UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

003933

DATE: September 13, 1978

SUBJECT: Zinc Omadine Industrial Microbiostat EPA Registration#1258-840
Caswell#923 (Zinc 2-pyridinethiol-1-oxide)

FROM: William Dykstra, Ph.D
Toxicology Branch/HED

TO: James Banks
Product Manager#33



Registrant: Olin Corporation
120 Long Ridge Road
Stamford, Conn. 06904

Action Type: Data Review, Completeness Review and Labeling Review.

Recommendations:

1. Based on primary eye irritation, the product signal word is Danger. The label should be changed to Danger, followed by the precautionary statements: "Keep Out of Reach of Children. Corrosive. Causes Eye Damage and Skin Irritation. Do not get in eyes, on skin, or on clothing. Wear goggles or face shield and rubber gloves when handling. Harmful or fatal if swallowed, inhaled or absorbed through skin. Avoid breathing vapors or spray mist. 'First Aid". In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For eyes, call physician. Remove and wash contaminated clothing before reuse."

2. This product should be considered as a candidate for restricted use.

3. The toxicology studies submitted are not adequate to support the current registration or to support a re-registration. In addition to the studies classified as supplementary data which are required to be upgraded (see recommendation #7), the following toxicology studies are required in order to assess the human hazards produced by exposure to the product during the use patterns:

a. A 90 subchronic dermal toxicity study (with neurotoxicity assessment) on the active ingredient, Zinc omadine. This study must demonstrate a "no observable effect level" for treatment. The minimum requirements are 10 animals/sex/dose level with four treatment dose levels, one of which must be at the level of use dilution for cutting oils. The active ingredient must be applied at least 8 hours/day in an oil solvent, to intact skin on the fur clipped trunks of either NZW Rabbits or Yorkshire pigs. In addition, there must be an untreated control and a solvent control. The following parameters must be observed: general observations, body weights, food consumption, clinical chemistries, hematologies, ophthalmologic examinations, FEG behavior examinations and complete histopathological examination of all animals with particular attention given to ocular, muscular, neuromuscular, and neurological tissue.



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b. Dermal oncogenicity/chronic toxicity - 1 species

4. The complete report of the I.B.T. Dominant Lethal Study (I.B.T. #623-08161) must be submitted for evaluation.

   This study was alluded to under Mutagenic Studies in Toxicology Summary of Zinc Omadine, page 21, J.H. Wedig. Additional mutagenic testing may be required in the future.

5. Toxicology studies performed by I.B.T. laboratories must be validated. I.B.T. studies are noted in Recommendation #7.

6. This recommendation is deferred to for consideration by OSHA, NIOSH or some other government agency that may be interested in conducting an epidemiological survey which attempts to evaluate any potential correlations between industrial workers exposed dermally to % zinc omadine (or other omadine salts) and clinical symptomatologies with particular attention to ocular (blindness and corneal opacity) and neuromuscular (paralysis and penile prolapse) syndromes.

7. Many of the studies submitted and reviewed are classified as supplementary data. This category of classification does not support the registration. Except for the toxicology studies in recommendations #3 and #4, they are not all required for this registration.

   The unresolved questions regarding each study must be addressed satisfactorily by the registrant for possible upgrading of classification to a level which supports the registration. A summary of the studies reviewed and classified, including the toxicology studies necessary to support the registration, are as follows:

1. Dermal Application to the Abraded Dorsal Surface of Sexually Mature Female Yorkshire Pigs: Supplementary Data

2. Test for Acute Toxicity to rats: Supplementary Data

3. Test for Acute Toxicity to Rabbits: Core Minimum Data, 3a + 3b; Supplementary Data 3C + 3D.

4. Test for Mucous (eye) irritation: core minimum data.

5. Skin Absorption Toxicology in Rabbits: Supplementary Data

6. Toxicologia Observations on the Effect of Adding ZnPt to the Diet of Rats: Supplementary Data.

7. Summary of Toxicology Studies performed on ZnPt: Supplementary Data

8. Toxicology of Pyridinethiones: Supplementary Data

Preliminary Neurological Evaluation of Generalized Weakness in ZnPt-treated Rats: Supplementary Data

10. Urinary Excretion and Metabolism of Salts of 2-pyridinethiol-1-oxide following intravenous administration to Female Yorkshire Pigs: Core Minimum Data

11. Teratologic Evaluation of Dermally Applied Zinc pyrithione on Swine: Core Minimum Data

12. Absorption, Distribution and Excretion of ZnPt in Rabbits: Core Minimum Data

13. The Effects of Pyridinethiol oxide on the Central Nervous System:

14. Comparative Percutaneous Absorption of Pyrithions: Core Minimum Data, except for discussion of safety margin for human uses.

15. A percutaneous Teratology Study of Zinc pyrithione in Rabbits: Core Minimum Data

16. Absorption of Zinc pyrithione onto Hair and Skin: Supplementary Data

17. Antimicrobials: Experimental Contact Sensitization in Man: Core Minimum Data

18. Evaluation of Product Performance: Supplementary Data; the referenced 90 day study of Subacute percutaneous toxicity with a 2% ZnPt solution is required for registration.

19. Pharmacological properties of Bis-(1-hydroxy-2-(1H-pyridine-thionato) Zinc: Core Minimum Data

20. Percutaneous toxicity of pyridinethiones in a DMSO vehicle: Supplementary Data

21 a. The Anti-Seborrheic Qualities of ZnPt in a cream vehicle: Supplementary Data

21 b. Anti-seborrhoeic qualities of ZnPt in a cream vehicle: Safety Evaluation: Supplementary Data

22. Zinc Pt: Percutaneous Absorption and Residual Amount of Skin Surface: Supplementary Data

23. Intravenous Toxicity of ZnPt and several Zn Salts: Supplementary Data

24. Safety Evaluation of ZnPt in a shampoo formulation: Supplementary Data

25. Results of Patgologic Findings on Rats Receiving ZnPt: Supplementary Data

26. Acute oral toxicity with Zinc omadine in ALbino rats: Core Minimum Data. This study is an I.B.T. study and needs to be validated.

27. Summary of Unpublished Studies on the Toxicology of ZnPt: Supplementary Data. The 90 day subacute study in rabbits is required for registration. However, as reported, the study is considered as supplementary data since a NEL was not established for treatment.

28. Dermal absorption in Mice: Supplementary Data. This study is required for registrating.

29. Generalized Paresis in ZnPt treated rats: Supplementary Data

30. Report of the Histopathological Examination of Brain and Spinal Cord sections submitted by the Olin Corporation: Supplementary Data. This study is an I.B.T. study and needs to be validated.

31. Teratologic evaluation of Zinc omadine when applied to the skin of the Pig: Core Minimum Data. This study is an I.B.T. study and needs to be validated.

32. Dermal absorption in Domestic Pigs: Core Minimum Data

33. Acute Toxicity and Disposition of Omadine Salts following Intravenous Administration to Swine: Core Minimum Data

34. Evaluation of Potential Hazards by Dermal Contact: Core Minimum Data.

Product - Zinc Omadine Industrial Microbiostat

| Ingredient | Percent Weight |
|---|---|
| Zinc 2-pyridinethiol-1-oxide | 95 |
| Inerts | 5 |
| | 100 |



Directions for Use:

Directions for Aqueous Metal Coolant and Cutting Fluid Solutions. To inhibit bacterial growth add an initial dose of 75 ppm Zinc 2-pyridinethiol-1-oxide to the solution (0.75 lbs Zinc omadine powder per 10,000 lbs of solution) and repeat this dosage every 25 days or as needed.

Directions for control of Mildew and "pink stain" microorganisms for PVC plastics (own-food use). To inhibit the growth of mildew and "pink stain" microorganisms, a use level of 0.1 to 0.2% of Zinc Omadine Powder (based on total formulation weight) is recommended. It may be added at any time during the formulation procedure. Use care to avoid clumping.

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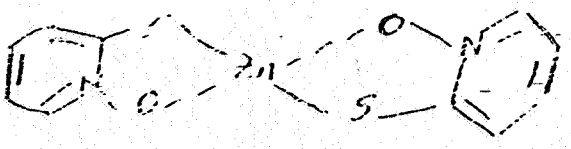
Structure:



Chemical Name: Zinc 2-pyridine thiol-1-oxide

Common Name: Zinc Omadine, Zinc pyrithione



Empirical formula: $C_{10} H_8 N_2 O_2 S_2 Zn$

Physical - Chemical Constants: Powder color - off white
M.P. - 240 °C
pH - 10% in $H_2O$ 6.5-7.5
- 2% in $H_2O$ 6.8-7.3
Solubility in $H_2O$ - 10-20 ppm

Review:

1. Tables: Dermal Application to the Abraded Dorsal Surface of Sexually mature Female Yorkshire Pigs.

Classification: Supplementary Data

(a) In order for the data presented to be capable of meaningful interpretation and further classification, the registrart must provide the following detailed information:

(1) Name of Laboratory, Authors, Data of study and signed final report.
(2) Complete experimental protocol
(3) Complete detailed methodology with references, including position of C-14 label in compound
(4) Complete general and clinical observations during study

2. a. Test for Acute Oral Toxicity to Rats, Food & Drug Res. Lab. (Food and Drug Research Laboratories, Inc., August 6, 1969, Lab. No. 90655 a)

Test Material: White cream (received July 14, 1969); Marking: Zinc Omadine; 48% Aqueous dispersion; Zinc pyridinethione

One group of FDRL strain adult rats (5M & 5F), 204 ± 1 gm BW, received by gastric intubation a dosage of 396 mg/kg BW of test material. Observation for 14 days.

Results: Five of the 10 rats dosed died in 1, 1, 1, 7, and 11 days (sex of dead rats not specified)

Body Weight: not reported for survivors

Toxic Signs: not reported

Necropsy: not reported

Conclusion: Oral dosage with 396 mg/kg of the test material resulted in 50% mortality.

Classification: Supplementary Study

(1) Body weight, toxic signs, necropsy and sex of dead rats not reported.

(2) $LD_{50}$, including 95% confidence limits not calculated.

2. b. Test for Acute Oral Toxicity to Rats (Food & Drug Research Laboratories, Inc., Aug. 15, 1969, Lab.#906556) -

Test Material: White cream (received July 14, 1969); marking: Zinc Omadine; 48% aqueous dispersion; Zinc pyridinethione.

One group of FDPL strain adult rats (5M & 5F), 196 ± 16 gm Body Weight, received by gastric intubation a dosage of 396 mg/kg BW of test material. Observation for 14 days.

Results: Nine of the ten rats dosed died: 6 on day 1 and 2 on day 2.

Body Weight: not reported for survivor



Toxic Signs: not reported

Necropsy: not reported

Conclusion: Oral dosage with 396 mg/kg of test material resulted in 90% mortality.

Classification: Supplementary Study

(1) Toxic Sign and necropsy not reported
(2) $LD_{50}$, including 95% confidence limits not calculated
(3) The results of this test test (2.b.) differ markedly from test (2.a) using a similar test material.

3.a. Test for Acute Dermal Toxicity to Rabbits, Food & Drug Res. Labs. (Food and Drug Research Laboratories, Inc. March 11, 1968, Lab.#88793 a-c

Test Material: Very pale brownish white material; Zinc omadine 50% Aqueous dispersion; Lot No.67467 and Lot No. 67576

Four Albino Rabbits per three levels (2M & 2F) in weight range of 1.8-2.8 kg depilated and one-half abraded over trunk received 4, 8, and 16 ml/kg BW of test material under an impervious cuff for 24 hours. Observation for 14 days.

Results: no deaths, $LD_{50}$ > 16 ml/kg BW (both sexes)

Toxic Signs: edema and erythema

Body Weight: no losses in survivors

Necropsy: unremarkable

Classification: Core Minimum Data TOX Category III: CAUTION

3.b. Test for Acute Dermal Toxicity to Rabbits (FDRL No.88794 a-c, March 11, 1968)

Test Material: Zinc omadine powder, very pale brownish white powder, Lot No.Z067593 and Lot. No.#Z067596

Four Albino Rabbits per three levels (2M & 2F) in weight range of 1.7 to 2.8 kg depilated and one-half abraded over trunk received 2, 4 and 8 gm per kg BW of test material under an impervious cuff for 24 hours. Observation for 14 days.

Result: No deaths, [illegible], $LD_{50}$ > 8 gm/kg (both sexes)

Toxic Signs: erythema and edema

Body Weight: losses in survivors at 8 gm/kg

Necropsy: unremarkable



Classification: Core Minimum Data

TOX Category III: CAUTION

3.c. Test for Acute Dermal Toxicity to Rabbits. (FDRL No.#88494a, Nov. 30, 1967)

Test Material: Very pale brownish white powder; marking; Zinc Omadine (Zinc pyridinethione); Z067347 510-P304

Two albino rabbits per three levels (1M & 1F) in weight range of 2.7 to 3.6 kg depilated over trunk received 2, 4, and 8 gm/kg of test material under an impervious cuff for 24 hours. Observation for 14 days.

Results: All of the rabbits died in 1 to 3 days. $LD_{50}$ < 2 gm/kg (both sexes)

Toxic Signs: Diarrhea

Necropsy: Thymus & lungs hemorrhagic

Classification: Supplementary Data

(1) $LD_{50}$ not calculated
(2) Only 2 animals per dose level tested
(3) Results differ markedly from 3.b.

Test Material: Zinc Omadine; 50% Aqueous Dispersion; S067349. 610-ZP-1

Two albino rabbits (1 M & 1F) weighing 2.8(m) and 3.4(f) kg depilated over trunk received 20 ml/kg of test material under an impervious cuff for 24 hours. Observation for 14 days.

Results: Both rabbits died in 3 and 4 days $LD_{50} \leq 20$ ml/kg

Toxic Signs: edema & erythema

Necropsy: Subcutaneous vascular dilation, lung congestion and hemorrhage

Classification: Supplementary Data

(1) $LD_{50}$ not calculated
(2) only two animals used
(3) Results differ markedly from 3.a.



(4.a. Test for Mucous (Eye) Irritation, Food and Drug Res. Labs. (Food and Drug Res. Lab. No.#88496 a, Nov. 9, 1967)

Test Material: Very pale-brownish white powder; Zinc Omadine (Zinc pyridinethione); Z067347; 510-P304; SP15765

10 mg of test material was instilled into conjunctival sac of the right eye of each of six albino rabbits with the untreated left eye serving as a control. Observations and scoring according to Draize at 24, 48 and 72 hours.

Results: Severe corneal opacity in 5/6 rabbits at 72 hours; severe iridal irritation in 5/6 rabbits at 72 hours; severe lid redness, chemosis, and discharge in 5/6 rabbits at 72 hours; moderate in 1/6 rabbits Maximum score in 3/6 rabbits at 72 hours.

Conclusion: Corrosive, severe ocular irritant

Classification: Core Minimum Data

(1) only 10 mg, rather than 100 mg, used
(2) observations at 7 days not made

TOX Category I: DANGER

...use of the extreme toxicity to the eye - it is not deemed necessary ... test this compound at a higher level and the core classification can ...e elevated to Core Minimum.

4.b. Test for Mucous (Eye) Irritation (FDRL No.38496 b, Nov. 9, 1967)

Test Material: viscous suspension of very pale brownish-white material; 50% Aqueous Dispersion of Zinc Omadine (Zinc pyridine-thione) Z067349; 610-ZP-1; SP2S765

0.1 ml of test material was instilled into the right eye of each of six albino rabbits with the untreated left eye serving as a control. Observations and scoring according to Draize at 24, 48, and 72 hours.

Results: Very severe opacity, iridal irritation, lid redness, chemosis and discharge in 6/6 rabbits at 72 hours. Maximum score (110/110) for 6/6 rabbits at 72 hours.

Conclusion: Corrosive, severe ocular irritant.

Classification: Core Minimum

TOX Category I: DANGER

5. Skin ABsorption Toxicology in Rabbits, Drug Detection and Development Organization, Inc.

A. Sodium Omadine



Test Material: Sodium Omadine

(Pilot Studies)

Four NZW rabbits received 20 mg/kg of test material to intact skin on fur clipped trunks under an impervious cuff for 24 hours. Observation for 24 hours.

Results: One rabbit died in opisthotonic posture

Seven NZW rabbits received 20 mg/kg of test material to intact skin on fur clipped trunks for 5 days (1 application each day) under an impervious cuff.

Results: One rabbit died after 24 hours

(Main Study)

Ten NZW rabbits received 200 mg/kg of test material to abraded skin on fur clipped trunks under an impervious for 24 hours. Observation for 14 days.

Results: 2 rabbits died in 24 hours and one rabbit died on the 13th day

Body Weight: not performed

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Necropsy: not performed

Toxic Signs: not performed

Conclusion: The dry powder studies suggest a possibility of a flat slope for acute dermal lethality.

Classification: Supplementary Data

(1) $LD_{50}$ not calculated (with slope and 95% confidence limits)
(2) Body Weight, necropsy, toxic signs not reported
(3) Concentration of A.I. in dry powder not given

Test Material: Sodium Omadine Solutions

Two groups of 5 rabbits each were used in these studies. They were similarly prepared, with abrasions, for dosing daily over 5 days with freshly prepared solutions at 10 and 20 mg/ml for applications of 2 ml/kg (20 and 40 mg/kg of test compound sodium omadine). The pH of the 10 mg/ml solution was 7.8 and the pH of the 20 mg/ml solution was 8.2. The rabbits were restrained for the applications and until drying was complete, after which they were covered with dams and restored to cages.

Results: One rabbit died on the 2nd day (after one dose) and one rabbit died on the third day (after two doses); the remaining 3 survived until the completion of the scheduled regimen whence these were necropsied. These deaths occurred in the 20 mg/kg group only, and no rabbits died at the 40 mg/kg level. No adverse effects were evident in any of the survivors, but the weakness and CNS involvement was noted in those rabbits which died. Necropsy revealed bladder distension in one survivor at 40 mg/kg.

Conclusion: The studies with sodium omadine solutions suggest dermal penetration and the possitility of a flat slope for acute dermal lethality.

Classification: Supplementary Data

(1) complete necropsies not performed on all animals
(2) Histopathology not performed on dead rabbits
(3) A NEL not established for this study
(4) Does not follow subacute dermal protocols, e.g., Both sexes, Body Weight, Clinical Chemistries, etc...



3. Copper Omadine - Suspensions

Two groups of 5 rabbits each were used in these studies. Both of these experiments utilized suspensions of the copper omadine made fresh daily to concentrations of 20 mg/ml. The first study used a suspension with a pH of 7.2 and the second study utilized a suspension series adjusted to pH 8.3 with NaOH. In both groups the skins were abraded. Application for 5 days.

Results: In other groups there [illegible] effects in general or on the skin. The skins of all animals, despite daily washing prior to subsequent dosings, maintained a dark green tinge or color. Urinary retention permitted direct sampling of urines, or from metabolism cages in miniscale amounts. There was no evidence of atopia, as seen in one previous instance.

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Conclusion: Daily dosing of copper omadine at 20 mg/ml for 5 days produced no deaths or toxicity.

Classification: Supplementary Data

(1) only one dose level tested
(2) Complete necropsy & histopathology not reported
(3) Does not follow subacute dermal protocol. e.g., Both sexes, Body Weight, Clinical Chemistries, etc...

C. Zinc Omadine - Suspensions

There were four studies involving suspensions of this compound. All animals were prepared as previously noted, 5 rabbits per group. Two groups were done with pH adjusted to correspond with sodium omadine solutions (supra), and two groups employed the non-adjusted suspensions. In each case, doses of 20 and 40 mg/kg were applied topically for 5 days - to the two groups adjusted, as well as to the two non-adjusted.

Results: There were no deaths or signs of compound effects grossly in any of the four groups of five rabbits during the course of this study. Once again, however, bladder distension was the rule rather than the exception and final urine samples were directly obtained at time of necropsies. One rabbit of the 40 mg/kg daily of the non-adjusted suspension material showed bladder atonia.

Conclusion: The series of Omadine Studiessuggests further investigation of CNS and muscle responses are necessary.

Classification: Supplementary Data

(1) Only summaries were presented. Actual results were not given
(2) Does not follow subacute dermal protocol, e.g., Both sexes, body weight, clinical chemistries, etc...

D. Compound "SJ"



(1) Oral Toxicity: TOX Category IV: CAUTION
(2) Primary Skin Irritation: TOX Category IV: CAUTION
(3) Primary Eye Irritation: TOX Category I: DANGER

Classification: Invalid Data

(1) Compound "SJ" has not been chemically identified. It is characterized as slightly soluble in water, effervesces slightly and also emits a distinct chlorine odor. It does not appear to be an omadine compound.

5. Toxicologia Observation on the Effect of Adding Zn Pyridinethiene to the Diet of Rats for a period of Two Years. (August 18, 1958, Paul S. Larson, Professor of Pharmacology, Medical College of Va.)

Note: This report is unsigned

Test Material: Zinc pyridinethione (technical composition - not stated)

Sixty young male and 60 young female albino rats were divided into groups of 10/sex and both sexes were placed on the following dietary levels of Zinc pyridinethione: 0, 2, 5, 10, 25 and 50 ppm. Finely ground Purina Dog Chow Kibbled Meal served as the basic diet and into this was added with thorough mixing amounts of ZnP (15% in Pyrax) calculated to achieve the above concentrations of active ingredients. The diets were freshly prepared every two weeks.

The rats were individually caged and were weighed once a week. Blood studies were made during the eleventh and twenty-fourth months. Organ to body weight ratios were determined on the two-year survivors for liver, kideny, spleen, heart and testes. Histopathologic studies were made on all two-years survivors and on all rats dying during the study in which tissues were not obviously too autolyzed: Tissues examined were: heart, lung, liver spleen, kidney, gastroenteric, bone marrow, brain, spinal cord, muscle, eye, bladder, pancreas, adrenal, thyroid and gonad.

Results: Survival data show that females fed 25 and 50 ppm diet did not survive. Only 3 out of 10 male control rats on the 50 ppm diet, death was commonly preceded by development of hind limb paralysis. This was also seen in female rats dying on the 25 ppm diet and male rats dying on the 50 ppm diet, but with less consistency. Data on growth at representative periods showed that dietary concentrations of 2, 5, and 10 ppm tended to have an accelerating effect on weight gain in female rats. This increase in body weight also occurred in male rats receiving 2, 5, 10 and 25 ppm. Significant depression of growth resultd in female rats receiving 50 ppm and a tendency in this direction appeared in female rats receiving 25 ppm after one-year on diet. In male rats receiving 50 ppm there was also a tendency toward growth suppression. Average of hematology data showed high polycyte vs. lymphocyte counts in the male rats receiving 50 ppm for two-years. Organ to body weight ratios were unremarkable.

Histopathologic findings were unremarkable.

Classification: Supplementary Data

(1) Adequate numbers of animals were not used.
(2) Toxic signs and clinical observations not reported.
(3) Chemical Analyses of diet not performed.
(4) Inadequate histopathological examination.
(5) No standard deviations for growth data, hematologic values.
(6) No food consumption data was recorded.
(7) No Clinical chemistries were performed.
(8) Only three male controls completed the study.
(9) A NOEL was not established in this study. At a dietary level of 2 ppm, increased body weight occurred in both male and female rats during the study.
(10) Report is unsigned.

7. Summary of Toxicologic Studies Performed on Zinc-2-pyridinethiol-1-oxide (ZnPt), Grove Laboratories (Grove Laboratories, Report number and date not given, Report unsigned)

Summary of Studies

Three rabbits were given orally 2 ml or 20 mg of ZnPt in carbopol gel*/kg/day and two of them died within 24 hours; the surviving rabbit received 9 additional daily doses of 20 mg/kg, one of 30 mg/kg, and, then, after 4 days rest, 20 mg/kg topically for 20 days; it showed neuromuscular toxicity (paresis).

In subacute dermal toxicity studies in rabbits, 25 of 29 animals given daily applications of 2 or 4 ml of 1% ZnPt in carbopol gel or in hydroxythylcellulose, i.e., 20 mg (23 animals) or 40 mg (6 animals) ZnPt/kg/day for 5 to 25 days showed neuromuscular involvement (weakness or paresis of hind and later forelegs), poor sensory response, depression and prostation; 28 of 29 also exhibited other signs of toxicity (emaciation, dehydration, respiratory distress or pneumonia, GI disturbances, possible liver changes, and rather marked irritation). The zinc contents of the liver and pancreases of some of the test animals (analyses by Scientific Associates, a private laboratory). Guinea Pigs dosed

*Composition: 1% Zinc Salt, 15% polyalkylene glycol, 10% glycerin, 0.4% carboxyvinyl polymer, 0.25% monoisopropanolamine, 0.005% thimerosal and 74.32% water with 1% Zinc salt in carbopol gel topically showed a lower incidence of neuromuscular signs than rabbits. There was no mention of local skin irritation in this species.

Scientific Associates conducted 14-day dermal toxicity tests on formulations submitted to them by the Grove Laboratories. They obtained results similar to those by the Grove Laboratories and, in addition, muscular fasiculations underlying and adjacent to the site of application were observed.

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[redacted]ien given repeatly to animals, ZnPt in the diet appears to be more toxic than ZnPt formulations by stomach tube. In the rat non-tolerated dietary levels are as low as 1.25 mg/kg/day (estimated from food consumption). Neuromuscular reactions have been previously described by P.S. Larson (Medical College of Virginia) in rats, by Hinek (Procter & Gamble) in rabbits, and by Sehalffer (E.R. Squibb & Sons) in chicks. Hinek showed that rabbits completely recovered from the paresis in a short time when the drug was withheld. Larson's explanation for the paresis in rats was (1) peripherally the copper salt attenuated or blocked myoneural transmission and exerted some direct depressant action on the muscule, while (2) centrally it blocked monosynaptic and polysynaptic potentials in the cord without altering dorsal or ventral root condition.

Conclusion: Neuromuscular involvement from ZnPt exposure has been demonstrated in several species by various routes of exposure.

Classification: Supplementary Data

(1) Actual reports with data were not submitted. Only a summarized report and tables were submitted.

8. Toxicology of Pyridinethiones, (Procter and Gamble, Report Number and Date not given, Report unsigned)

A. Table#1 - percutaneous toxicity of NaPt + ZnPt in a Shampoo Base.

Table#2 - Percutaneous absorption and excretion the urine of $S^{35}$ labelled NaPt & ZnPt in Rabbits.

Table#3 - Oral Toxicity of ZnpT given by Stomach.

Table#4 - Oral toxicities of ZnPt given in Diet.

Table#5 - Oral Toxicity of ZnPt in the Diet of a Monkey.

Table#6 - Oral Toxicity of ZnPt & NaPt given to monkeys by Stomach Tube.

Table#7 - Effect of Antidotes on the Intravenous Toxicity of ZnPt in Dogs.

Table#8 - Percutaneous Screening

Classification: Supplementary Data

(1) Actual reports with Data not submitted.

B. Toxicologic Studies on the Effect of Adding Zn Pyridinethione to the diet of Dogs (Read 2/26/57 from P.S. Larson, Copies of reports to Dr. Brown)

Ten mongrel dogs were used. Prior to placing them on experiment, they were wormed twice and vaccinated against distemper. The dogs were divided into two groups of four (two of each sex in each group) and one group of two (one of each sex) one group of four (dogs 1-4) was placed on a diet of finely ground Purina Dog Chow Meal containin 50 ppm ZnPt. The concentration of ZnPt was increased to 100 ppm at the beginning of the 3rd week, to 200 ppm at the start of the 5th week, and to 400 ppm at the start of the 7th week. At the start of the 14th week, dog 1 was retained on the 400 ppm diet, dog 2 was returned to control diet and dogs 3 & 4 were placed on a 300 ppm diet. At the start of the 18th week, dogs 1, 2 and 3 were retained on the same diet, but dog 4 was placed on 1600 ppm diet. This status was continued until the study was terminated during the 23rd week.

The second group of four (dogs 5-8) and the group of two (dogs 9 & 10) were placed on a diet deficient in all vitamins other than D and K. The dogs were kept on this diet for two weeks following which dogs 5-8 had 50 ppm of ZnPt added to the diet while dogs 9 & 10 served as diet controls. At the start of the 5th week, the ZnPt concentration was raised to 100 ppm. From the 3rd week on, the dogs in both of these groups developed a progressively increasing distaste for the diets. By the end of the 5th week the weight lossess were so great and the intake of food so reduced that continuation on these diets did not appear to be compatible with survival. Therefore at the start of the 6th week, dogs 5-8 were switched to Purina Dog Chow Meal containing 200 ppm ZnPt and dogs 9 & 10 were placed on untreated Purina Stock diet. At the start of the 7th week, dogs 5-8 were switched to 400 ppm and thereafter followed the same schedule as dogs 1-4.

Ophthalmologic examination of each dog was made prior to placing them on experiment and was repeated at intervals thereafter.

Results: Body Weight data shows that dogs (1-4) receiving ZnPt in the basic diet of Purina Dog Chow showed no adverse effects on general health or body weight. Ocular findings were as follows: Through seven weeks on diet (all dogs on 400 ppm at this point), ocular findings were uniformly negative except for sporadic conjunctival injection and discharge appearing in some dogs but clearing without treatment. The first pupillary changes were noted during the 8th week and were characterized by sluggish response to light stimulus in all test animals with diminished excursion of the pupils in some. By the 10th week, all but two of the light reflex. By the 12 th week all dogs showed this phenomenon. Thereafter, the dilated pupil remained constant for the rest of the period but light reflex returned to a variable degree in two dogs that were switched to unadulterated diet at the start of the 14th week continued to have widely dilated pupils and loss of light reflex for the remainder of the study.

Following development of pupillary dilation and loss of the light reflex, periodic studies were made on the effect of instilling 0.5% eserine or 2% pilocarpine solution into the eye. Initially (10th week) normal pupillary constriction was produced by eserine together with indication of resumption of light reflex. In contrast, the constrictor response to pilocarpine was exaggerated and there was indication of spasm of the sphincter. In later studies, some of the dogs lost all response to eserine, but all retained the exaggerated response to pilocarpine. In dogs that continued to respond to erserine, some degree of return of the light reflex accompanied the response.

An additional puppillary finding that persisted to the end consisted of normal constriction of the pupil under sodium pentobarbital anesthesia and during the induction stage the light reflex returned in varying degree.

Fundoscopic examinations were completely negative throughout the study except for questionable early changes in the nerve-heads noted in 3 dogs (2 dogs at 800 ppm and 1 dog on 1600 ppm). These changes were characterized by slight pallor and diminished or absent visculization of the capillaries. These changes did not progress sufficiently to be considered of significance. No evidence of blindness was seen at any time.

Conclusion: Whether the pupillary changes noted stem from a functional depression of the autonomic innervation or from histological degenerative changes cannot be decided from the information presently available since no histopathology was performed.

Classification: Supplementary Data

(1) Controls used not appropriate
(2) Inadequate numbers of animal
(3) Clinical chemistry, hematologies, urinanalyses, necropsies and histopathology not performed.

C. Studies on the Acute Oral Toxicity of Zn pyridinethione and Na pyridinethione (Tech.) and Purified to Rats (Studies conducted by Paul S. Lerson, Oct. 21, 1956)

Groups of ten male and ten female albino rats about 175 gm in weight, were used and were fasted for about 5 hours prior to dosing via stomach tube. The Zn pyridinethione was used as a 2% (w/v) suspension in 1% aqueous solution of methocel and was administered at mg/kg doses of 105, 200, 210 and 220 (males) and 130, 140, 150, 165 and 180 (females). The sodium salts were administered as 5% (w/v) aqueous solutions immediately following their preparation. The purified Na pyridinethione was administered at mg/kg doses of 800, 900, 950 and 1000 (males) and 550, 600, 650, 700 and 800 (females). The technical Na pyridinethione was administered at mg/kg doses of 800, 850, 900 and 950 (males) and 600, 700, 800 and 900 (females). Deaths were spread over a three day period following dosing with most deaths occurring in the first 36 hours.

: Oral $LD_{50}$ = 200 ± 10 mg/kg (males)
= 140 ± 10 mg/kg (females)

ridinethione

OX Category II: WARNING

lla pyridinethione purified — Oral $LD_{50}$ = 900 ± 70 mg/kh (males)
= 660 ± 60 mg/kg (females)

ila pyridinethione technical — Oral $LD_{50}$ = 900 ± 20 mg/kg (males)
= 770 ± 60 mg/kg (females)

TOX Category II: WARNING

Toxic Signs: not reported

Necropsy: not reported

Body Weight: not reported



Classification: Supplementary Data

(1) Composition of test material not stated.
(2) Toxic signs, body weights and necropsies not reported.

D. Three Month Study on the Effects of Adding Zinc Pyridinethione to the Diet of Rats (P.S. Larson, July 20, 1956; report is unsigned)

Two groups of rats were started on this experiment. The first group consisted of 60 young male and 60 young female albino rats which were divided into groups of 10 and one group of each sex was placed on each of the following dietary concentrations of Zinc pyrindinethione: 0, 15, 75, 375, 938 and 1875 ppm. The second group consisted of 60 young male and 60 young female albino rats which were divided into groups of 10 and one group of each sex was placed on each of the following dietary concentrations of Zinc pyridinethione: 0, 15, 75, 188, 375 and 750 ppm. Finely ground Purina Dog Chow Kibbled Meal served as the basic diet and into this was incorporated, with thorough mixing, amounts of zinc pyridinethione (15% in a wettable powder) calculated to achieve the above concentrations of the active ingredient. The rats were individually caged and were weighed once a week. Blood studies were made during the 13th week on all three month survivors in the second group of rats. At the time of sacrificing the rats in the second group, organ to body weight measurements were made for liver, kidney, and testes. Tissues taken for histopathologic examination were heart, lung, liver, kidney, spleen, gastro-enteric, thyroid, adrenal, pancreas, gonad, bladder, bone marrow, eye, brain, spinal cord and fore hind limbs.

Results: Signs of intoxication include diarrhea and marked weakness of the hind limbs. Female rats fed 75, 188, 375 and 750 ppm and male rats fed 188, 375 and 750 ppm did not survive the experiment in numbers comparbale to controls. Hematological values were unremarkable. Survival and body weight data for 15 ppm male & female rats was similar to controls. Organ/body weight ratios were increased for testes & liver in male rats at 75 ppm and for livers and kidneys in female rats at 75 ppm.

stopathological studies were made on the following rats from group 1: females & 6 males receiving 1875 ppm. and 2 female & 2 males control rats. Similar studies were made on the following rats from group 2: 3 female & 3 male rats receiving 750 ppm; 5 female and 5 male rats receiving 375 ppm; 6 female & 4 male rats receiving 188 ppm; 7 female & 10 male rats receiving 75 ppm; 10 female & 10 male rats receiving 15 ppm; 8 female & 10 male control rats . No lesions attributable to treatment were found. NEL is considered to be 15 ppm in the diet. However, Histopathology tables were not submitted.

Conclusion: The weakness of the hind limbs could not be explained on a morphologic basis and the possibility of a functional effect to explain this toxic sign is proposed.

Classification: Supplementary Data



(1) Strain of rats unspecified.
(2) Chemical composition of test material is unspecied.
(3) Unclear from results which rats exhibited toxic signs.
(4) Report is unsigned.
(5) Histopathological Tables not submitted.

E. Addendum Report

Toxicologic Effects of Administering Na pyridineth one orally to Dogs
(Received 8/26/57 from P.S. Larson)

Na pyridinethione in aqueous solution was administered by stomach tube to 4 mongrel dogs for a period of 4 weeks. The animals were fed Purina Dog Chow Checkers ad libitum and were weighed each day. Doses were given twice a day, 7 days a week. For the first week, each dose was 5 mg/kg (as a 0.5% solution) and, for the succeeding 3 weeks, was 10 mg/kg (as a 1.0% solution). This dosage increase was dictated on the basis of the lack of toxic symptoms during all but the first day of the first week.

Results: Toxic symptoms during the first week consisted of Nausea in dog #4 and vomiting in dog #2. Body weight data showed that dog #4 lost weight significantly over the treatment period dog #4 was comatose on the day before the end of the 4 week period and was sacrificed and autopsied at that time. The other dogs were sacrificed at the end of 4 weeks. Tissues taken for histopathological examination were brain and eyes.

Ophthalnologic findings were as follows: By the end of the first week there was beginning sluggish pupillary response to light stimulus in dog #1 and #3 and dogs #2 and #4 showed similar effects a week later.

Fundoscopic examinations revealed the development of severe changes as the experiment progressed. The changes occurred in generally segmental distribution, with the upper nasal fields being involved first. This was quickly followed by extreme involvement of the remaining quadrants. The changes were characterized by loss of pigmentation, minimal pigment redistribution, and the development of an over-all gray back-round color. The vessels were quite thin and tenuous, and neither hemorrhages or exudates were noted.

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Conclusion: There was a profound degree of atrophy of both retina and the underlying choroid with the gray-white background color being the sclera showing through. Acutal evaluation of the site of action must await microscopic examination. There was a loss of capillaries on the optic nerve-head, with the development of apparent pallor of the cup. The distinct impression was gained that these animals were blind by the end of the study.

Classification: Supplementary Data

(1) Histopathologic data not submitted
(2) Report is unsigned.

9. Preliminary Neurological Evaluation of Generalized Weakness in Zinc pyrithione-treated Rats, Wedig, Olin Corp. (Date of Experiment not given.)

Running Title: Generalized Weakness in Zinc Pyrithione Intoxication

Male rats of the CD strain, 250-300 gm BW, were divided into 33 pairs, matched by weight, and fed 250 ppm of Zinc pyridinethione ad libitum. Pair fed controls were given only the amount of feed eaten by the treated animals during the previous 24 hours. Organs examined (gross and microscopic) were adrenal, pancreas, thyroid, parathyroid, pituitary, bone marrow, spleen, heart, kidney, bladder, liver lung, skeletal muscle, eye, brain, spinal cord, sacral and brachial plexus and sciatic, femoral, radial, medical and ulnar nerves. Blood study included CBC with differential. LBC, glucose, BUN, Calcium, potassium, sodium, SGOT, CPK, LDH, Hb, HCt. Chloride, Cholinesterase, pH, $pO_2$, $pCO_2$. Gastrointestinal tract bacteria were examined. Neurophysiological studies on sciatic nerve condution and gastrocnemius and soleus muscle were performed on 12 pairs of rats.

Results: Weight loss began within 24 hours of treatment initiation. Food Consumption fell and zinc omadine consumption fell from 10.9 to 5.3 mg/kg/day. Strain differences in response were not observed. Locomotor abnormalities began 8 to 10 days post-treatment and were characterized by Stiff gait and weakness which usually calminated in hind limb paralysis within 48 hours. Death usually occurred with 12 days loss began within 24 hours. Penile prolapse was observed in all severely affected animals. 8 pairs were withdrawn from the clinical signs were present, and given ad libitum control diet. Weight loss continued for 3-4 days in treated animals. The progressive hind limb weakness was associated with muscle atrophy. Affected muscles had a weaker contractile response to sciatic nerve stimulation than controls, but sciatic nerve conduction velocities were similar to controls. Reduction of muscle fiber diameter from the soleus, gastrocnemius and sacrospinalos muscles was observed, along with reduction in muscle weight, when compared to pair fed controls. Rats showing motor dysfunction for 4 to 11 days had mean soleus weights of 85.9 mg, compared to weights of 138.7 mg in control muscles. Histopathological and blood changes were otherwiae negative.

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Conclusion: The mechanism of hind limb paralysis was not identified in this study. Zinc pyridinethione at 250 ppm in the diet caused paralysis in 8 days.

Classification: Supplementary Data

(1) Females not tested.
(2) NOEL not established.
(3) Histopathology data not submitted.
(4) Hematology data not submitted.



10. Urinary Excretion and Metabolism of Salts of 2-Pyridinethiol-1-oxide following Intravenous Administration to Female Yorkshire Pigs, Adams, Wedig, et al. Toxicology and Applied Pharmcology 36, 523-531 (1976)

A single dose of zinc pyridinethione (ZPt; 5 mg/kg; oil-in-water emulsion), sodium pyridinethione (Spt; 50 mg/kg; aqueous solution), or the magnesium sulfate adduct (MDS; 4 mg/kg; aqueous solution), which included 5 μCi/kg of 2,6-$C^{14}$ labeled material, was injected via a jugular vein cannula into female Yorkshire pigs, 2 pigs per compound, in order to study the plasma half-life, the urinary excretion rate, and the metabolism of these antimicrobial and antifungal agents during a 96 hour period.

Results: At the doses employed, all of these agents produced cholinergic effects (parasympathetic and somatomotor) which lasted for 30-60 minutes Plasma decline in radioactivity was a biphasic exponential function for each compound. $T_{\frac{1}{2}}$ for this initial 2-phase of plasma disappearance (0.25 to 8 hr. after injection) ranged from 2.0 to 2.9 hours and the slower, secondary B-phase was characterized by $T_{\frac{1}{2}}$ of 26.6 to 36.3 hours. The urinary excretion in terms of the percentage of total dose excreted within 96 hours ~~post-injection~~ Thin-layer radiochromatographic analysis indicated that 2,2'-(pyridyl-N-oxide) disulfide was the primary metabolite of SPT whereas the primary metabolite for both ZPt and MDS appeared to be 2-(pyridyl-N-oxide) sulfonic acid.

Conclusion: The plasma $T_{\frac{1}{2}}$ for B-phase and the recovery of only 56% and 54% of ZPt and MDS suggest that bioretention is significant for these types of omadine compounds. Since there is significant bioretention, the potential for significant bioaccumulation is possible for ZPt and MDS.

Classification: Core-Minimum Data

(NOTE): Total radioactivity (dpm/gm tissue) was two to three times greater in renal, hepatic and pancreatic tissue samples from MDS and ZPt-treated animals than in animals receiving SPT (unpublished observations).

11. Teratologic Evaluation of Dermally Applied Zinc Pyrithione on Swine, Wedig, Kennedy, et al. Toxicology and Applied Pharmacology 36, 255-259 (1976)

A teratologic study in five groups of Yorkshire pigs, 4 pregnant female pigs per group, was performed by applying Zinc pyridinethione (30, 100, or 400 mg/kg day prepared as a 50% (w/v) suspension in Aquaphor cream) for 8 hours per day on the clipped dorsal surface from Days 8 through 32 of gestation. The design of the experiment also include a naive and a vehicle control group.

estation Day 100, the animals were sacrificed A carsarian section was performed, and the number and position of live, dead, and/or resorbed fetuses were noted. They were removed from the uterine horns, weighed, examined for external abnormalities, the sex noted, and the crown-rump distance measured. Each fetus was x-rayed (lateral and dorsal whole-body). A dissection was performed on each fetal pig with particular attention paid to size, shape, and location of major organs. A gross necropsy was performed on each of the dams. Statistical evaluation was used appropriately.

Results: The body weight gains in the 400 mg/kg Days 8-32 of gestation were reduced compared to the other groups. The numbers of implantation and resorption sites and viable fetuses among the test groups was not significantly different than the control groups. No evidence of any teratogenic or embryotoxic effect was observed in the fetuses from dams treated with Zinc pyridinethione. No adverse systemic or behavioral effects were noted in any of the treated animals.

Conclusion: Under the conditions of this experiment, ZPt does not appear to be teratogenic or embryotoxic to Yorkshire pigs at a dose of 400 mg/kg applied dermally during Days 8 to 32 of gestation.

Classification: Core Minimum Data

Note: This is an I.B.T. study and needs to be validated.

2. Absorption, Distribution, and Excretion of Zinc Pyridinethione in Rabbits, Klaassen.

Toxicology and Applied Pharmacology 35, 581-587 (1976).

The IV administration was made via the marginal ear vein, orally by stomach tube and dermally under a impervious cuff for 4 hours. Solutions were aqueous. Hereafter, distribution and excretion was determined after the intravenous, oral and aqueous dermal administeration of ($C^{14}$)- and ($Zn^{65}$)- Zinc pyridinethione (ZPt) to groups of three NZW rabbits per group. Each rabbit received either ($C^{14}$)- or ($Zn^{65}$) ZPt. Urine was collected at hourly intervals, and blood samples were taken at timed intervals throughout the experiment. Animals were sacrificed 6 hours after an intravenous or oral dose of ZPt and 8 hours after dermal application. The concentration of $C^{14}$ and $Zn^{65}$ were measured in the kidney, liver, lung, heart, spleen, stomach, intestine, pancreas, testes, muscle, spinal cord, brain and eye. The soleus and gastrocnemius muscle were used as representative muscles.

Radioactivity by determine for $Zn^{65}$ in a Packard Auto - gamna spectrometer and $C^{14}$ by combustion and liquid scintillation counting.

Results: After intravenous administration, the $C^{14}$ disappeared from the blood rapidly and within 6 hours, 75% was excreted into the urine; while the concentration of $Zn^{65}$ in the blood remained relatively constant and only 0.05% was excreted in the urine. The tissue concentrations of $Zn^{65}$ were about ten times higher than $C^{14}$ 6 hours after administration, with 5% of the $C^{14}$ and 55% of $Zn^{65}$ was found in each gram of liver whereas only 0.1% of the administered $C^{14}$ in the blood and plasma were nearly equal, whereas the concentration of Zn in the blood

much higher than it was in the plasma. After oral administration of ZPt, of the $C^{14}$ and 0.03% of the $Zn^{65}$ was excreted into the urine within hours. The distribution of $C^{14}$ and $Zn^{65}$ in the various tissues 6 hours after oral administration shows that the percentage of the administered dose in each tissue was about one-tenth that found after IV administration whereas the concentration of $Zn^{65}$ in some tissues was higher than that of $C^{14}$; the difference was not as marked as that observed after intravenous administration. The concentration of $C^{14}$ and $Zn^{65}$ was high in the stomach and intestinal wall, presumably due to adsorbed ZnPt.

Eight hours after dermal application of Zpt, 0.05% of the $C^{14}$ was excreted into the urine, and the same amount was found in the major organs of the rabbit. Less than 0.002% of the dermally applied $Zn^{65}$ was found in the urine and 0.008% was found in the major organs.

Conclusion: This study demonstrates that the organic and inorganic portions of ZnPt dissociate to some extent in their distribution and excretion from the body, the omadine ($C^{14}$) portion is excreted much more rapidly than the Zinc portion ($Zn^{65}$). Both portions of ZnPt can penetrate the skin to a limited extent, but the Zinc portion does so less readily.

Classification: Core Minimum Data

13. The effects of Pyridinethiol oxide on the Central Nervous System, Nelson, Woolsey, Murphy Reprinted from Excrepta Medica International Congress Series No. 100 Proceedings of the 7th International Congress of Neuropathology, Zurich, September, 1965.

Seventeen adult male albino rabbits, 2.5 to 4.0 kg BW, received 2-4 ml daily topical applications of a carbapol gel mode 1-3% in ZnPt. Five rabbits were treated with the carbapol gel alone. In both groups the material was rubbed onto the shaved skin (intact) over the animals flanks. The gel was left in contact with the skin during the entire period during applications. Daily neurological examinations were done.

Results: After 7 to 15 daily treatments with ZnPt the rabbits developed a consistent group of signs and symptoms including decreased spontaneous activity, hind limb weakness, and diarrhea; with continued treatment weakness of both forelegs, inanition and death occurred. Rabbits treated with carbapol gel alone remained healthy. EEGs were obtained from 4 rabbits before and during the ZnPt treatment. Diffuse progressive slow wave activity developed in 3 animals. Studies on the 4th animal are incomplete. Autopsies were performed on 12 rabbits who had been severely paralyzed a minimum of 3 days. No significant structural alterations were seen in the brains, spinal cords, peripheral nerves, muscle, abdominal or thoracic viscera from 8 to the 12 rabbits. Autopsy revealed widespread granulomatosa encephalomyelitis in 3 and less extensive involvement in the 4th rabbit severely paralyzed. Central necrosis was present in some granulomas. Lesions were found in grey and white cortex, hippocampus, hypothalemus, brain stem and spinal grey matter. Indications of an oval infective organisms, 1-3 $\mu$ structures. were found in cytoplasm of macrophages or lying freely in tissue spaces. Necrosis of renal collecting tubules was seen in 1 rabbit. The suggestion was made that ZnPt may act as an immuno-suppressive agent permitting a latent protozoan infection to develop.

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Conclusion: No explanation is available for the progressive quadraparesis.

Classification: Supplementary Data

(1) Only one dose level tested.
(2) A NEL was not established.
(3) Histopathological and neurological data not submitted.

14. Comparative Percutaneous Absorption of Pyridinethiones, Howes, Black

Toxicology 5, 209-220 (1975)

Female Colworth Wistar Rats, 110-120 gm BW, female Dunkin Hartley Guinea Pigs, 240-280 gm BW, and New Zealand White Rabbits of either sex (2.5-3.5 kg) were used throughout this study.

The turnover of Na ($H^3$) PT and Na ($S^{35}$) PT in these three species was studies by administering aqueous test solutions (1.0 ml to rats, 2.0 ml to guinea pigs and 5.0 ml to Rabbits) by intraperitoneal injection. The animals were placed in metabolism cages and urine and feces were monitored for $H^3$ or $S^{35}$ daily for 5 days. The turnover of Zn ($H^3$) Pt Na and ($H^3$) Pt administered subcutaneously to rats was also studied, as was Zr ($H^3$) Pt.

Results: All three species rapidly excreted the injected isotope principally via the urine. The comparative penetration by the three PT samples was Na > Zr > Zn from all treatments. The comparative peermeability of the animals' skins to these PTs was rabbit > rat > guinea pig. NaPt penetration was found to be dependent upon duration of contact and concentration in the test solution whereas the penetration of ZnPt was found to be proportional to concentration but independent of duration of contact of the test solution.

Classification: Core Minimum Data, except

For discussion of safety ~~except~~ for human uses.

(a) Toxicology Branch, however, does not concur with the discussion section of the article which extrapolates the findings of this study to indicate that an adequate margin of safety exists for use of shampoo products containing up to 1% (w/v) of ZnPt. The extrapolation is in part, based on a 2-year feeding study by Larson, quoted by Snyder et al done in 1958, which in fact, according to Toxicology Branch standards, does not establish a 10 ppm NEL. The study in question is #6 of this review and is regarded as supplementary Data for numerous reason. A NEL was not established in this study by Larson.

15. A percutaneous Teratology Study of Zinc Pyridinethione in Rabbits, Nolen, Patrick, Dierckman.

Toxicology and Applied Pharmacology 31, 430-433 (1975)

Four groups of 15 pregnant NZW female rabbits received dermal applications on the fur clipped trunks for 2 hr, daily from Day 7 through Day 18 of gestation at doses of 0 (no treatment), 0 (vehicle control), 1.0 or 2.5 gm/kg of a cream-type shampoo containing 2% Zinc pyridinethione.

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dams were weighed every 3 days during treatment in order to adjust dosages and the new hair growth clipped to keep the area denuded. During this period the dams were carefully observed for signs of stress and signs of toxicity, particularly CNS involvement. Food and water consumption were checked visually, but no consumption records were maintained. On day 28, the dams were sacrificed with sodium pentobarbital and their fetuses removed. The number of resorption sites and corpora lutea of pregnancy were recorded. The fetuses were blottled dry, weighed and inspected for gross abnormalities. One-third of each litter was cleared with KOH and stained with alizarin red S, using a modification of the method of Staples and Schnell (1964), for the detection of skeletal defects. The remaining two-thirds were examined for soft tissue malformations by the method of Wilson (1965). The data were analyzed statistically by analysis of variance and Chi-square.

Results: In the groups treated with vehicle, either with or without ZnPt, the weight gains were similar, although less than the sham controls, indicating that the topical application of ZPt in the shampoo base had no effect of the weight gains in dams. There were no significant differences in any of the reproductive paprameters measured and no significant increases in the incidences of either skeletal or soft-tissue defects in the groups treated with ZPt compared to controls. Overall, the incidence of abnormal fetuses was about 6% which is characteristic of the New Zealand Rabbit.

Classification: Core Minimum Data

16. Absorption of Zinc Pyrithione onto Hair and SKin, 1974, Society of Cosmetic Chemists of Great Britain, T. Okumura, S. Hayashi, F. Tokiwa, and S. Houn. Presented at the 'FSCC VIIIth International Congress on Cosmetics - Quality and Safety' organized by the Society of Cosmetic Chemists of Great Britain at London on 26-30th August, 1974.

In this study, a chemically and radiochemically pure Sulfur-35 labelled sample of Zinc pyridinethione was synthesized from sulfur-35 labelled thiourea and incorporated into a shampoo formulation. The absorbed amounts of this zinc pyridinethione onto human hair, rat hair, and rat skin were measured with liquid scintillation counter and a 2TT gas flow water counter

Results: When the human hair was treated with a shampoo containing 1% zinc pyrithione for 3 min at 40°C, the amount absorbed was found to be 3.8 ug/100 mg. The absorbed amount onto human hair increases with increasing concentration and reaches saturation at a concentration of 1%, beyond which the adsorbed amount does not depend on the concentration. On the other hand, the adsorbed amounts onto the rat hair and rat skin were found to be 16 ug/100 mg and ug/1 $cm^2$, respectively. The adsorbed amount of $S^{35}$- ZPt increases with increasing time, temperature and concentration, and also increase with repeated applications of the shampoo containing $S^{35}$-Zpt. A good correlation is seen between the clinical effectiveness and the experimental adsorption data. The adsorbed $S^{35}$ - ZnPt stays only on the external surface of skin and no $S^{35}$ - ZnPt penetrates into the dermis through the stratum corneum.

Classification: Supplementary Data

) Detailed Reports not presented.

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17. Antimicrobials: Experimental Contact Sensitization in man, Marzulli, Maibach

J. Soc. Comet. Chem. 24, 399-421 (1973)

These studies were conducted on normal male human paid subjects aged 21-50. Various modifications of the well known Draize test were used. This test is derived from Jadassohn's patch test introduced around the turn of the century. Basically, each test was divided into three consecutive phases. The initial or induction phase consisted of a 3½ week period of repeated chemical insults to the skin aimed at initiating the sensitization process. This was followed by a 2-week incubation, or so-called period of rest, during which a completion of immunologic events is thought to occur. Finally, there was challenge or elicitation phase in the form of a new contact to determine if sensitization had in fact taken place.

The test material (0.5 gm) was applied to the upper lateral portion of the arm, covered with an occlusive patch and removed after 48 to 72 hours. Usually, 10 epicutaneous applications were administered successively to the same site for induction. Following a period of rest for 2 weeks, the challenge patch was applied, aloowed to remain for 72 hours, and the reaction read. Scores are 1-4 based on severity of reaction.

Results: There was no evidence of skin sensitization in the small test sample studied (10 subjects) as shown below:

Response of human subjects tested with Zinc pyridinethione (Draize Meth.)

| Induction Conc(%) | Challenge Conc(%) | Sensitized(%) | |
|---|---|---|---|
| 3 (petrolatum) | 3 (petrolatum) | 0/10 | 0% |
| 3 (petrolatum) | 0.5 (DMSO) | 0/10 | 0% |
| 1 (DMSO) | 3.0 (petrolatum) | 0/10 | 0% |
| 1 (DMSO) | 0.5 (DMSO) | 0/10 | 0% |

Conclusion: Zinc pyrithione does not appear to be a skin sensitizer.

Classification: Core Minimum Data.

18. Evaluation of Product Performance, Society of Cosmetic Chemists of Great Britain, Clear Zinc Pyrithione Preparations.

Two day symposium, 12-14th November, 1973, Albany Hotel Nottingham Teny Gerstein. J. Soc. Cosmet. Chem. 23, 99-114 (Feb. 3, 1972)

Essentially this article has no toxicological significance. The referenced 90-day study of subacute percutaneous toxicity with a 2%, pH8.8, solubilized ZnPt (done by Burnett, C.M., Intern. Rept., Revlon Research Center) must be submitted as a complete report for evaluation and classification.

Classification: Supplementary Data

Note: This study is required for registration. The referenced 90-day study of subacute percutaneous toxicity with a 2% ZnPt solution is required to be submitted.

19. Pharmacological Properties of Bis-(1-hydroxy-2(1 H-Pyridinethionato) Zinc (ZPT), Kyoto University, Kyoto, Department of Pharmacology, Faculty of Pharmaceutical Sciences. Pharmacometrics, 4 (5), 883-890 (1970)

Samples of ZnPt and Na Pt were suspended in 1% tragacantha in water.

The $LD_{50}$ of ZnPt, when it was administered intraperitoneally, subcutaneously and perorally to mice was 26.8 mg/kg, 730 mg/kg and 160 mg/kg, respectively. ZnPt was shown to relax the isolated aorta-and ileum-preparation and to inhibit the contraction of auricular strip at the dose of more than $10^{-5}$ gm/ml. It is therefore unlikely that this is a specific reseptor mediated reaction. In dogs, ZnPt produced a sustained fall in blood pressure after intravenous injection of 40 mg/kg. This is probably due to relaxation of the sessel wall and to cardiac inhibition. The intravenous administration of 40 mg/kg of ZnPt induced arousal waves in spontaneous EEG of rabbits. No irritant action of ZnPt on the kidney was observed at the dose of 25-50 mg/kg/day after oral administration to mice for three days. ZnPt also had no irritant action on intact guinea-pig skin, however it produced a slight irritant on mucous membrane of rabbit eye. ZnPt irritated rabbit skin by intracutaneous injection. The above pharmcological studies are classified as follows:

1) Acute Toxicity: Core Minimum Data
2) Effect on isolated aorta: Core Minimum Data
3) Effect on isolated cardiac atrium: Core Minimum Data
4) Effect on blood pressure and respiration: Core Minimum Data
5) Effect on isolated intestine: Core Minimum Data
6) Effect on EEG and ERG: Core Minimum Data
7) Activity as a renal irritant: Core Minimum Data
8) Activity as eye irritant: Core Minimum Data
9) Activity as a skin irritant: Core Minimum Data

Classification: Core Minimum Data

20. Percutaneous Toxicity of Pyridinethiones in a Dimethyl-sulfoxide vehicle, Collom, Winek J. Pharmaceut. Sci. 53 (12), 1973-? (1967)

This study concerns the effects of sodium, Zinc and Cadmium salts of pyridinethione in a DMSO vehicle after daily application to the skin of rabbits. Albino rabbits of both sexes with a weight range of 2 to 3 kg were used in this study. The study was performed on both abraded and unabraded skin sites on fur clipped trunks of rabbits using daily dose levels of 300 mg/kg NaPt in water or DMSO, 400 mg/kg of CdPt in water or DMSO, and 400 mg/kg of ZnPt in water or DMSO. A water control with Pt salts and two DMSO control animals without Pt salts were used for each group. No impervious cuff was used.

Results: The results are summarized below:

| Material | INCOORDINATION No. affected/no. dosed | | Days | Paralysis No. affected/no dosed | | Deaths |
|---|---|---|---|---|---|---|
| DMSO-NaPT | 10 | 10 | 1-3 | 10 | 10 | 10/10 |
| $H_2O$-NaPT | 2 | 2 | 5 | 2 | 2 | 2/2 |
| DMSO-CdPT | 1 | 10 | 2 | 0 | 10 | 0/10 |
| $H_2O$-CdPt | 1 | 2 | 5 | 1 | 2 | 0/2 |
| DMSO-ZnPt | 16 | 16 | 2-7 | 16 | 16 | 13/16 |
| $H_2O$-ZnPt | 1 | 7 | 6 | 1 | 7 | 2/7 |
| DMSO | 0 | 6 | - | 0 | 6 | 0/6 |

Twelve animals developed eye drainage, three developed sluggish pupillary responses, and two developed corneal opacities. Thirteen animals died between days 9 and 17.

Lung necrosis was present in 7 of the 12 animals which died after dosing with NaPt and in 14 of the 17 which died after ZnPt treatment. All treated animals lost weight during the week of treatment and the following week of observation.

The control animals which were dosed with DMSO did not develop any of the outward signs of intoxication and gained from 30-445 gms during the course of dosing. None of the animals developed corneal opacities or irritations of the eye. All of the animals treated with Pt salts, either in DMSO or $H_2O$, showed skin irritation at the site of application which cleared when the treatment was terminated.

Conclusion: DMSO apparently aided in the penetration of both NaPt and ZnPt in comparison with water. The sodium salt readily penetrated the skin when applied in an aqueous solution, but when applied in DMSO, the onset of toxic signs and paralysis and death resulted earlier in the treatment regimen. The animals all lost weight which is attributed to their inability to eat because of the hind quarter paralysis. DMSO did not aid in the penetration of CdPt. The indicates an apparent lack of penetration regardless of vehicle. Whether or not the skin was abraded had no effect on penetration of the NaPt, ZnPt or CdPt.

Classification: Supplementary Data (1) A NEL was not established for treatment.

21.a. The Anti-Sebarrheic Qualities of Zinc Pyrithione (Zinc pyridine-2-thiol-1-oxide in a cream vehicle), Brauer et al.

The Journal of Investigative Dermatology 1966, Williams & Wilkins.

This is essentially a review article and the toxicology studies reported, herein, must be submitted as detailed, complete final reports for evaluation and classification.

The Toxicology Studies are:

1. Antimicrobial Activity: ZnPt is antimicrobial.
2. Human Patch Tests: ZnPt is not a sensitizer.
3. Clinical Experiences: ZnPt is non-irritating

Classification: Supplementary Data

21.b. Anti-seborrhoeic Qualities of Zinc pyrithione in a cream vehicle II. Safety Evaluation. D.L. Opdyke C.M. Burnett and E.W. Bracer, Fd. Cosmet. Toxicol. 5, 321-326 (1967)

This is essentially a review article and the toxicology studies reported, herein, must be submitted as detailed, complete final reports for evaluation and classification.

The Toxicology studies are:

1. Acute oral toxicity: $LD_{50}$ = 309 mg/kg (both sexes)
2. Eye irritation: slight conjunctivitis with 0.5% ZnPt
3. Percutaneous toxicity: slight irritation with 0.5% ZnPt
4. Human patch-test procedure: ZnPt is not a sensitizer

Classification: Supplementary Data

22. Zinc Bis (2-pyridylthio)-1,1[1]-dioxide: Percutaneous Absorption and Residual Amount of Skin Surface of Zinc Bis (2-pyridylthio)1,1[1]-dioxide, Okamoto, et al.

Original text is in Japanese.

Free translation supplied by B. Minn, E.W. McChesney 8/28/69. Distribution of peroral injection, percutaneous absorption and the residual amount on the skin surface of ZnPt labelled with $S^{35}$ or $Zn^{65}$ were studies. Following peroral injection, the compound was decomposed in the stomach. The $Zn^{65}$-labelled compound was excreted mainly in the feces, the $S^{35}$ compound in the urine. The percutaneous absorption of Zinc omadine following application as shampoo, ointment and aqueous suspension to the skin was very slow and very little. The residual amount on the skin after application of these preparations was equivalent to less than 1% of the amount of Zinc omadine applied. It was found that ZnPt becomes widely distributed throughout the organisms, and the Zn splits off from the pyridyl part. The $S^{35}$- omadine is 38% excreted in the urine while the $Zn^{65}$ ion is excreted in the feces (48%).

Translators note: We disagree with some of the statements and conclusions in the article, since they do not seen supported by the data. As a glaring example, Fig. 3 shpws that 6 hours following the oral administration of the $Zn^{65}$ compound over 70% of the dose was found in the stomach but Table II shows only 37-50% in that organ. Similarly, Fig. 4 shows about 48% of the dose in the feces at 24 hours, but Table II shows only 2%. It is not clear what the authors mean by the term "distribution? Also in the text, page 329, they say that the amount of omadine retained on the skin per 80 $cm^2$ was 931 ug; therefore for a human head (estimated area = 800 $cm^2$) the amount would be 931 ug retained. This does not seem to follow at all, and there are other similar items of obscure reasoning.

Classification: Supplementary Data

(1) Translators note adds unresolved questions to study.

23. Intravenous Toxicity of Zinc Pyridinethione and Several Zinc Salts, Winek and Buehler, Toxicology and A-plied Pharmacology 9, 269-273 (1967)

This is essentially a summary article and the toxicology studies reported, herein, must be submitted as detailed, complete final reports for evaluation and classification.

The toxicology studies are:

1. Acute Intravenous toxicity in dogs, rabbits and monkeys.
2. Antidotal treatment
3. Intravenous toxicity of Zinc Salts.

Classification: Supplementary Data

Acute Toxicity Results of Intravenous Toxicity

| Compound | Species | No. of animals | Dosages mg/kg | Toxic Effect |
|---|---|---|---|---|
| ZnPt | Dog | 5 | 25 | CNC depression, dilated pupils, death in 24 hr. |
| ZnPt | Dog | 1 | 5 | none apparent |
| ZnPt | Dog | 1 | 15 | slight pupil dilation |
| ZnPt | Dog | 1 | 20 | cholinergic effects |
| NaPt | Dog | 1 | 50 | emesis |
| ZnPt | monkey | 2 | 25 | death in 24 hr. |
| NaPt | monkey | 1 | 50 | no pupil dilation |
| ZnPt | rabbit | 12 | 10 | death in 24 hours |
| NaPt | rabbit | 11 | 150 | none |
| NaPt | rabbit | 1 | 200 | muscle relaxation; death |
| NaPt | rabbit | 1 | 300 | muscle relaxation; death |

Percutaneous Toxicity in Rabbits with ZnPt Shampoo 2% ZnPt $LD_{50}$ 20 gm shampdo/kg, 20 mg/kg/day for 90 day, no toxicity from shampoo 20 mg/kg/day for 28 days, irritation of skin, no systemic toxicity.

4. Primary Irritation and Sensitization of 2% ZnPt.

   a. ZnPt is not a sensitizer in shampoo.
   b. ZnPt is non-irritating at 2% shampoo.

5. Eye Irritation in Rabbits Using ZnPt Shampoo.

| Test material | Treatment | Ave. Score | Corneal opacity | No. of eyes normal in no. of days |
|---|---|---|---|---|
| Undiluted Shampoo | no rinse | 82.0 | 3/3 | 1 in 42, 2 not 42 |
| Undiluted Shampoo | rinse | 3.3 | 0/3 | 3 in 1 |
| 10% Shampoo | no rinse | 28.0 | 2/3 | 1 in 4, 2 in 7 |
| 10% Shampoo | rinse | 10.6 | 0/3 | 3 in 1 |
| Undiluted Control | no rinse | 83.6 | 3/3 | 1 in 14, 2 not 42 |
| Undiluted Control | rinse | 30.0 | 3/3 | 1 in 2, 2 in 3 |
| 10% Control | no rinse | 19.0 | 1/3 | 2 in 3, 1 in 7 |
| 10% Control | rinse | 11.3 | 0/3 | 3 in 3 |

25. Results of Pathologic Findings on Rats Receiving ZnPy, Medical College of Virginia, Medical Univeristy of South Carolina.

Results: Raw histopathologic findings on the 2-year rats fed the Zinc Salt. No treatement related changes were found.

Classification: Supplementary Data

(1) Report is unsigned.
(2) This histopathology report may refer to Larson 2-year feeding study with ZnPt.

26. Acute Oral Toxicity Study with Zinc Omadine in Albino Rats, Industrial Bio-Test Labs., Inc. (IBT No. A911, Jan. 24, 1972)

Test Material: Zinc Omadine, Lot#Zo-7146

Five groups of Four albino COBS rats (2M & 2F) received by oral intubation doses of 118.5, 177.8, 266.7, 400 and 600 mg/kg of test material in a 10% (w/v) suspension in corn oil. Observation was for 14 days.

Results: Oral $LD_{50}$ = 266.7 mg/kg (both sexes)

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Signs: hypoactivity, muscular weakness, diarrhea
Weight: Survivors gained weight
Necropsy: Gastrventeritis
Classification: Core Minimum Data

TOX Category II: WARNING

Summary of Unpublished Studies on the Toxicology of Zinc Pyrithione, Henderson, Wedig, Olin Corp. Jan. 23, 1973.

Many of the studies summarized and reviewed previously. The toxicology studies summarized, herein, and not previously reviewed must be submitted as detailed, complete final reports for evaluation and classification.

The toxicology studies included:

(1) Acute oral toxicity studies - reviewed
(2) Acyte dermal toxicity studies - reviewed
(3) Eye irritation study - reviewed
(4) Skin irritation and absorption studies - reviewed
(5) Subacute oral studies - reviewed
(6) Chronic oral studies - reviewed
(7) Subacute dermal study - not submitted

This study is germane to the complete toxicological profile of Zine omadine.

(8) Stinging Sensation - not submitted.
(9) Oral teratogenuc study - IBT, 1971 - not submitted.

Classification: Supplementary Data

Note: The 90-day subacute dermal study in rabbits is required for registration (Study #7)

28. Dermal Absorption in Mice, Niometric Testing, Inc. (Experiment Ref. No. A-1099, Aug. 20, 1975)

Test Materials: Zinc omadine, sodium omadine, omadine MDS.

The $C^{14}$ was labeled to the two and six positions in the pyridine ring, prepared by New England Nuclear. Three DBA mice were used for each of the three omadines. One day prior to treatment an approximate area of 35 $mm^2$ was clipped free of hair on the back of each animal. The animals were housed in individual metabolism cages to collect urine and feces. After each sample of urine and fecal matter was obtained, the cages were washed. A 0.02 ml aliquot of the test material containing approximately 10 u curies was applied by injunction to the back of each animal for 8 hours, followed by washing. Urine & feces were collected for 0-4, 4-12, 12-24, 24-48, 48-72 hour time periods following dosing. At necropsy, samples of brain (cerebrum and cerebellum,

liver, kidney, skeletal muscle (composite of four different sites), fat (renal and subcutaneous), skin fron below dose application site, tissue immediately below the dose application site and bone marrow were frozen for possible future use.

Results: All of the animals treated with Zinc omadine, sodium omadine and omadine MDS survived the 72 hour treatment regimen. A mild erythema was seen at the application site of all animals. No untoward behavioral signs were noted. The percentage of $C^{14}$ recovered in the urine rose rapidly to a peak rate of excretion which was observed at 24 hours with each of the three omadines. These urinary levels were maintained until 72 hours. The total percent of $C^{14}$ recovered in the urine was only 3% for Zinc omadine, 3.2% for sodium omadine, and 1% for omadine MDS. Less than 0.005% of the $C^{14}$ was recovered in the feces.

Conclusion: The absence of mass ($C^{14}$) balance in this experiment prevents any meaningful conclsion regarding the absorption, distribution or excretion of $C^{14}$ - ZnPt, NaPt, or omadine MDS in these studies. Since only about 3% of the total radioactivity was accounted for in the report, the following two possibilities are apparent:

(A) The remaining 97% of the $C^{14}$ is still in the animals.
(B) The remaining 97% of the $C^{14}$ did not penetrate into the animals.

Classification: Supplementary Data

(1) Complete mass balance of $C^{14}$ is needed to determine if absorption and bioretention of the applied omadine salts occurred in these mice.

Note: This study is required for registration.

29. Generalized Paresis in Zinc Pyridinethione - treated Rats. Studies which Investigated Possible Sites and Modes of Action, Yale University School of Medicine, D.R. Synder & E.J. Gralla.

This study has been previously reviewed as report #9 (Preliminary Neurological evaluation of generalized Weakness in Zinc Pyrithione treated rats). The conclusions submitted in that report are applicable here also. This report, however; contains the histopathology and blood chemistries data, previously unsubmitted.

Classification: Supplementary Data

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30. Report of the Histopathological Examination of Brain and Spinal Cord Sections Submitted by the Olin Corporation, Industrial Bio-Test Labs, Inc. I.B.T. No. 641-00192, Jan. 29, 1975.

Results: No treatment related effects were observed in tissues examined from rats fed ZnPt at 0, 2, 5, 10, 25, and 50 ppm for two years. The study was conducted originally by Paul Larson (received as report #6)

Classification: Supplementary Data

Note: This is an I.B.T. study and needs to be validated.

31. Tetratologic Evaluation of Zinc Omadine When Applied to the Skin of the Pigs, Industrial Bio-Test Labs, Inc. I.B.T. No. 651-04101A, August 5, 1975

This report has been previously review as report #11.

Classification: Core Minimum Data

Note: This is an I.B.T. study and needs to be validated.

32. Dermal Absorption in Domestric Pigs, Biometrics Testing, Inc. Experiment Reference No. A-937 & A-1000 April 26, 1974.

Test Material: Zinc omadine, sodium omadine and omadine MDS. There were $C^{14}$ labelled salts.

Twenty-six sexually mature Yorkshire Pigs, 186-224 lbs BW, were used in experiment. Test material were uniformly applied on intact and abraded skin for 8 hours a day. Blood samples taken at 30 min, 2, 4, 8, 12, 24, 72 and 96 hours following single dosage and 120, 144 and 168 hours in the repeated dosage animals. Urine and feces were collected at 12, 24, 48, 72, and 96 hours, and at 120, 144 and 168 hours in the repeated dosage animals. Blood chemistries were BUN, SGPT, SAP & blood glucose. At necropsy, tissues & organs were selected for radioassay (frozen) or histopathology (10% formalin) from brain (cerebrum and cerebellum), liver, kidney, skeletal muscle (4 sites), fat (renal & subcut.), GI tract, dose application site, tissue directly below dose application site. The above tissues were radioassayed by liquid scintillation. TLC analysis of urine, blood, feces & wash samples. A Structural Outline of the study is shown below:

STRUCTUAL OUTLINE UNABRADED SKIN

| Compound | Animals | Dosage (mg/kg) $C^{14}$ | Repeat |
|---|---|---|---|
| ZnPt | 4 | 100 | none |
| ZnPt | 2 | 100 | 5 days |
| ZnPt | 2 | 400 | none |
| NaPt | 4 | 50 | none |
| NaPt | 2 | 200 | none |
| PtMDS | 4 | 20 | none |
| MDS | 2 | 80 | none |

ABRADED SKIN

| | | | |
|---|---|---|---|
| ZnPt | 2 | 100 | none |
| ZnPt | 2 | 50 | |

All animals survived the treatment. No untoward behavioral signs observed. A mild erythema was seen at the application site. Blood chemistries were unremarkable gross necropsies were unremarkable. Radioassays necropsy material, urine, blood, feces & washings from test site recovered 86.83-98.2% of the $C^{14}$. Greater than 90% of the recovery was obtained from washings of the application site. Treated skin and subadjacent tissues contained a small amount of applied material. Urinary excretion was no greater than 3% with intact skin and 5% in animals with abraded skin. Urine, feces & blood were at backround 48 hours after dosage. No other necropsy material contained receoverable levels of radiolabelled material.

Classification: Core Minimum Data

33. Acute Toxicity and Disposition of Sodium Omadine, Zinc Omadine and Omadine-MDS following Intravenous Administration to Swine, Medical College of Virginia, Dr. Max Adams, Dr. Robert Jordan and Dr. Joseph Borzelleca (Report is unsigned, Date not given)

Test Material: $C^{14}$ samples of ZnPt, NaPt, and omadine MDS.

Two pigs per compound received I.V. ear vein injections of $C^{14}$ labelled NaPt (50 mg/kg), Omadine-MDS (4 mg/kg) and ZnPt (5 mg/kg). Control observations were made prior to drug administration and urine and blood samples were taken at 15 min., 30 min, 1, 2, 4, 8, 24, 48 and 72 hours after drug injection. 96 hours after following drug administration, pigs were stunned & exsanguinated. Tissue samples were frozen for later assays. Blood, urine were prepared for TLC analysis with std. compounds.

Results: Each of the omadines produced cholinergic signs for 30-60 minutes. Transient elevation of serum glucose (2 hours) was obtained by ZnPt. Other blood chemistries (BUN, creatinine, CPK, SGOT/were unremarkable. Each of the labeled omadines was rapidly cleared from the plasma during the distributive phase (0-15 minutes) as evidenced by the lowvalues for percentage of administered dose remaining in the plasma at 15 min. $T_{\frac{1}{2}}$ values for the $\alpha$-phase of the omadines was 2-3 hours. $T_{\frac{1}{2}}$ values for the B-phase were 26.6 to 36.3 hours indicating the presence of a second pool of omadine which is more firmly bound to tissue or plasma constituents and less readily exchangeable. 95% of the $C^{14}$ NaPt was recovered in the urine in 96 hours. However, only 45-65% of ZnPt & omadine MDS was recovered in the urine during 96 hours. Radioactivity in tissues showed large amounts of residual radioactivity in liver, kidney & pancreas. Significant amounts of radioactivity were found in all tissues examined in pigs receiving ZnPt-$C^{14}$. In addition to liver & kidney, other tissues with relatively high concentrations of radioactivity include the lungs, segments of the G-I tract, and the skin. TLC analysis of blood and urine suggests that NaPt-$C^{14}$ converts to omadine disulfide which is cleared in the urine as the major metabolite. When either ZnPt-$C^{14}$ or omadine-MDS-$C^{14}$ were administered to pigs, the principle urinary metabolite appeared to be the 2 (pyridyl-N-oxide) sulfonic acid with significant amounts of an unidentified metabolite.

Classification: Core Minimum Data

34. Evaluation of Potential Hazards by Dermals Contact (Food & Drug Res. Labs. Inc., March 29, 1974, OE No. 4074-1272)

Test Material: 1% preparation of ZnPt suspended in water containing 0.67% Tween 80. and as a 10% preparation in Tween 80.

The repeated insult patch test was conducted on 100 volunteers per 1% & 10%. Fifteen applications were made followed, after 2 week rest, by a challenge application. The reactions were classified as primary irritation, fatiguing agent or sensitizing agent on the basis of visible clinical responses.

Results: No visible skin changes after the 1st appl. signifying reaction to injury were observed in any of the 100 subjects for either 1% or 10%. Visible skin changes signifying reaction to injury were observed in 1 (1%) and 2 (10%) out of 100 subjects during applications 2 through 15. No visble skin changes signifying reaction to injury were observed in any of the 100 subjects at the challenge application in either 1% or 10% preparations.

Conclusion: ZnPt is not a sensitizer at 1% or 10% in human subjects.

Classification: Core Minimum Data

TOX/HED:th:Reto Engler:9/8/78