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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Sodium Omadine, Case #0209

FROM: Arliene M. Aikens, Chemist
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Health Effects Division (7509C)

THRU: Karen Whitby, Ph.D., Acting Chief
Risk Characterization and Analysis Branch
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and

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TO: Walter Waldrop, Acting Chief
Reregistration Branch
Special Review and Reregistration Division (7508W)

The Human Health Assessment for the Sodium Omadine (Case #0209) Reregistration Eligibility Decision Document is attached. This chapter includes the Toxicology Assessment by John Whalan (TOXB I) and the Occupational/Residential Exposure Assessment by Winston Dang (OREB). Pesticide use data considered in this case were provided in the LUIS Report and information from BEAD.

The active ingredient in this reregistration case is Sodium Omadine, a non-food use pesticide. Based on the toxicity and registered use patterns (LUIS Report, 2/7/95) of the active ingredient, HED concludes that labelling modifications and additional confirmatory data are required, as delineated in the attached HED chapter of the RED.

In this document, HED provides a risk characterization for handler (mixer/loader/applicator) exposure during the pumping and pouring of liquids (preservatives and metalworking/cutting fluids) that contain sodium omadine. Dermal and inhalation exposure to the primary handler pumping and pouring solutions containing sodium omadine fall in ranges which would not be of concern.

Machinist inhalation and dermal exposure (post application) during the operation of machinery cooled by sodium omadine-containing metalworking and cutting fluids is considered to be within the purview of OSHA. While HED assumes that due to dilution, the post application exposure of the machinist would be lower than that for primary applicators handling the concentrate, we recommend that SRRD confer with OSHA regarding the need for exposure/risk assessments for the machinist. Furthermore, HED defers to OSHA to add any precautions they deem appropriate for machinists.

HED recommends for the reregistration of sodium omadine, the active ingredient in RED Case No. 0209.

CC: Karen Whitby (RCAB), Paula Deschamp (RCAB), John Whalan (TOXB I), Winston Dang (OREB), Arliene Aikens (RCAB).

HUMAN HEALTH ASSESSMENT OF SODIUM OMADINE

REREGISTRATION CASE No. 0209

A. Human Health Assessment

1. Toxicology Assessment

The toxicological data base for sodium omadine is substantially complete and will support reregistration eligibility. Toxicology data gaps are delineated in the conclusions of this RED chapter.

a. Acute Toxicity

Test	Results	Category
81-1 Acute Oral LD_{50} (rat)[1]	LD_{50} = 2000 mg/kg ♂ LD_{50} = 1100 mg/kg ♀ LD_{50} = 1500 mg/kg ♂+♀	III
81-2 Acute Dermal LD_{50} (rabbit)[2]	LD_{50} = 1900 mg/kg ♂ LD_{50} = 1800 mg/kg ♀ LD_{50} = 1800 mg/kg ♂+♀	II
81-3 Acute Inhalation LD_{50} (rat)[3]	LC_{50} = 1.26 mg/l ♂ LC_{50} = 0.81 mg/l ♀ LC_{50} = 1.08 mg/l ♂+♀ (4-hour analytical)	III
81-4 Primary Eye Irritation (rabbit)[4]		
81-5 Primary Dermal Irritation (rabbit)[5]	Slight transient erythema and edema.	IV
81-6 Dermal Sensitization (guinea pig)[6]	Not a sensitizer in a maximization test (Magnusson-Kligman) up to dose levels which were irritating.	
81-6 Dermal Sensitization (human)[7]	Not a sensitizer in humans challenged 4 days per week for 3 weeks, then challenged after a 1-week hiatus.	

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[1] MRID No. 402478-01
[2] MRID No. 402478-02
[3] MRID No. 403390-01
[4] MRID No. ~~not~~ available
[5] MRID No. 402478-03
[6] MRID No. 402478-04
[7] MRID No. 403874-01

Technical Sodium Omadine: A 40% aqueous solution is both a technical and an end-use product.

End-Use Products: There are five registered end-use products. There are no toxicology data for the mixtures (numbers 3, 4, and 5):

1. Sodium Omadine® 40% Aqueous Solution (Registration No. 1258-843)

2. Sodium Omadine® 10% Aqueous Solution (Registration No. 1258-1213)

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

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

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

The following toxic signs were observed in the above acute studies:

Clinical signs observed in Wistar Albino rats administered an acute oral dose of sodium omadine (40% solution) included lethargy, diarrhea, prostration, ptosis, brown staining on the nose/mouth and anogenital areas, wetness or alopecia at the anogenital area, and ocular discharge. Necropsy revealed abnormalities of the lungs (hemorrhagic, congested), liver (dark mottled), spleen (dark, pale), heart (dilated), stomach (red areas), intestines (red or yellow areas, distended, containing mucus), brown staining of the nose/mouth and anogenital areas, and red discoloration of the nose in animals with unscheduled deaths; anogenital staining and/or alopecia were observed in treated animals at the scheduled sacrifice. **(MRID No. 402478-01)**

Clinical signs observed in New Zealand White rabbits given an acute dermal dose of sodium omadine (40% solution) included few feces, lethargy, yellow nasal discharge, emaciation, prostration, negative righting reflex, ataxia, ptosis, bloated abdomen, unkempt appearance, decreased body temperatures, soiling of the anogenital area, pupillary dilation, wetness of the nose/mouth area, wetness and yellow staining of the forelimbs, loss of hindlimb control, black

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and yellow staining of the nose/mouth area, mucoid diarrhea, and wetness and brown staining of the anogenital area. Necropsy revealed abnormalities of the treated skin, lungs, liver, spleen, gall bladder, urinary bladder, kidneys, and gastrointestinal tract; redness of the conjunctival area; red coloration of the body wall and body fat; red discharge of the mouth/nose area; excessive fluid in the peritoneal cavity; and brown staining of the anogenital area. **(MRID No. 402478-02)**

Clinical signs observed in Sprague-Dawley rats acutely exposed by the inhalation route to sodium omadine (40% solution) included increased salivation, hindlimb impairment, prostration, red facial stains, and yellow stained abdomen and genital areas. **(MRID No. 403390-01)**
Primary eye irritation in rabbits. The primary eye irritation study in rabbits (Food & Drug Research Laboratory studies no. 88496c and 88496d) screened in the Phase IV review was determined to be unacceptable for reregistration. A replacement study was not submitted. **(No MRID No.)**

Dermal dosing of New Zealand White rabbits with sodium omadine (40% solution) resulted in slight erythema and edema lasting ≤48 hours. Barely perceptible erythema but no edema was observed in 1 animal at 72 hours post-exposure. **(MRID No. 402478-03)**

In a maximization test, sodium omadine (40% solution) was not a sensitizer in male Hartley guinea pigs given irritating doses. This study was not acceptable because positive control data were not submitted with the study. **(MRID No. 402478-04)**

Sodium omadine was reported to be negative for inducing dermal sensitization in human volunteers when challenged after exposure to the test material for 4 days/week for 3 weeks and given a 1-week hiatus prior to challenge. The study was determined to be unacceptable because the purity of the sodium omadine used in the study was not reported. **(MRID No. 403874-01)**

b. Subchronic Toxicity

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

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

Both males and females dosed at 0, 0.5, and 2.0 mg/kg/day had similar body weights throughout the study. The 8.0 mg/kg/day groups consistently gained less weight than the other groups, and weighed as much as 21% and 22% less than controls for males and females, respectively. Significant decreases in weight gains were seen for males (30%) and females (47%). The body weight and clinical observation data suggest a steep dose response.

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

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

The neurotoxicity portion of the study (82-7) was classified Core Supplementary because cage observations were limited, many of the usual FOB parameters were not performed, grip strength measurements and motor activity were not quantified, guideline procedures for preparation of neural tissues (including perfusion) were not followed, and the histological examination of neural tissues was inadequate. **(MRID No. 407569-01)**

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

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

There were no dose-related effects on eye health or clinical pathology. Statistically significant increases in relative brain, pituitary, heart, lung, liver, kidney, and spleen weights in the high-dose males and females were attributed to retarded growth. There were no dose-related effects on absolute organ weights. The only dose-related gross lesion was wasting of the hindlimb skeletal muscle in 3/20 mid-dose females, and in 2/20 males and 19/20 females in the high-dose.

The gross findings were confirmed histopathologically as a reduction of muscle fiber diameter, fatty replacement, and an increase in the number of sarcolemmal nuclei. The subcutaneous panniculus muscle displayed atrophy in the mid-dose females and the high-dose males and females. In addition, degeneration of sciatic nerve fibers and minimal atrophy in the paravertebral muscles was seen in 10/20 high-dose females. Degenerated fibers showed a loss of myelin. The LOEL was 50 mg/kg/day in males and 15 mg/kg/day in females, based on atrophy of the hindlimb muscles and subcutaneous panniculus muscles. The NOEL was 15 mg/kg/day in males, and 5 mg/kg/day in females.

At 50 mg/kg/day, both sexes had decreased weight gain compared to controls, and females showed minimal atrophy of the paravertebral muscle, neurotoxic symptoms, and degeneration of some sciatic nerve fiber bundles. **(MRID No. 409362-01)**

In the rat inhalation toxicity study, sodium omadine (40% aqueous solution) was administered by whole-body inhalation to male and female Sprague-Dawley rats for 6 hours/day, 5 days/week, for 13 weeks at analytical concentrations of: 0, 0.00046, 0.0011, and 0.0038 mg/L. The high concentration of 0.0038 mg/L was increased to 0.0081 mg/L at week 6 because of the lack of signs of toxicity. Air control groups were included. Particle size EAD's were 1.1-1.4 μm with GSD's of 1.81-2.09. The systemic NOEL(s) were 0.0081 mg/L in males and 0.0011 mg/L in females. The systemic LOEL was 0.0081 mg/L in females, based on clinical signs of hindlimb dysfunction, histopathologic skeletal muscle regeneration, and decreases in female body weight and body weight gain. **(MRID No. 411782-01)**

c. Chronic toxicity

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

No evidence of toxicity was seen at the 5 mg/kg/day dose other than emesis in some monkeys. Emesis was observed in all monkeys at higher doses. Male body weights were unaffected by dosing, but female body weights were decreased as much as 8%, 17%, and 23% at the 5, 25, and 75/150 mg/kg/day doses, respectively. At 150 mg/kg/day, one female was sacrificed *in extremis* at week 6. At 75 mg/kg/day, one male and one female died at weeks 13 and 35, respectively; the cause of death was not apparent for either animal. Clinical signs noted in the dead female and sacrificed female included prostration, decreased activity, emesis, thinness, weak appearance, and cold extremities. Emesis and ptyalism were seen in the male that died. Hematologic changes (i.e., decreases in erythrocyte count, hemoglobin, and hematocrit levels) were slight and considered of minor toxicological importance. The NOAEL was 5 mg/kg/day. The LEL was 25 mg/kg/day based on emesis and decreased female body weight. **(MRID No. 411781-01)**

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d. Carcinogenicity

In an 80-week dermal carcinogenicity study, sodium omadine 40% aqueous solution (41.2% purity) was administered topically to groups of 50 male and 50 female CD-1 mice at dosage levels of 0, 5, 15, or 40 mg/kg/day.

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

The 40 mg/kg/day dose is defined as a free-standing systemic NOEL, based on the range-finding study. The dermal NOEL was 15 mg/kg/day. The dermal LEL was 40 mg/kg/day based on an increase in epidermal hyperplasia at the skin application site. The high-dose was considered to be inadequate to assess carcinogenicity (RfD Committee report, 5/16/95). **(MRID No. 421008-01)**

Sodium omadine (41.2% purity), 40% aqueous solution, was administered daily by oral gavage to groups of 70 Crl:CD(SD)BR Sprague-Dawley rats/sex at dosage levels of 0, 0.5, 1.5, or 5.0 mg/kg/day for 2 years. The highest dose was reduced to 3.5 mg/kg/day after 12 weeks because of excessive weight loss in females. At the highest dose tested (5.0/3.5 mg/kg/day) there was a significant decrease in mean body weight (as much as 10%) and body weight gain in females throughout the study; a marked increase in nerve fiber degeneration in the sciatic nerve and spinal cord in both sexes; and an increased incidence of retinal atrophy in both sexes. Under the conditions of the study, an increase in neoplasia was not observed at any site. Dosing was considered adequate to assess carcinogenicity. The NOEL was 0.5 mg/kg/day. The LOEL was 1.5 mg/kg/day, based on significant increases in the incidence of degeneration of the skeletal muscle of the hindlimbs in both sexes. **(MRID No. 421009-01)**

e. Developmental Toxicity

In a developmental toxicity study, New Zealand White rabbits were given sodium omadine by daily dermal application for 6 hours at doses of 0, 1, 2.5, or 5 mg/kg/day on gestation days 6-19, inclusive. Although there was no evidence of maternal or fetal toxicity at any dose, the 5 mg/kg/day dose is defined as a free-standing NOEL since a range-finding dose of 7.5 mg/kg/day was frankly toxic. **(MRID No. 404872-01)**

f. Reproductive Toxicity

In a two-generation reproduction study, Crl:CD(SD)BR rats received sodium omadine 40% aqueous solution (41.2% purity) by gavage at dose levels of 0, 0.5, 1.5, or 3.5 mg/kg/day. The highest dose level was changed from 4.5 mg/kg/day to 3.5 mg/kg/day after 3 weeks of dosing because of marked toxicity at 4.5 mg/kg/day.

The Parental NOEL was 0.5 mg/kg/day. The Parental LOEL was 1.5 mg/kg/day in females, and 3.5 mg/kg/day in males, based on increased incidence of histologic atrophy in the upper hindlimb skeletal muscles (reduction in fiber diameter) in F_1 females (3/25), F_0 males (7/23), and F_1 males (9/25). Additional parental effects seen at 3.5 mg/kg/day included increased histologic atrophy in the upper hindlimb skeletal muscles in F_0 females (19/24), and F_1 females (20/23); and significantly decreased body weight in F_0 and F_1 females.

The Reproductive NOEL was 1.5 mg/kg/day. The Reproductive LEL was 3.5 mg/kg/day, based on slightly decreased number of pups per litter born in both generations (possibly a consequence of reduced mating success due to hindlimb atrophy), delayed development in pups from both generations (including open ears and eyes and startle response), and decreased pup body weight and weight gain in both sexes. **(MRID No. 410972-01)**

g. Mutagenicity

Sodium omadine 40% aqueous solution (41.4% purity) did not induce forward gene mutations at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells up to actual concentrations, based on analytical determinations of 0.08 μg/ml -S9 or 11 μg/ml +S9. Actual doses ≥0.08 μg/ml -S9 or 27 μg/ml +S9 were severely cytotoxic (i.e., <10% cell survival). **(MRID No. 404115-01)**

In the in vivo Micronucleus Assay, sodium omadine (41.4% purity), 40% aqueous solution, did not cause micronucleus induction in the bone marrow cells of male or female CD-1 mice at 30, 48, or 72 hours after the intraperitoneal administration of 575 mg/kg (238 mg/kg/active ingredient). Clinical signs of toxicity (decreased body tone, body drop, and abnormal gait in all animals, ptosis in 9/10 animals, lacrimation in 6/10 animals, and tremors in two females) and target cell cytotoxicity [significantly decreased ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) at 72 hours] were observed at this level. **(MRID No. 403437-01)**

Sodium omadine 40% aqueous solution (41.4% purity) did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes treated with doses up to 220 ng/ml (300 ng/ml, based on analytical determinations). Concentrations ≥71 ng/ml (≥80 ng/ml) were cytotoxic. **(MRID No. 403875-01)**

h. Metabolism

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The absorption, distribution, metabolism, and excretion of sodium omadine were studied in groups of Sprague-Dawley rats administered a single oral dose of 0.5 or 25 mg/kg ^{14}C-sodium omadine, 0.5 mg/kg/day of sodium omadine for 14 days followed by a single oral dose of ^{14}C-sodium omadine (0.5 mg/kg), or a single (i.v.) dose of 0.5 mg/kg ^{14}C-sodium omadine.

Sodium omadine was rapidly absorbed, metabolized, and excreted in rats at all dosing levels. Total recovery of administered radioactivity was 85%-95% at 4 days postexposure. The urine is the major route of excretion of sodium omadine (73-85% of the dose); the feces are only a minor route of excretion (5-12% of the dose). Sodium omadine and its metabolites were not excreted in expired air.

In the single oral low-dose group and the i.v.-dose group, most of the administered radioactivity was excreted within the first 12 hours postdosing. In the repeated oral low-dose group and in the single oral high-dose group, the majority of the administered radioactivity was excreted within 24 and 48 hours postdosing, respectively. There was no evidence of bioaccumulation of sodium omadine or its metabolites in the tissues.

The metabolic profiles in the urine were similar in all dose groups; 12 urinary metabolites (A-L) were characterized. The major metabolite in rat urine was 2-pyridinethiol-1-oxide-S-glucuronide (Metabolite K) (41.4%-67.2% of the recovered radioactivity), while unchanged parent compound was not detected in the urine. **(MRID No. 412690-01)**

i. Neurotoxicity

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

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

Both males and females dosed at 0, 0.5, and 2.0 mg/kg/day had similar body weights throughout the study. The 8.0 mg/kg/day groups consistently gained less weight than the other groups, and weighed as much as 21% and 22% less than controls for males and females, respectively. Significant decreases in weight gains were seen for males (30%) and females (47%). The body weight and clinical observation data suggest a steep dose response.

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

The study LOEL was 2.0 mg/kg/day based on evidence of neurotoxicity in males and females (neurogenic skeletal muscle atrophy) and the NOEL was 0.5 mg/kg/day. **(MRID No. 407569-01)**

j. Toxicology Data Requirements

The current toxicology database is adequate to support medium occupational exposure requirements for an antimicrobial active ingredient [with the exception of guidelines 81-3 (with the 10% a.i.), 81-4 (with the 40% a.i.), and 81-6 (with the 40% a.i.)]. The manufacturing product contains 40% a.i. in aqueous solution. The end use products contain diluted manufacturing product (3.6 to 40% a.i.). Because the handler [(M/L/A) which is under EPA purview] would be dealing with small volumes of a low percentage active ingredient, HED views this as low exposure. The oil which the machinist would be exposed to would contain 0.005 to 0.5% active ingredient.

HED recognizes that regulation of exposure of machinists to metalworking fluids is under the purview of OSHA. Based on recent telephone conversations [Edward Stein (OSHA), John Whalen (NIOSH), and Andrea Blaschka (EPA)] it was determined that an interagency workgroup, known as the O.N.E. Committee, is discussing the roles and responsibility of each Agency in regulating the uses of metalworking fluids, paints, and other products in the industrial setting. The current thinking of the O.N.E. Committee is that OSHA will retain responsibility for machinists. A definitive policy has not yet been established. (Telephone communication: John E. Whalan, May 1995). This document continues with the assumption that OSHA will retain this responsibility. As stated above, available information indicates that the amount of active ingredient present in the metalworking fluid would most likely be even lower than that to which the handler (M/L/A) would be exposed. Therefore, it is presumed that the active ingredient would represent a lesser hazard to the machinist than the metalworking fluids which are irritating in nature (Al Nielson, personal communication).

Bridging: The registrant has repeatedly requested that the Agency use "data bridging" between pesticide products which contain the "omadine" moiety in the active ingredient. There are a number of omadine containing active ingredients used in pesticide products, namely sodium omadine, zinc omadine, omadine MDS, and omadine TBAO. The Agency has reviewed this issue

and found that "data bridging" is not acceptable between different omadine containing active ingredients because of the differences in chemical and toxicologic properties between the active ingredients (meeting with Olin on September 18, 1985 and John E. Whalan memorandum, dated February 7, 1986).

k. Other Toxicological Endpoints

The endpoint for risk assessment of short-term (1 to 7 days) dermal exposure to the active ingredient, sodium omadine, is a NOEL of 5 mg/kg/day, based on a dermal developmental toxicity study in rabbits (MRID 404872-01). The endpoint for risk assessment of intermediate (1 week to several months) term dermal exposure is a NOEL of 5 mg/kg/day, based on a 90-day dermal toxicity study in rats (MRID 409362-01). The endpoint for risk assessment of intermediate term inhalation exposure is a systemic NOEL of 0.0011 mg/L, based on a 90-day inhalation study in rats (MRID 411782-01). Sodium omadine was not found to be a dermal sensitizer in the tests conducted. (Less-Than-Lifetime report 3/17/95.)

l. Reference Dose

The RfD is 0.005 mg/kg/day. This value is based on the NOEL of 0.5 mg/kg/day from the chronic rat study, with an uncertainty factor of 100 (10 for intra-species and 10 for inter-species). The rat reproduction study with a parental NOEL of 0.5 mg/kg/day supports the RfD as a co-critical study. Systemic (neurotoxic effects) were observed at the next higher dose level of 1.5 mg/kg/day. The active ingredient is classified in Group D for carcinogenicity. This pesticide has not been reviewed by the FAO/WHO Joint Committee on Pesticide Residues (JMPR). (RfD Committee report, 5/16/95.)

B. Exposure Assessment

a. Dietary Exposure

The active ingredient, sodium omadine, is registered as a non-food use pesticide. Currently, there are no known dietary exposures to sodium omadine. A dietary exposure assessment of sodium omadine is not required for currently registered uses.

b. Occupational and Residential

The Sodium Omadine Registration Standard issued in 1985 required a special human exposure study (Guideline 80-A-SS). This requirement was imposed because HED did not know the extent of human exposure. A protocol for the human exposure study was reviewed by the Agency and

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found incomplete. Neither a revised protocol nor data from a human exposure study were received by the Agency. In place of the human exposure study additional longterm toxicology studies (chronic toxicity, oncogenicity, and general metabolism) were submitted. These data have been reviewed for this occupational risk assessment. Additionally, the registrant Olin Chemicals, is a participant in the CMA (Chemical Manufacturer Association) Antimicrobial Exposure Assessment Study. Therefore, HED has sufficient data to assess M/L/A and is no longer requiring a special human exposure study. There are no registered residential uses for sodium omadine; thus, an exposure assessment of residential use is not required in this RED.

This assessment of occupational exposure addresses only the potential M/L/A exposures during the pouring and pumping of liquids which contain sodium omadine as the active ingredient (refer to the section "Regulatory Background for Toxicology Data Requirements" regarding routine exposure of machinists to sodium omadine).

Sodium omadine [1-Hydroxy-2-(1H)-pyridinethione, sodium salt] is a broad spectrum antimicrobial pesticide used as a preservative in certain manufactured materials and an additive in manufactured process fluids (metalworking, cutting, cooling and lubricating fluids) which may otherwise be subject to deterioration through bacterial and/or fungal growth. Formulated products may contain 3.6% to 40% sodium omadine as the active ingredient in aqueous solution. Sodium omadine is used primarily as a preservative in metalworking and cutting fluids. It may also be used in lubricants in the synthetic fiber industry; and in analytical and diagnostic reagents for clinical and chemical analysis. For the purposes of this occupational exposure assessment, Sodium omadine (antimicrobial/microbiocide) uses are considered to be similar in the metalworking and fiber industries.

Machine shops are the major site in the U.S. where sodium omadine is used as a preservative in metalworking and cutting fluids. Approximately 95% of the sodium omadine produced in the U.S. is used in metalworking and cutting fluids. It is estimated that antimicrobials may be poured or pumped into metalworking or cutting fluids between 2 and 256 times per year (several times per week (CMA Study Review: W. Dang: 5/1/95). A worst case scenario for the use of sodium omadine, as well as for the related occupational exposure, therefore would be pouring or pumping of sodium omadine solutions (40% a.i.) into metalworking or cutting fluids, several times per week. Approximately 80% of the use sites in the United States for metalworking and cutting fluids are small machine shops.

The manufacturing product contains 40% (w/v) sodium omadine as the active ingredient in an aqueous solution. The manufacturing product is diluted in most end use products, which contain sodium omadine as the active ingredient at levels from 3.6% to 40%.

HED determined that an occupational/residential exposure assessment is required for active ingredients if: (1) certain toxicological criteria are triggered and (2) there is a potential exposure to handlers (mixers, loaders, applicators, etc.) during use or for persons entering treated sites immediately after completion of product applications. The toxicity and exposure criteria are met

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for requiring an occupational exposure assessment of the active ingredient sodium omadine in this RED. However, the occupational handler exposure during product pouring and mixing is considered to be the only concern in the sodium omadine RED, for uses in metalworking and cutting fluids. As stated previously, the regulatory authority for assessing exposures of machinists to sodium omadine, during uses of metalworking and cutting fluids falls under OSHA jurisdiction. However, available information indicates that these exposures would be low.

Handler (M/L/A) Exposure

The registrant, Olin Chemicals, is a participant in the CMA (Chemical Manufacturer Association) Antimicrobial Exposure Assessment Study. The MCS (Maximum Credible Sum) unit of exposure developed in the Antimicrobial Exposure Assessment Study is applicable to assess exposure in the sodium omadine RED (CMA Study Review: W. Dang: 5/1/95).

According to the product labels the highest level of sodium omadine (EPA Reg. 1258-843) in a formulated product is 40% sodium omadine active ingredient in aqueous solution. Based on label use information a maximum of 12.5 pounds of the formulated product is added to 10,000 pounds of water-based fluids to make metalworking, cutting, cooling, and lubricant fluids. On this basis, a total of 5 pounds of the active ingredient is handled during this mixing process (12.5 pounds X 0.4 = 5 pounds).

For "In-Can" preservative use in vinyl acetate latex emulsions, 1.15 pounds of the formulated product (40% a.i.) is added to 10,000 pounds of emulsion. On this basis, 0.46 pounds of active ingredient is handled (1.15 pounds X 0.4 = 0.46 pounds).

In general, HED believes that exposure to the machinist will be low due to dilution of the a.i. in metalworking fluids. However, HED is concerned about the potential for exposure to those small handlers (small machine shops who may load, mix and apply this pesticide to the metalworking fluid) who use metalworking and cutting fluids on a daily basis. The majority of metalworking and cutting fluid users are in small (one person) machine shops (approximate 80% nationwide). The machine operator is likely to be the same person who loads, mixes, and applies (addition) the pesticide in the metalworking and cutting fluids. The primary handler exposure would be limited to dermal and inhalation exposure routes during pouring and pumping the pesticide. The main inhalation and dermal exposure concerns are from the open-pouring of the sodium omadine formulation into the metalworking and cutting fluids. However, the levels of exposure to the active ingredient, sodium omadine, may vary widely because its use depends on the amount of coolant used, as well as upon the use frequency for metalworking and cutting fluids (small shops are likely to recycle metalworking and cutting fluids for economic reasons, since spent coolant requires hazardous waste disposal).

HANDLER EXPOSURE DURING LIQUID POURING				
Use Setting	UE* (μg/lb ai)	lb ai/ used	BW** (kg)	Actual Daily Exposure (μg/kg/day)
Preservative	140	0.46	60	1.07
Metalworking Cutting Fluids	133	5	60	11.08

* UE = Unit Exposure for combined inhalation and dermal exposures. Mean UE (cited above) was derived from the CMA Study.

** BW = Body Weight (average 60 kg for female worker based on the developmental toxicity endpoint). Actual Daily Exposure (μg/kg/day) = (UE X lb ai/used)/BW

HANDLER EXPOSURE DURING LIQUID PUMPING				
Use Setting	UE* (μg/lb ai)	lb ai/ used	BW** (kg)	Actual Daily Exposure (μg/kg/day)
Preservative	7.5	0.46	60	0.06
Metalworking Cutting Fluids	325	5	60	27.08

* UE = Unit Exposure for combined dermal and inhalation exposures. Mean UE (cited above) was derived from the CMA Study.

** BW = Body Weight (average 60 kg for female worker based on the developmental toxicity endpoint). Actual Daily Exposure (μg/kg/day) = (UE X lb ai/used)/BW

As indicated in the above tables, it would appear that exposure to metalworking cutting fluids by way of a closed system (pumping) can result in higher exposure than the open system (pouring). The use of closed system includes disconnecting the hoses and inserting a dipstick to measure the amount of biocide added to the tank. The open pouring method does not require these activities.

Post-Application Exposure

Potential exposures to persons after application of products containing the active ingredient include:

1). Potential exposure, especially inhalation exposure, to industrial/manufacturing workers immediately after sodium omadine use.

2). Potential exposure, including dermal and inhalation exposure, when substances (such as metal cutting fluids) which contain sodium omadine are used.

Based on the use patterns and the chemical properties of sodium omadine (pale yellow free-flowing powder at room temperature, low vapor pressure, and stable at 100° C for 120 hours, etc.), inhalation exposure to industrial/manufacturing workers immediately after sodium omadine use is likely to be minimal (during and after application process).

As stated previously, HED believes in general that exposure to the machinist will be low due to dilution of the a.i. in metalworking fluids. The oil which the machinist would be exposed to would contain 0.005 to 0.5% a.i.. However, it should be noted that post application exposure to machinists falls under OSHA purview and therefore, was not assessed. Post application exposure to maintenance/repair workers in the industrial setting is believed to be minimal. HED defers to OSHA to add any precautions they deem appropriate for machinists.

Based on current registered use patterns for sodium omadine, the post-application exposure criteria are not met for requiring post-application exposure data. Post-application exposure data are not required.

Handler (M/L/A) PPE

There are special toxicology concerns related to the active ingredient, sodium omadine, that warrant active-ingredient-based PPE. These concerns are related to developmental toxicity. For each end-use product, PPE requirements for pesticide handlers will be set during reregistration in one of two ways:

1. If EPA has no special concerns about the acute or other adverse effects of an active ingredient, the PPE for pesticide handlers will be established based on the acute toxicity of the end-use product. For occupational-use products, PPE will be established using the process described in PR Notice 93-7 or more recent EPA guidelines.

2. If EPA has special concerns about an active ingredient due to very high acute toxicity or to certain other adverse effects, such as allergic effects or delayed effects (cancer, developmental toxicity, reproductive effects, etc):

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- In the RED for that active ingredient, EPA may establish minimum or "baseline" handler PPE requirements that pertain to all or most occupational end-use products containing that active ingredient.
- These minimum PPE requirements must be compared with the PPE that would be designated on the basis of the acute toxicity of each end-use product.
- The more stringent choice for each type of PPE (i.e., bodywear, hand protection, footwear, eyewear, etc.) must be placed on the label of the end-use product.

There are special toxicological concerns about use of the active ingredient, sodium omadine, which warrant the establishment of active-ingredient-based PPE requirements. HED recommends the following PPE: Chemical resistant gloves, long-sleeves, long-pants, shoes, and socks.

Post-application Entry Restrictions

At this time there are no registered uses of sodium omadine within the scope of Worker Protection Standard for Agricultural Pesticides. HED recommends against restricted-entry interval following application. A restricted-entry interval will be required, if sodium omadine uses within the scope of the Worker Protection Standard are registered in the future.

C. Risk Characterization

a. Dietary

The active ingredient, sodium omadine, is registered for non-food use. Dietary risk characterization of sodium omadine is not required based on the current non-food uses.

b. Occupational and Residential

Sodium omadine is not registered for homeowner uses; thus, risk characterization of residential exposure is not required based on the currently registered use pattern. Machinist inhalation and dermal exposure (post application) during the operation of machinery cooled by sodium omadine-containing metalworking and cutting fluids is considered to be within the purview of OSHA (See: Section J. Regulatory Background for Toxicology Data Requirements in this RED).

For this RED, EPA provides a risk characterization for handler (mixer/loader/applicator) exposure during the pumping and pouring of liquids (preservatives and metalworking/cutting fluids) that contain sodium omadine. EPA considers dermal and inhalation exposure to the primary handler pumping and pouring solutions containing sodium omadine to be in the range which would not be of concern.

The active ingredient sodium omadine is classified in acute toxicity category: II for dermal exposure; III for inhalation exposure, III for oral exposure and IV for dermal irritation. Data are not available to determine the acute toxicity category for eye irritation. Based on available toxicity data and use patterns for the sodium omadine registrations, HED has determined that estimation of risk, for handler exposure to the active ingredient, during pouring and pumping applications is required. Occupational handler exposure during pouring and pumping of solutions containing sodium omadine is characterized in this RED.

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ESTIMATED HANDLER MOE(s): DURING LIQUID POURING					
Use Setting	UE* (μg/lb ai)	lb ai/ used	BW** (kg)	Actual Daily Exposure (μg/kg/day	MOE
Preservative	140	0.46	60	1.07	4700
Metalworking Cutting Fluids	133	5	60	11.08	450

* UE = Unit Exposure for combined dermal and inhalation exposures. Mean UE (cited above) was derived from the CMA Study.

** BW = Body Weight (average 60 kg for female worker based on the developmental toxicity endpoint). Actual Daily Exposure (μg/kg/day) = (UE X lb ai/used)/BW
NOEL = 5 mg/kg/day
MOE = NOEL ÷ Daily Exposure

ESTIMATED HANDLER MOE(s): DURING LIQUID PUMPING					
Use Setting	UE* (μg/lb ai)	lb ai/ used	BW** (kg)	Actual Daily Exposure (μg/kg/day)	MOE
Preservative	7.5	0.46	60	0.06	83,000
Metalworking Cutting Fluids	325	5	60	27.08	185

* UE = Unit Exposure for combined dermal and inhalation exposures. Mean UE (cited above) was derived from the CMA Study.

** BW = Body Weight (average 60 kg for female worker based on the developmental toxicity endpoint). Actual Daily Exposure (μg/kg/day) = (UE X lb ai/used)/BW
NOEL = 5 mg/kg/day
MOE = NOEL ÷ Daily Exposure

All of the MOEs evaluated are greater than 100. Thus, for the currently registered uses of sodium omadine, HED has no concerns regarding potential risks to workers during the pouring and pumping of liquids that contain sodium omadine as the active ingredient.

Exposure Risk Mitigation

With the use of the recommended PPE, the potential for occupational handler exposure and health risk, within the regulatory purview of EPA, to the active ingredient sodium omadine is minimal. This is based on the available toxicity information, use patterns, exposure assessment and risk estimates for the active ingredient in this reregistration case.

HED RECOMMENDATIONS

Toxicity Data: The following confirmatory data are required:

Guideline 81-4:	Acute primary eye irritation study in the rabbit for sodium omadine with 40% a.i. (The Food and Drug Research Laboratory studies submitted (No(s). 88496c and 88496D) were determined to be unacceptable.)
Guideline 81-3:	Acute inhalation toxicity study for sodium omadine with 10% a.i. as required in the 1985 Sodium Omadine Registration Standard.
Guideline 81-6:	Acute dermal sensitization study for sodium omadine with 10% a.i. as required in the 1985 Sodium Omadine Registration Standard.

Labeling: HED recommends the following label modifications:

All end-use products which contain sodium omadine and are intended primarily for occupational use are to include wording on the label as indicated below:

Handler (Mixer, Loader, Applicator, Etc.) Personal Protective Equipment (PPE):
"The PPE for pesticide handlers will be based on the acute toxicity of the end-use product."

Application Restrictions:
"Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."

Engineering Controls:
"When handlers use closed metering systems, the handler requirements may be reduced or modified to long-sleeve shirt, long pants, shoes, and socks."

User Safety Requirements:

"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washable, use detergent and hot water. Keep and wash PPE separately from other laundry."

User Safety Recommendations:

"Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet."

"Users should remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing."

"Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."

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