

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SODIUM PYRITHIONE

Chemical Code # 002144, DPN # 50254
SB 950 # 873

Original date: August 26, 2004

I. DATA GAP STATUS

Chronic/Onco Combined, rat	No data gap, possible adverse effects
Subchronic Dermal, rat	No data gap, possible adverse effects
Subchronic Inhalation, rat	No data gap, no adverse effect
Subchronic Oral, rat	No data gap, possible adverse effect
Chronic toxicity, dog	Data gap, no study submitted.
Chronic toxicity, monkey	Data gap, no adverse effect indicated.
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, possible adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects.
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 114629 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T040826

Original by: Kishiyama & Silva, 8/26/04

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 50254 - 027 114629 ASodium Omadine⁷: 104 Week Oral (Gavage) Combined**

Carcinogenicity and Toxicity Study in the Rat,@ (Husband, R.F.A., Newman, A.J., Lee, P.N.; Toxicol Laboratories Limited; Laboratory Project ID #: OLA/3/90; 5/28/91). Sodium Omadine⁷ (40% a.i.) was administered in a single daily gavage to Crl:CD(SD)BR (VAF Plus) rats (50/sex/dose - oncogenicity; 20/sex/dose - chronic) at 0 (distilled water), 0.5, 1.5, or 5.0 (changed after 12 weeks of treatment to 3.5) mg/kg/day for 104 weeks. Chronic NOEL = 0.5 mg/kg (Hind limb muscle wasting was observed in a majority of surviving rats in both the chronic and oncogenicity groups at 3.5 mg/kg/day from week 89 to termination. Body weights were decreased in females at 3.5 mg/kg/day. Degeneration in the spinal cord, sciatic nerve and skeletal muscle and retinal atrophy were observed in both sexes at 3.5 mg/kg/day. Treatment related reduced red cell mass was observed in females at ≥ 1.5 mg/kg during weeks 27 and 53. RBC in females was reduced 4 and 10%, respectively at 1.5 mg/kg and 6 and 9%, respectively at 3.5 mg/kg during weeks 27 and 53. Hb in females was reduced 5% and 4% during week 27 at 1.5 and 3.5 mg/kg, respectively. Relative male lung weights at ≥ 1.5 mg/kg and relative male liver weights at 3.5 mg/kg were increased.) There were no treatment-related increases in oncogenicity. Possible adverse effects (Nerve and muscle degeneration) ACCEPTABLE. (Kishiyama & Silva 6/23/04)

50254 - 029 (12 parts): Same study as 027 114629.

CHRONIC TOXICITY, RAT

Subchronic:

**** 50254 - 018 069181 “Sodium Omadine[®]: 90 Day Oral (gavage) Toxicity Study in the Rat,” (Husband, R.F.A., Wood, C.M., Shirley, E.; Toxicol Laboratories Limited, England, Laboratory Project ID: OLA/2/88; 7/1/88). Sodium Omadine⁷ (41.2% Sodium pyrithione) was administered via single daily gavage to Crl:CD (SD)BR (VAF plus) rats (20/sex/dose) for 90 days at 0 (distilled water), 0.5, 2.0 or 8.0 mg/kg/day. NOEL = 0.5 mg/kg/day (Animals at 8.0 mg/kg showed emaciation, hunched posture and abdominal distension. In addition, hypoactivity and/or piloerection and/or ataxia (hind limbs) occurred in 11/20 males and 11/20 females at 2.5 - 6 hours post dosing on day 1. Head searching was also observed in 1 male. Mild ataxia to total paralysis of the hindlimbs was observed in 4/20 males and 11/20 females. Paralysis in females was sufficiently severe as to lead to 10 being killed for humane reasons. Muscle atrophy (hindlimb, panniculus +/- para-vertebral) was observed microscopically in both sexes at ≥ 2.0 mg/kg. Both sexes (primarily males) had decreased**

response to hindlimb tactile placing, compared to controls. Total food consumption for 13 weeks was decreased an average of 8.6% and 10% at 8 mg/kg/day for males and females, respectively. Body weights were decreased in both sexes at 8.0 mg/kg/day (20 - 21% decrease). Possible adverse effect: Neurological impairment associated with muscle atrophy was induced in both sexes at 8.0 mg/kg. (Kishiyama & Silva, 7/27/04).

**** 50254 - 016 072037 ASodium Omadine⁷: 90 Day Dermal Toxicity Study in the Rat,@ (Taupin, P.J.Y., Wood, C.M.; Toxicol Laboratories Limited, Herefordshire, England; OLA/5/88; 11/88.) Sodium Omadine⁷ (40% pure) was administered dermally (with occlusion) to Crl:CD(SD)BR rats (20/sex/dose) at 0 (distilled water), 5, 15 or 50 mg/kg/day (apparently a.i.) for 90 days (6 hr/day, 7 days/week). Body weights were reduced up to 14 and 21% for males and females, respectively, at 50 mg/kg/day. Food consumption was reduced up to 9 and 15% (Week 3) in males and females, respectively, at 50 mg/kg/day. This was a transitory effect. NOEL = 5 mg/kg/day (Emaciation, hunched posture and stiffness of hind leg movement was apparent in females at 50 mg/kg/day. Skeletal muscle atrophy (upper hind limbs) was observed in both sexes at ≥ 15 mg/kg. Paravertebral muscle atrophy and sciatic nerve degeneration were observed in females only at 50 mg/kg and at ≥ 15 mg/kg/day, respectively. Subcutaneous panniculus muscle atrophy was observed in males at 50 mg/kg and in females at ≥ 15 mg/kg.) Acceptable. Possible adverse effect: Muscle and nerve degenerative effects in both sexes. (Kishiyama & Silva, 8/5/04)**

****50254 - 024 075166 AThirteen Week Subchronic Inhalation Toxicity Study on Na Omadine in Rats,@ (Ulrich, C.E.; International Research and Development Corporation, Mattawan, MI; Laboratory Project Identification 397-042; 5/3/89). Sodium Omadine (40% a.i.) was administered by inhalation (aerosol) to Charles River CD rats (15/sex/dose) at 0.46, 1.1 and 3.8 mg a.i./m³ (increased to 8.1 mg/m³ after 6 weeks) for 13 weeks (6 hours/day, 5 days/week). NOEL for females = 1.1 mg/m³ (There was a statistically significant decrease in female body weights and an increased hindlimb impairment at 3.8/8.1 mg/m³ in 4/15 females with 3 of these showing minimal regeneration of the skeletal muscle. Spinal cord (3 sections) and sciatic nerve within normal limits.) NOEL for males $\geq 3.8/8.1$ mg/m³ (There were no effects on males at any dose.) Although there were no effects in males at the high dose and the high dose had to be raised, the doses were justified based on effects observed in 2 pilot studies. Acceptable. No adverse effect. (Kishiyama & Silva, 7/26/04)**

CHRONIC TOXICITY, DOG

No study submitted

CHRONIC TOXICITY, MONKEY

50254 - 023 075165 ASodium Omadine⁷: One Year Oral Toxicity Study in Cynomolgus Monkeys,@ (Johnson, D.E.; International Research and Development Corporation, Mattawan, MI; IRDC Study 397-047; 4/14/89). Sodium Omadine⁷ (40% a.i.) was

administered via a single daily gavage to Cynomolgus monkeys (5/sex/group, 7 days/week) for 1 year, at 0, 5, 25, and 150 mg a.i./kg. The high dose of 150 mg was reduced to 75 mg/kg/day after week 6, due to adverse effect on survival. NOEL < 5.0 mg/kg/day (Increased mortality 150/75 mg/kg/day. There was an increased incidence in ptyalism at 75 mg/kg/day, early in the study, in both sexes. The incidence of emesis was increased with dose at all dose levels. Although not statistically significant, mean body weights were, intermittently during the study, decreased by $\geq 11\%$ for all treated groups. Mid and high-dose groups had decreased red cell parameters which were reported (page 34) to be of minor biological significance, since they were within the range of historical control values. Relative kidney to body weights in males (≥ 5 mg/kg) and relative liver weights in males (≥ 25 mg/kg) and in females (75 mg/kg) were increased. There was no histopathological manifestation of these increased organ weights.) Not acceptable and not upgradeable (numerous deficiencies). (Kishiyama & Silva, 7/21/04).

ONCOGENICITY, MOUSE

Rangefinding Study:

50237 - 0149 210211 "8-Week Dietary Dose Range Finding Study in Mice," (Atkinson, C., Perry, C.J., Aitken, R.; Inveresk Research International, Musselburgh, Scotland; IRI Project #: 436144; Report #: 5021; 10/26/87). Troysan Polyphase P 100 (3-iodo-2-propynyl butyl carbamate (IPBC), Batch P-2848-8603-P100; 97% pure) was fed in diet to CD-1 mice (10/sex/dose) at 0, 50, 250, 500 and 1000 mg/kg/day for 8 weeks. Systemic (chronic) NOEL = 50 mg/kg/day (At ≥ 250 mg/kg/day (M) and at 1000 mg/kg/day (F) there were decreased body weights. Food consumption was decreased in both sexes at ≥ 500 mg/kg/day. In males there was a decrease in absolute heart (≥ 250 mg/kg/day), kidney (≥ 500 mg/kg/day) and spleen (1000 mg/kg/day) weights and an increase in absolute liver weights (≥ 250 mg/kg/day). Males showed an increase in relative liver weights at ≥ 250 mg/kg/day. In females there was a decrease in absolute heart, kidney and lung weights at 1000 mg/kg/day and an increase in absolute liver weights at 1000 mg/kg/day. Females showed increased relative liver weights at ≥ 250 mg/kg/day. At 500 mg/kg/day (M: 2/10) and 1000 mg/kg/day (M: 6/10) and at 1000 mg/kg/day (F: 2/10) had darkened liver. There was increased centrilobular enlargement at ≥ 250 mg/kg/day (M) and at ≥ 500 mg/kg/day (F). There was an increase in centrilobular brown pigmentation at ≥ 250 mg/kg/day (M) and at ≥ 500 mg/kg/day (F). In both sexes at ≥ 500 mg/kg/day there was an increase in Kupffer-cell brown pigmentation. There was an increase in brown-pigmented concretion in bile and in portal tract inflammation in livers of both sexes at 1000 mg/kg/day. There was also a slight increase in single cell necrosis at ≥ 250 mg/kg/day and in focal necrosis at 1000 mg/kg/day in livers of males. The report noted that there was a dose-related redistribution of intracellular lipid that was more evident at doses below 500 mg/kg/day. It was stated that the changes at the higher doses might have been masked by the other hepatocyte changes occurring at the same time. The amount of intracellular lipid was decreased in the treated animals, and the effects were most evident in the hypertrophied hepatocytes.) Possible adverse effect indicated (hepatotoxicity). M. Silva, 11/15/04

Definitive Study:

**** 50254 - 026 114627 “Sodium Omadine[®]: 80 Week Dermal Carcinogenicity Study in the Mouse,”** (Husband, R.F.A., Newman, A.J., Lee, P.N.; Toxicol Laboratories Limited, Herefordshire, England; Laboratory Project Number OLA2/7/90; 2/20/91). Sodium Omadine[®] (41.2% pure) was administered dermally (without occlusion) to Crl:CD-1 (ICR) BR (VAF Plus) mice (50/sex/dose) at 0, 5, 15 or 40 mg/kg/day for 80 weeks. Application site was neither rinsed nor occluded following dosing. Systemic NOEL = 5 mg/kg/day (There was a slight, but statistically decreased female kidney weights (absolute and relative) at ≥ 15 mg/kg. This effect may or may not be of toxicological significance. Sodium omadine at ≥ 15 mg/kg/day was related to an increased incidence in minimal epidermal hyperplasia at the treatment site in both sexes.) No treatment-related oncogenicity was observed at any dose. Acceptable, with no adverse effect. (Kishiyama & Silva, 7/30/04)

REPRODUCTION, RAT

**** 50524 - 022 073429 “Sodium Omadine[®]: Rat Two-Generation Reproduction Toxicity Study,”** (Ridgway, P., Wood, C.M.; Toxicol Laboratories Limited, Herefordshire, UK; Laboratory Project ID: OLA/9/88; 1/89). Sodium Omadine⁷ (41.2% a.i.) was administered via a single daily gavage to Crl:CD(SD)BR rats (25/sex/dose/generation) at 0 (distilled water), 0.5, 1.5 or 4.5 (reduced to 3.5 from week 4 of F0 parental generation) mg/kg/day during pre-mating (M/F) and gestation, lactation and weaning (F) for 2 generations. Reproduction NOEL = 1.5 mg/kg/day (Mating and fertility was reduced in the F0 generation at 3.5 mg/kg for both sexes. The copulation and fertility indices were reduced at 3.5 mg/kg. The mean number of estrus cycles/mating was increased over controls.) Systemic NOEL = 0.5 mg/kg/day (Body weights were statistically significantly lower than controls in both sexes of F0 generation at 3.5 mg/kg/day from week 3. Food consumption was decreased in F0 females during week 3 of pre-mating and during gestation at 3.5 mg/kg. There was an increased incidence of upper hind limb muscle atrophy in both sexes of F0 and F1 parents at 3.5 mg/kg as well as in F1 females at ≥ 1.5 mg/kg. Reduced body weight was observed in F1 parental males (weeks 19-23) and females (weeks 4-5, 16-17; throughout pregnancy and lactation) at 3.5 mg/kg. Food consumption was reduced for F1 females prior to mating at 3.5 mg/kg. Deaths were increased at 3.5 mg/kg in both generations.) Pup NOEL = 1.5 mg/kg (Mean number of F1 and F2 pups born at 3.5 mg/kg was less than controls. Bodyweights in F1 and F2 female pups were decreased at 3.5 mg/kg on lactation days 14 and 21. On lactation day 15 in F1 and F2 pups had a decrease in number of pups with startle response and a decrease in number of pups with ears open on day 3 at 3.5 mg/kg.) ACCEPTABLE. Possible adverse neurotoxic reproductive effects. (Kishiyama & Silva 6/4/04)

TERATOLOGY, RAT

**** 50254 - 025 114625 ATeratology Study in Rats,@** (James, J.M.; International Research and Development Corporation, Mattawan, MI; Study 397-017; 1/21/80). Sodium omadine (93.6% pure) was administered dermally (without occlusion) to mated female Charles River COBS⁷ CD⁷ rats (25/dose) at 0 (vehicle), 0.5, 1.5, 3.0 and 7.0 mg/kg/day during Gestation Days 6 through 15. Negative Control (vehicle): Aquaphor⁷ Cream (off-white, semi-solid,

cholesterolized absorbent in a Eucerite⁷ Ointment Base) and Positive Control: Aristocort⁷ (triamcinolone acetonide white cream, 0.1%) were used in the study. Maternal NOEL = 3.0 mg/kg/day (Incidences of post-implantation loss and late resorptions were increased with Sodium Omadine⁷ at 7.0 mg/kg/day. Erythema was observed in a dose-related manner in all treated groups, but most notably at 7.0 mg/kg/day and at this dose there was also desquamation at termination. A high level of kyphosis, matting and staining of the anogenital haircoat and an inability to move forelimbs and/or hindlimbs was noted at 7.0 mg/kg/day. There were 5 deaths at 7.0 mg/kg. Body weight and body weight gain were severely decreased at 7.0 mg/kg/day during the entire gestation period and throughout treatment.) Developmental NOEL = 3.0 mg/kg/day (Fetal weights were statistically significantly decreased and the incidence of late resorptions was increased with Sodium Omadine⁷ at 7.0 mg/kg/day. Fetal weights were statistically significantly decreased at 7.0 mg/kg/day. At 7.0 mg/kg/day, there was an increased incidence in bent ribs, bent limb bones, reduced ossification in skull and hyoid, unossified #5 and/or #6 vertebrae and Aother@ areas of decreased ossification in fetuses.) Acceptable. No adverse effect. (Kishiyama & Silva, 8/19/04)

TERATOLOGY, RABBIT

** 50254 - 019 069182 ADermal Developmental Toxicity Study in New Zealand White Rabbits with Sodium Omadine⁷,@ (Keller, K.A.; International Research Development Corporation, Mattawan, MI; Report #: 397-044; 12/11/87). Sodium Omadine⁷ (purity = 43.83% a.i.) was administered dermally (6 hours/day, with collars, without occlusion) to artificially inseminated New Zealand White rabbits (20/dose) at 0, 1, 2.5 and 5 mg/kg/day (presumably as a.i.) during gestation days 6 through 19. There was no dermal irritation. Maternal NOEL = 2.5 mg/kg/day (There was a decrease in body weight change at 5.0 mg/kg/day during the treatment period.) Developmental NOEL \geq 5 mg/kg/day (There were no treatment-related effects at any dose.) Although the transitional body weight change in dams was the only sign of toxicity, the rangefinding study results justified the dose selection for this definitive study. Acceptable. No adverse effects. (Kishiyama & Silva, 8/19/04)

GENE MUTATION

** 50254 - 020 069185 ASodium Omadine⁷ CHO/HPRT Mammalian Cell Forward Gene Mutation Assay,@ (Stankowski, L.F.; Pharmakon Research International, Inc., Waverly, PA; Laboratory ID: PH 314-OL-001-87; 5/20/87). Sodium Omadine⁷ (41.4% pure) was used on Chinese hamster CHO-K1-BH4 cells at 0.5 to 5.0 ug a.i./ml (+ S9) and 0.005 to 0.035 ug a.i./ml (no S9) to evaluate mutagenic potential. Treatment was for 5 hours, duplicate cultures, followed by 19 hours before plated for cytotoxicity. After 7 days, cells were plated with 6-thioguanine for mutant growth. Only one trial for mutation frequency was performed. There were no treatment-related increases in mutation frequency at any dose.

The positive controls functioned as expected. ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 5/28/04).

CHROMOSOME EFFECTS

**** 50254 - 020 069183 ASodium Omadine⁷ Micronucleus Test,@ (Sorg, R.M., Pharmakon Research International, Inc., Waverly, PA; Laboratory Project ID: PH 309-OL-001-87; 3/30/87). Sodium Omadine⁷ (41.4% a.i.) was administered a single intraperitoneal to CD-1 mice (5/sex/dose/sacrifice time) at 0 (distilled water) and 238 mg a.i./kg and their bone marrow was examined at 30, 48, or 72 hours post-treatment. Dose was selected on the basis of a rangefinding study to 1000 mg/kg (414 mg/kg a.i.) at which dose all 4 (2/sex) died within 4 hours. Clinical signs included decreased body tone, lacrimation, abnormal gait and tremors. Triethylenemelamine (TEM 0.5 mg/kg) served as a positive control. There were no sodium omadine-related increases in micronucleated polychromatic erythrocytes at 575 mg/kg (equivalent to 238 mg/kg a.i.) at time points up to 72 hours post dosing. This is based on the inability of sodium omadine to increase number of micronuclei/1000 polychromatic erythrocytes/animal. ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 5/26/04).**

DNA DAMAGE

**** 50254 - 020 069184 ASodium Omadine⁷ Rat Hepatocyte Primary Culture/DNA Repair Test@ (Barfknecht, T.R.; Pharmakon Research International, Inc., Laboratory Project ID: PH 311-OL-001-87; 3/16/87). Sodium Omadine⁷ (purity = 41.4%) was used on primary rat hepatocytes *in vitro* at 0, 7.1, 22 and 71 µg/ml to evaluate the potential to induce DNA damage. Sodium Omadine⁷ did not increase the number of net nuclear grains in rat hepatocytes at any dose. 2AAF (positive control) functioned as expected. ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 5/28/04).**

NEUROTOXICITY

**** 50237 – 137 & 0151 207093, 211914 & 211915 “Acute Oral Neurotoxicity Study with 3-Iodo-2-Propynyl Butyl Carbamate (IPBC) Administered by Gavage in CD[®] Rats,” (Weiler, M.S.; Covance Laboratories, Inc., Madison, WI; Laboratory Study ID#: Covance 7071-101; 8/31/01). IPBC (3-iodo-2-propynyl butyl carbamate; 99.3 - 101% pure) was administered by gavage in a single dose to Crl:CD[®](SD)IGS BR rats at 0 (corn oil), 100, 300 and 1000 mg/kg. Three sets of animals were treated as follows: Set 1: Functional Observation Battery (FOB)/Motor Activity (MA) and blood ChE pretest and at Time of peak effect day 1, including Brain ChE (12 rats/sex/dose). Set 2: FOB/MA, blood ChE pretest and at Time of Peak Effect on day 1 (3 to 6 hours after dosing) and on days 8 and 15. Brain ChE day 15 (12/sex/dose). Set 3: Six/sex/dose necropsied day 15 for neurohistopathology following *in situ* perfusion. Systemic NOEL < 100 mg/kg (There were numerous clinical effects observed in both sexes of Set 2 animals at 1000 mg/kg (hunched, hypoactive, liquid feces, few feces, periorbital squinting in**

eyes, effects on skin, and behavioral effects). There was a statistically significant decrease in motor activity in both sexes of Set 1 and 2 animals at ≥ 100 mg/kg on day 1. In Set 2 males (day 15), there was a statistically significant decrease in motor activity at ≥ 100 mg/kg. There was a statistically significant decrease in body weight gain in both sexes (Set 2) at ≥ 300 mg/kg days 1 - 8, in both sexes at 1000 mg/kg throughout the study. Set 3 males at ≥ 300 mg/kg had statistically significantly decreased body weight gain days 1-8 and 1-15. There was a statistically significant decrease in plasma ChE at ≥ 300 mg/kg (day 8) and at 1000 mg/kg (day 15) in Set 2 females.) Neurotoxicity NOEL = 300 mg/kg (Locomotor activity, Sets 1 & 2 on day 1 was statistically significantly decreased in both sexes at 1000 mg/kg. There was a statistically significantly decreased approach response in males at 1000 mg/kg (Sets 1 & 2). In Set 2 on day 8, there was a decrease in approach response in females at 1000 mg/kg. Females in Sets 1 & 2 had a statistically significant decrease in number of rears on day 1 at 1000 mg/kg.) Previously reviewed as unacceptable (Silva, 10/21/03), upon submission of positive controls (DPR volume/record #: 50237 – 0151/211914 & 211915) the study is upgraded to acceptable. No adverse effect. Silva, 11/16/04.

MISCELLANEOUS

Acute Studies:

**** 50254 - 021 069186** AAcute Inhalation Toxicity Evaluation on Na Omadine in Rats,@ (Drummond, J.G.; International Research and Development Corporation, Laboratory Project ID: 397-045; 8/28/87). Sodium Omadine⁷ (40% pure) was administered in a single 4-hour inhalation (whole body) exposure to Charles River CD⁷ Sprague-Dawley derived albino rats (5/sex/dose) at 0.14, 0.58, 0.79, 0.95 and 1.4 mg/L. EAD ranged from 2.3 to 3.2 μ m and GSD of 1.92 to 2.28. Treatment related effects were reduced body weight gain, increased salivation, impaired function of hindlimbs (at 0.58 mg/L and higher) and mortality. LC₅₀ = 1.26 (0.76 – 2.10) and 0.81 (0.45 – 1.45) mg/L for males and females, respectively. Acute toxicity category III, as supplied, uncorrected for a.i. content. No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 2/24/04)

**** 50254 - 021 069187** ALD₅₀ in Rats,@ (Cerven, D.R., MB Research Laboratories, Inc., Project #: MB 86-8370 A; Protocol #: 67 R/A; 5/87). Sodium Omadine⁷ (purity = 40% ai) was administered in a single gavage to Wistar rats (5/sex/dose/treatment) at 1.0, 1.1, 1.2 and 1.5 g/kg (both sexes) and at 1.9, 2.0 and 2.5 g/kg (males only). Animals were observed for 14 days post-dosing. Necropsy of dead animals revealed abnormalities of the lungs, liver, spleen, heart, gastrointestinal tract, staining of the nose/mouth and staining of anogenital areas. Surviving animals appeared normal at necropsy, except 1 male at 2.0 g/kg and 3 females at 1.1 g/kg with brown staining at nose/mouth. LD₅₀ = 2.0 g/kg (1.7 – 2.3 g/kg for males) and 1.1 g/kg (0.58 – 1.3 g/kg for females) The LD₅₀ values are based on Sodium Omadine⁷ as supplied and not corrected for the 40% purity. Toxicity Category III. The study is currently acceptable due in part to the fact that the code for interpretation of data (page 9 missing from the report) was available in 50254 - 021 069188). Kishiyama & Silva, 2/24/04

**** 50254 - 021 069188** AAcute Dermal Toxicity in Rabbits/LD₅₀ in Rabbits,@ (Cerven, D.R.; MB Research Laboratories, Inc., Spinnerstown, PA; Project #: MB 86-8370 B; Protocol #: 175-01; 5/4/87). Sodium omadine (purity = 40% a.i.) was administered once dermally (with occlusion) to New Zealand White rabbits (5/sex/dose) at 1.5, 1.65, 1.8 and 2.0 g/kg (Limit test) for 24 hours before being washed off. Skin irritation was evaluated on days 1, 7, 14 and 21. Doses were not corrected for a.i. content. Volume applied was increased to increase the dose. Observations were performed at 1, 2 and 4 hours, and for 21 or 28 days post-dosing. Results showed body weight loss at all doses throughout the study, clinical signs of toxicity and effects observed at necropsy were observed in both animals that died on study and in animals surviving to termination. Clearing of skin irritation was noted by day 21, sometimes by day 14. LD₅₀ for males and females combined was 1.8 (1.6-2.1) g/kg of body weight, with a Toxicity Category = II. Acceptable. (Kishiyama & Silva, 2/24/04).

**** 50254 - 021 069189** APrimary Dermal Irritation in Albino Rabbits,@ (Cerven, D.R., MB Research Laboratories, Inc., Spinnerstown, PA; Project #: MB 86-8370 C; Protocol #: 166-01; 4/28/87). Sodium omadine⁷ (40% pure; Batch #: F113D1) was dermally administered (semi-occluded) to 6 New Zealand White rabbits at a volume of 0.5 mls for 4 hours. Skin observations were performed at 30 - 60 minutes after removing the wrap, then again at 24, 48 and 72 hours (up to 14 days, if necessary). Results showed a Avery slight@ and Aslight@ erythema and eschar formation at 4 1/2 - 5 hours post-dose (entirely gone in 5/6, 1 Avery slight@ remaining by 72 hours) and Avery slight@ to Aslight@ edema formation at 4 1/2 - 5 hours (entirely gone in 6/6 by 72 hours). Category IV. Acceptable. (Kishiyama & Silva, 2/25/04)

50254 - 021 069190 AGuinea Pig Maximization Test (Magnusson-Kligman),@ (Fritz, L.K.; MB Research Laboratories, Inc., Spinnerstown, PA; Project #: MB 86-8370 F; 4/28/87) Sodium omadine⁷ (40% pure) was administered once intradermally (Induction A) and twice topically (Induction B and Challenge) to the exposed skin area of 10 male Hartley guinea pigs. Allergic response was determined from reactions to the Challenge dose. Results showed: **Induction A:** Erythema scores were severe on the intradermal sites dosed with FCA and FCA + test material and mild to severe on the sites dosed with test material only. **Induction B:** Erythema was mild to severe after a 48-hour exposure to a 10% of the test material. **Challenge:** After a 24 hour exposure to 5% dilution of test material, mild erythema was observed in 2/10 animals at 24.5 hours post dose. At 48 hours, 3/10 had mild erythema. This study is not acceptable and not upgradeable (no positive controls). Possible adverse effect indicated (Positive for skin sensitization by this test) (Kishiyama & Silva, 2/27/04).

50254 - 021 069191 "Evaluation of the Skin Irritating and Sensitizing Propensities of Sodium OMADINE[®] Antimicrobial Agent, Sample H51196A in Humans," (Ader, A.W.; Product Investigations, Inc., Conshohocken, PA.; Report #: PI-4750; 8/18/87). Sodium omadine[®] (40% pure; sample #: H51196A) was affixed by webril pads containing 0.2 ml of neat material to the skin of each human subject (11 males & 44 females, age range 21 - 82)

under impermeable adhesive patches. The test was conducted in 2 phases: 1) primary/activation (induction) phase to determine primary irritation potential on intact and pathology-free skin and to test potential for antigenicity by activating the immune system. 2) Assess primary irritating propensity and elicit visible evidence of hypersensitivity reaction. Twelve applications (3 - 4/week) were made over 4 weeks on the same site, with a rest period of approximately 6 days. In the challenge phase (week 5), 4 more applications were made to a naive site on the back. **Primary/Activation (Induction) Phase:** Adverse changes ranging from Grade 1 (13/47 erythema, faint) to Grade 4 (4/47, 1 occasion/individual: redness plus general elevation [induration or edema] on contact site and/or papule formation or coalescence of discrete, elevated areas) were observed at the treated sites in 20 subjects at this stage of testing. According to the report, the appearance and clinical course of the responses were typical of a weak cumulative primary irritant. **Challenge Phase:** Adverse changes of Grade 1 intensity were observed at treated sites of 4 subjects (one occasion/individual). The intensity, frequency and clinical course of these responses indicated a weak cumulative irritant effect. There was no indication of a treatment-related sensitization reaction in any subject. These data are supplemental. M. Silva, 3/2/04

Metabolism:

**** 50254 - 011 087611 ASodium Omadine⁷ Disposition and Metabolism in Rats After Oral and Intravenous Administration,**@ (Chadwick, M., Silveira, D.M., McComish, M.F., Nomeir, A.A.; Arthur D. Little, Inc., Acorn Park, Cambridge, MA; Laboratory Project ID #: ADL 59798A; 8/25/89). ¹⁴C-Sodium Omadine⁷ (98% radiochemically pure) was administered to Sprague-Dawley rats (5/sex/group) at 0.5 mg/kg i.v., 0.5 mg/kg p.o. and 0.5 mg/kg p.o. following unlabeled Sodium Omadine⁷ (41.41% a.i.) at 0.5 mg/kg for 14 days, or at 25 mg/kg p.o. Radiolabel was determined in serial blood samples from all groups and in tissues of the p.o. groups at 96 hrs. Urine within each test group was pooled from individual rats and analyzed for metabolites. Sodium Omadine⁷ was absorbed at 90% of the dose administered (p.o.). Absorption was determined by comparing urinary excretion of Sodium Omadine⁷ derived radioactivity after p.o. and i.v. administration. Pharmacokinetics after oral administration (and also i.v.) showed an initial peak of radioactivity followed by a second broader peak. Compound equivalents were eliminated from blood at several rates, with a slow (14 day) terminal elimination rate observed in all orally dosed test groups. Sodium Omadine⁷ was excreted primarily in urine (73-85% of the dose in 96 hours). Excretion was more extensive and rapid after administration of 0.5 mg/kg i.v. or p.o. (80-85%, 12 hours) than after repeated dosing at 0.5 or 25 mg/kg (73-76%, primarily during the first 24 hours). Fecal excretion ranged from 3-12% in 96 hours for the 4 test groups and 2-3% of the dose was found in tissues and carcasses of the orally treated groups at 96 hours. In all 3 oral groups the highest concentrations were in blood cells, liver and kidney. After all treatments the total recoveries were between 85-95%. There were 12 metabolites in urine from all 4 groups, including a major metabolite (47-67% of dose). Differences in metabolite patterns in urine were dependent on relative amounts of urinary metabolites excreted, routes, dose levels, dose schedules and sex of rat. Acceptable. M. Silva, 8/25/04
