1
3.0	1/24	16.2	15.2	14.1	1.1	3.7	3
7.0	0/20	17.1	14.4	12.6	1.8	2.7	57

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The rate of resorption in the dosed groups resembled that in the vehicle and positive controls. A vehicle control and a high dose dam each had total resorption of their conceptus. The mean fetal body weights were moderately lower in the positive control group and the high dose group. The vehicle control group and the 0.5, 1.5, and 3.0 mg/kg/day dose groups had similar occurrences of malformations and variations. The high dose group had a marked increase in malformations due to limb and rib anomalies. The positive controls had three fold higher incidences of limb and rib anomalies compared to the high dose group, as well as other anomalies. Most of the variations in both groups were due to incomplete ossification. This was probably a secondary maternal toxic effect in the high dose group, and not a teratogenic response.

This study is CORE MINIMUM. Dermally applied Sodium Omadine® was not teratogenic in rats at doses that caused severe maternal toxicity and death.

TERATOLOGY STUDY of Dermally Applied Sodium Omadine® in Rabbits

Huntingdon Research Centre; Report SR305; October 30, 1980; MRID # 00077156

Protocol: Sexually mature, nongravid female New Zealand White rabbits (2.8-4.7 kg) were housed for one hour with males of proven fertility. Does that were inseminated were dosed with 10 i.u. of a luteinizing hormone to assure ovulation. Groups of 10-12 pregnant rabbits were dosed daily on gestation days 6 through 18 at doses of 0 (vehicle control), 0.5, 2.0, and 8.0 mg/kg/day. The formulations used were 0, 0.05, 0.2, and 0.8% Sodium Omadine®, respectively, in a 5% shampoo base. A shaved 10 cm square area of the dorso-thoracic-lumbar region was dosed daily and covered with an occlusive dressing. Each dose was removed and the skin rinsed after 6 hours of contact. The dams were observed daily for toxic signs and dosing site irritation was scored by the method of Draize. Food consumption was measured daily and body weights were measured regularly. On gestation day 29, the dams were killed and examined grossly for congenital abnormalities and changes in reproductive organs. The brain, spinal cord, peripheral nerves, and skeletal muscles of some dams were also examined microscopically in order to account for impaired movement. The uteri and ovaries were examined to determine:

a. the number of corpora lutea
b. the number and distribution of live young
c. the number and distribution of embryonic/fetal deaths (resorption and abortion)
d. individual fetal weights
e. fetal abnormalities

The fetuses were weighed, sexed, and examined for external and visceral abnormalities. Microscopic evaluations of abnormalities were performed as needed. The heads and skeletons were examined for anomalies.

Results: One rabbit died and another was sacrificed moribund prior to dosing in the low dose group. Another rabbit in this group was sacrificed moribund on day 14; it had anorexia, no feces, dyspnea, dark eyes, weight loss, blood in the cage, necrotic lungs, and a dark liver. This death was probably not compound-related. A high-dose rabbit died on day 18 with reddened hocks, hunched posture, impaired hind limb movement with marked trembling, blood in the cage, anorexia, impaired righting reflex, arched neck, tachypnea, lethargy, weight loss, stained

anogenital fur, pale liver, and lung lobes adhered to the pericardium with a purulent material. Dose-related incidences of impaired mobility and possible muscle wastage of the hindquarters were observed in some of the mid- and high-d groups. A histopathologic examination of CNS and peripheral nerve tissue and skeletal muscle for some of the dosed and control animals revealed some muscular degeneration.

Skin irritation was seen in all dosed and control groups. It consisted of slight to well-defined erythema and slight to moderate edema which was dose-related in severity and frequency. Skin irritation in the low-dose group resembled that in the control group. Decreased food consumption during the dosing interval (days 6-18) was dose-related in the mid- and high-dose groups. Body weight gain for t low-, mid-, and high-dose groups was less than for the control group (11.8, 17.3 and 63.8% less, respectively). The reduced high-dose weight gain was due to the high incidence of conceptus loss. No compound-related gross lesions were observ in any surviving dams. The following represents the day 29 group mean litter da

Dose (mg/kg/day)	Pregnancy Rate	Live Fetuses	Mean Fetal Weight (g)	Post-implant. Loss	Abortions	Total Deaths
0.0	75.0%	7.8	42.3	15.3%	0.0	1.6
0.5	87.5%	8.7	41.0	17.5%	0.0	1.4
2.0	100.0%	7.8	44.2	9.6%	0.0	0.8
8.0	81.8%	0.7	47.9	92.8%	4.6	9.3

The low- and mid-dose groups resembled the control group. The high-dose group, however, was profoundly affected with severe post-implantation loss due to abortions and early resorptions. Six of the 9 pregnant high-dose dams had total resorptions or abortions. The mean fetal weights were roughly equivalent for all groups. The following table summarizes major malformations and visceral anomalies:

Dose (mg/kg/day)	Fetuses	Major Malformations Fetuses	Major Malformations %	Visceral Anomalies Fetuses	Visceral Anomalies %
0.0	70	1	1.4	1	1.4
0.5	63	0	0.0	0	0.0
2.0	93	2	2.2	9	9.7
8.0	6	1	16.7	1	16.7

The low-dose group had no major malformations or visceral anomalies. The mid- group had a moderately higher incidence of major malformations including forel flexure and anury, and a marked incidence of minor visceral anomalies includin mostly agenesis of the intermediate lung lobe, and also reduced gall bladder, iridial hemorrhage, and defects in the umbilicus and liver. Of the six high-d fetuses available for examination, one had a missing kidney and associated ure and blood vessels, and a misshapen, displaced kidney; another fetus had agenes of the intermediate lung lobe.

Skeletal anomalies were observed in all dosed and control groups. Skeletal a lies were categorized by the performing laboratory as either "Type A" or "Typ (quoted from the final report, page 68):

Type A (thoracic):

"By virtue of the pattern evident within the study and from similarities with anomalies recorded in previous rabbit studies with Omadines, increased incidences of these anomalies are considered to be related to treatment. By and large, they originate from disturbance in the development in the region betwee the lower cervical and lower thoracic vertebrae and include singly or in combination:

1. Absent, reduced, hemi, hemicentric and ankylosed thoracic vertebrae
2. Absent, fused or branched ribs
3. Anterior sternebral shift
4. More than two fused/connected sternebrae"

Type B (generally nonthoracic):

"These do not readily fit into the pattern of A type changes and occur mostly (but not entirely) at sites other than the thoracic region; they include:

1. Cranial anomalies, e.g. outral bones, fused frontal bones and reduced or irregular ossification of parietal bones
2. Minor irregularities in ossification or shape affecting cervical vertebrae and odontoid process
3. Reduced ossification of metacarpal or phalangeal bones
4. Minor sternebral anomalies
5. Anomalies affecting lumbar, sacral, or caudal vertebrae
6. Extra pre-sacral vertebra(e)"

The incidences of Type A and Type B skeletal anomalies observed in fetuses and litters are as follows:

Dose (mg/kg/day)	Fetuses	Litters	Fetuses and Litters Affected — Type A Anomalies: Fetuses	Type A Anomalies: Litters	Type B Anomalies: Fetuses	Type B Anomalies: Litters
0.0	70	9	0 (0%)	0 (0%)	7 (10.0%)	5 (55.6%)
0.5	63	7	9 (14.3%)	4 (57.1%)	7 (11.1%)	4 (57.1%)
2.0	93	12	6 (6.5%)	3 (25.0%)	16 (17.2%)	9 (75.0%)
8.0	6	3	5 (83.3%)	2 (66.7%)	4 (66.7%)	2 (66.7%)

No Type A thoracic skeletal anomalies were seen in the control group, but each dosed group had significant occurences, even at the low-dose. The high-dose group had the greatest percentage of affected litters, and a far greater percentag of affected fetuses. The litter percentage of Type B nonthoracic anomalies was similar in all groups, but the few surviving fetuses in the high-dose group had a seven-fold percentage increase in Type B anomalies compared to the controls.

This study is CORE MINIMUM. Type A (thoracic) skeletal anomalies were observed at all dose levels. The severity of these anomalies was not presented in the report. Dose-related maternal toxicity was also observed at all dose levels. Since a NOEL could not be defined for either maternal toxicity or type A teratogenic effect, an additional rabbit teratology study (dermal application) is requested to be performed at lower doses. Maternal toxicity should be observed at the highest dose tested.

Dermal ABSORPTION AND EXCRETION of Sodium Omadine-S^{35} in Monkeys and Rats

Institute of Experimental Pathology and Toxicology; June 18, 1969; MRID # 00036670

Monkeys

Protocol: Monkeys (Macaca mulatta) were topically dosed with an aqueous 1% soap solution of 92% ^{35}S-labeled Sodium Omadine® on the shaved skin of their abdomens. The monkeys were restrained and mildly anesthetized with sodium pentobarbital during the dosing procedure. One hour later, the dosing sites were wiped clean and washed. They were housed in metabolic cages. Three experiments were performed:

1. A group of eight monkeys was dosed once at a variety of doses and dose site areas. The monkeys were sacrificed at 24 hours for measurements of radioactivity in their urine and in unspecified tissues.
2. Another group of two monkeys was dosed once at 1.43 or 1.45 mg/rat on skin that was abraded with a dull razor. They were sacrificed after 24 hours and their treated skin, subjacent muscle, bladder tissue, and bile measured for radioactivity.
3. Two monkeys were dosed at 0.96 mg/rat on clipped normal skin for one hour each day for four days. Daily urine samples were collected for 11 days. Radioactivity was measured in the urine and bile, and in samples of treated skin, subjacent muscle, kidneys, bladder, liver, brain, and other unspecified tissues taken at necropsy on day 11.

Results: In Experiment 1, skin retention 24 hours after dosing ranged from 1.5 to 13.5% in the four monkeys measured. No other tissues sampled had any radioactivity. Urinary compound excretion 24 hours after dosing ranged from 0 to 1.6% of the dose and was not dose-related. The two animals that were continued on study had urinery dose levels of 0.7 and 0.8% at 48 hours and 0% at 72 hours. In Experiment 2, both monkeys dosed on abraded skin had considerably higher compound levels at 24 hours including 6.6 and 14.2% of the dose in urine, 9.0 and 33.9% in the dosing site skin, 3.7 and 8.6% in the subjacent muscle, and 1.2% in the bladder tissue. Only trace levels were found in the bile. Abrading the skin thus facilitated compound absorption in the monkey. In Experiment 3, four daily doses on the normal skin of 2 monkeys resulted in 0.21 and 0.35% compound retention in the dosing site skin on day 11. Minute quantities were also found in the subjacent muscle, kidneys, bladder, liver, bile, and brain. Urinary excretion during the study was 1.29 and 2.57% of the dose with the peak excretion occurring on either day 1 or 2.

Rats

Protocol: Groups of Sprague-Dawley rats were topically dosed with an aqueous 1% soap solution of 92% ^{35}S-labelled Sodium Omadine® on the shaved skin of their abdomens. The application was spread with a teflon rod. The dosing sites were wiped and washed after 15 minutes to remove the solution. Rats on study for more than one day were housed in metabolic cages. Four experiments were conducted:

1. A group of 25 rats was dosed once daily, while anesthetized, at 0.067 mg/cm^2 over 5.7 cm^2 (0.38 mg/rat) for five days. Five rats were sacrificed each day immediately after dose removal. The degree of dose retention in the skin was measured.
2. A group of 10 rats was given a single dose. Five of these rats were sacrificed immediately after dose removal, and the remaining 5 rats were sacrificed 4 hours later. Another group of 10 rats was given 4 consecutive doses at hourly intervals at the same dose level. Five of these rats were sacrificed immediately

after dose removal, and the remaining 5 rats were sacrificed 24 hours later. The dosing site skin and urine were measured for radioactivity at the time of necropsy.

3. A group of four rats was pretreated for 15 minutes with 2% sodium lauryl sulfate while another group of two rats was pretreated with water. Following removal of the pretreatment, the rats were dosed once with the soap solution at a dose of 0.67 mg/cm^2 over 5.7 cm^2 (3.82 mg/rat). The rats were sacrificed four days later and measured for dose retention in the skin.
4. Following topical dosing at 0.92 mg/cm^2 over 5.7 cm^2 (5.244 mg/rat), two rats were cannulated for the collecting of bile samples. Bile samples were obtained at 30 minute intervals for five hours. At the end of the study (not specified), radioactivity was measured in the bile, urine, dosing site skin, and subjacent muscle, and the liver. Two more rats were intravenously dosed with 0.96 mg/rat (0.1 ml) of the radiolabelled compound. They were cannulated while anesthetized for collection of bile samples. Samples for the 2 rats were collected at 30 minute intervals for 4.5 4.5 and 7.0 hours, respectively. Radioactivity in the bile and agonal liver samples were measured.

Results: Experiment 1 demonstrated that with each additional daily dose, the percentage of compound retention in the skin increased only slightly. Daily variability may have been due to absorption in the dosing site hair as it grew over the 5 day study. To overcome this problem, Experiment 2 was performed by dosing the rats either once, or four times in four hours. When rats were given a single dose, the amount of compound retained in the skin was 29% less 4 hours after dosing than immediately after dosing. The amount of compound found in the urine, though small, increased markedly after 4 hours (0.2 and 1.7% at 0 and 4 hours post-dosing, respectively). In the rats dosed four times in 4 hours, the amount of compound in the urine was significant (8.1 and 10.7% at 0 and 24 hours postdosing, respectively). One day after dosing, skin retention was reduced by 57%. The skin retention levels, however, were only slightly greater after the fourth dose than when only one dose was given. Experiment 3 demonstrated that pretreatment of the skin with 2% aqueous sodium lauryl sulfate resulted in almost no skin retention compared to pre-treatment with water (0.02 and 0.09% retention, respectively). In Experiment 4, the two rats measured for 5 hours had minute levels of the compound in the bile and subjacent muscle. Higher levels were found in the urine (0.11 and 2.84%), dosing site skin (0.59 and 4.93%), and liver (0.21 and 1.00%). The other two rats which were intravenously dosed and measured for 4.5 and 7.0 hours had 0.95 and 2.38% of their doses, respectively, in their bile. Peak bile levels occurred 3 hours after dosing in both rats. Agonal liver samples contained 7.3 and 14.0% of the dose, respectively. Thus, intravenous administration resulted in significantly greater radioactivity in the bile and liver of rats.

Summary: Skin retention was low in rats and monkeys dosed topically with Sodium Onadine®-S^{35}, and increased only slightly when administration was by multiple doses. Compound elimination was by the urine; the rate of excretion was determined not by the dose, but by the rate of dermal absorption. Urinary excretion was greater in the rat because of greater skin permeability. Absorption and skin retention were increased in the rat by pretreating the dosing site with 2% aqueous sodium lauryl sulfate and by abrading the skin of the monkey. Intravenous dosing resulted in elevated levels of compound in the bile and liver tissue.

This study is CORE SUPPLEMENTARY. The report was poorly written. The Methods section was confusing and inadequate, and there were contradictions and unreadable data. Inadequacies include the lack of animal data (age, weight, sex, and supplier),

a list of tissues examined, and the report number. An insufficient number of animals was used in some portions of this study. The rationale behind the selection of doses was not given. Probably all of the animals were anesthetized, but the report only mentioned several groups that were so treated.
