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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Zinc Omadine:** Review of a Dermal Sensitization Study in Guinea Pigs.

EPA ID# 088002-001258 DP Barcode D208111
Case No. 815252 Chem. ID No. 088002

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

John E Whalan 18 August 1995

TO: Bruce Sidwell (PM Team # 53)
Special Review and Reregistration Division (7508W)

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

Roger Gardner 8/18/95
RLG 8/21/95

I. Background:

Olin Corporation submitted the following Dermal Sensitization Study in Guinea Pigs dosed with zinc omadine powder H57558A (97.2% a.i.):

81-6 Delayed Contact Dermal Sensitization Test (Buehler Method).
Study No. MB 94-3570 F; August 29, 1994; MRID No. 433720-01

Old Study: Olin maintains that this study should replace an earlier one (Study No. MB 91-707 F; MRID No. 421467-05) in which zinc omadine powder E85656 TER (95% a.i.) was a mild dermal sensitizer. Olin considered the earlier study to be flawed because:

1. Nine induction doses were administered over three weeks. After a two-week waiting period, challenge doses were administered at the original induction site and a naive site.

2. The naive controls were treated with a 1% concentration of test article instead of the 50% concentrate used for the first and second challenge.

3. The second and third induction doses (first week of dosing) resulted in 30 to 90% of the animals responding with irritation scores of 1 and 2. By the ninth induction, 100% of the animals were responding with scores from 1-3. Such frank responses so early in the induction phase suggest the concentration used was too irritating.

4. The first challenge produced 6/10 animals with a score of 1 and 1/10 with a score of 2 at the original site of induction. Five animals responded with a score of 1 at the naive site.

When this study was reviewed by TB-I, it was apparent that the 50% dilution caused excessive irritation. It also seemed odd that challenge doses given to the same animals regressed from 50% to 10%, and finally to 1%. Thus the protocol was peculiar and the doses were extreme. While there did appear to be a sensitization reaction, most notably at the 1% dilution level, it may have been due to trauma rather than a true sensitization response. It was difficult to tell.

New Study: In the new study, no dermal irritation was seen in any animals dosed with the 100% concentration, yet induction doses in the old study using the 50% concentration caused moderate to severe erythema. Although the previous study used a lower concentration (50% v 100%), the guinea pigs were induced more frequently (3/week v 1/week). Assuming the test article is the irritant (rather than the mineral oil vehicle), the repeat study should have elicited frank irritation, though less severe than in the first study.

It is not clear why mineral oil was used in the two sensitization studies since an aqueous paste was used in an acute dermal study in rabbits (MRID No. 421467-01), and a primary dermal irritation study in rabbits (MRID No. 421467-04). In both these studies, very slight to slight erythema was observed.

A single 0.5 g dose of aqueous paste caused erythema in rabbits in the dermal irritation study, yet repeated 0.4 g doses of mineral oil moistened zinc omadine had no effect. Species differences aside, some irritation was expected in the sensitization study.

II. **Recommendations:**

TB-I agrees with the registrant that the old study is contestable for the reasons they have cited, and more. It should be replaced with a better study. Unfortunately, the repeat study is equally deficient, but for different reasons. The unexpected absence of any dermal irritation can be attributed to reduced bioavailability through the use of mineral oil. No rationale was offered for using mineral oil in place of water to moisten the test article.

Lastly, a positive control was not used; for this reason alone the new study should not have been submitted to TB-I. This study is **Unacceptable**, and does not satisfy data requirement 81-6 for a Dermal Sensitization study. Until an acceptable study is received, preferably using an aqueous paste, zinc omadine will be considered a dermal sensitizer.

Reviewed by: John E. Whalan JW May 9, 1995 **GUIDELINE:** 81-6
Section I, Tox. Branch I (H7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 5/18/95
Section I, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization Study in Guinea Pigs (Buehler Method)

MRID NO: 433720-01

CHEM. ID NO.: 088002

TEST MATERIALS: Zinc Omadine Powder, H57558A (97.2% a.i.; light beige powder; Lot No. 8203-DP-1)

SYNONYMS: Zinc, 2-pyridinethiol-1-oxide

STUDY NUMBER(S): MB 94-3570 F

SUBMITTED BY: Olin Corporation

TESTING FACILITY: MB Research Laboratories, Inc.

TITLE OF REPORT: Delayed Contact Dermal Sensitization Test (Buehler Method)

AUTHOR(S): Paul Chmura

REPORT ISSUED: August 29, 1994

SUMMARY: There was no evidence of dermal irritation at any point in this study. The study design was inadequate to evaluate the sensitization potential of zinc omadine.

STUDY CLASSIFICATION: This study is **Unacceptable**, and does not satisfy data requirement 81-6 for a Dermal Sensitization study. There was no positive control group to demonstrate the reliability of the test system and protocol. The selection of mineral oil to moisten the test article instead of water was a poor choice. This study received Quality Assurance review.

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PROTOCOL: Fifteen healthy male Hartley Albino guinea pigs (318-377 g) were individually housed in suspended cages. Bedding was changed twice weekly. Food and water were available *ad libitum*. Twenty-four hours prior to each dosing, the dorsal trunk skin was clipped free of hair to provide 5 cm x 10 cm dosing sites.

Zinc Omadine Powder was moistened with 0.1 ml of mineral oil to yield a 100% concentration. A group of 10 guinea pigs, the induced group, received 0.4 g induction doses of the 100% concentration on the left dorsal flank proximal cervical area. The site was covered with a Hilltop Chamber without a cotton pad, which in turn was occluded with a 2 inch wide strip of rubber dental dam wrapped with elastoplast tape.

After 6 hours of exposure, the dosing sites were washed with distilled water and towel-dried. One induction dose was administered each week for 3 consecutive weeks. Skin irritation scores were recorded 24 and 48 hours after each induction dose. The remaining 5 guinea pigs served as a naive control group, and received no induction doses. A positive control was not included in the study protocol.

Fourteen days after the last induction dosing, the induced and naive control guinea pigs received 0.4 g challenge doses by the same procedure as the induction doses, but on an untreated patch of skin. Skin irritation scores were recorded 24, 48, and 72 hours after the induction dose. The guinea pigs were observed daily for clinical signs and mortality. Body weights were recorded pretest, 24 hours after the last induction dose, and 24 hours after the challenge dose.

RESULTS: No dermal irritation was observed in any guinea pigs following the induction doses or the challenge doses. There were no clinical signs or deviations in body weights.

DISCUSSION: It is disturbing that no dermal irritation was seen in any animals dosed with the 100% concentration, whereas in a previous study (Study No. MB 91-707 F, November 25, 1991), induction doses using the 50% concentration caused moderate to severe erythema. Although the previous study used a lower concentration (50% v 100%), the guinea pigs were induced more frequently (3/week v 1/week). Assuming that the test article is the irritant (rather than the mineral oil vehicle), the repeat study should have displayed frank irritation, though less severe than in the first study. This was not the case.

It appears that the irritant in the first study may have been the mineral oil, considering that the doses in the second study were only moistened with mineral oil. The impact of mineral oil on bioavailability in the two studies is uncertain.

It is not clear why mineral oil was used in the two sensitization studies since an aqueous paste was used in an acute dermal study in rabbits (MRID No. 421467-01), and a primary dermal irritation study in rabbits (MRID No. 421467-04). In both these studies, very slight to slight erythema was observed.

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The original sensitization study had several deficiencies. Despite the extreme nature of the protocol, the study was accepted because there seemed to be a positive response hidden within the dermal trauma. TB-I is willing to replace the original study with a better one, but this repeat study is deficient on three counts:

1. No dermal irritation was observed when two other acute studies (81-2, 81-5) suggest there should have been some irritation.

2. Mineral oil was used to moisten the test article. Water would be a more logical choice.

3. There were no positive control data.