MEMORANDUM

SUBJECT: Review of "Dermal sensitization study in guinea pigs."

To: Jane Talarico
Special Review and Reregistration (H 7509C)

From: John C. Redden, Toxicologist
Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

Thru: Henry Spencer, Ph.D.
Acting, Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

ACTION:
The registrant has submitted for review MRID No. 411845-01 "Dermal sensitization study in guinea pigs."

CONCLUSIONS:

In MRID No. 411845-01 Group I guinea pigs were treated with 0.05 ml of a 0.06% (w/v) solution of 2,4-dinitrochlorobenzens (2,4-DNCB) in ethanol. Group II guinea pigs were treated with 50 mg simazine moistened with 1.0 ml deionized water (50% w/v). Simazine technical in the opinion of the Toxicology Branch is not a dermal sensitizer in guinea pigs. Under Guideline § 81-6 the study is classified as Core supplementary. The study can be upgraded if the test material purity is submitted.
DATA EVALUATION RECORD
SIMAZINE TECHNICAL

Dermal Sensitization Study in Guinea Pigs
(Modified Buehler Test)

STUDY IDENTIFICATION: Kuhn, J.O.: Dermal sensitization study in guinea pigs. EPA Guideline No. 81-6. (Unpublished study No. 6049-89 performed by Stillmeadow, Inc., Houston, TX, for Ciba-Geigy Corporation, Greensboro, NC; dated May 22, 1989.) MRID No. 411845-01.

APPROVED BY:
Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [Signature]
Date: Aug 7, 1991
1. **CHEMICAL:** Simazine technical.

2. **TEST MATERIAL:** The test material (batch code No. D330 3810 FL 850614) was described as a white powder; the material was of technical grade. Purity was not provided.

3. **STUDY/ACTION TYPE:** Dermal sensitization study (modified Bushel test) in guinea pigs.

4. **STUDY IDENTIFICATION:** Kuhn, J.O. Dermal sensitization study in guinea pigs. EPA Guideline No. 81-6. (Unpublished study No. 5040-89 performed by Stillmeadow, Inc., Houston, TX, for Ciba-Geigy Corporation, Greensboro, NC; dated May 22, 1989.) MRID No. 411845-01

5. **REVIEWED BY:**
   - Mary E. Cerny, M.S.
     - Principal Reviewer
     - Dynamac Corporation

   Signature: [Signature]
   
   Date: Aug 7, 1991

   - Margaret E. Brower, Ph.D.
     - Independent Reviewer
     - Dynamac Corporation

   Signature: [Signature]
   
   Date: August 7, 1991

6. **APPROVED BY:**
   - Nicolas P. Hajjar, Ph.D.
     - Department Manager
     - Dynamac Corporation

   Signature: [Signature]
   
   Date: Aug 7, 1991

   - Henry Spencer, Ph.D.
     - EPA Reviewer, Section III
     - Toxicology Branch I (H-7509C)

   Signature: [Signature]
   
   Date: Aug 24, 1991

   - Karl Baetcke, Ph.D.
     - EPA Branch Chief
     - Toxicology Branch I (H-7509C)

   Signature: [Signature]
   
   Date: 12/30/91
7. CONCLUSIONS:

Core Classification: CORE Supplementary. This study meets the
requirements set forth under Guideline 81-6 (152- B-15) for a
dermal sensitization study in guinea pigs. The study may be
approved with submission of the test material purity. (May 2/4/9)

Skin Sensitization Potential: Simazine technical was not a
dermal sensitizer in guinea pigs.

8. SUMMARY:

A. Prior to the definitive study, a screening test was
conducted to determine what dose level (or levels) of
simazine should be used in the sensitization test. This
preliminary study was not described in detail, but a 50%
(w/v) aqueous solution of simazine was the highest
nonirritating level of the test material (study p. 9).

Twenty short-haired male Hartley-Albino guinea pigs (Camill
Research Lab Animals, Wayne, NJ, and Harlan Sprague-Dawley,
Inc., Houston, TX) were used in the definitive study;
animals were described as being of "young adult" age and as
weighing between 305 and 400 g at the time of testing.
Animals were quarantined prior to study initiation. They
were divided into two groups of 10 guinea pigs each. Group
I guinea pigs were treated with 0.05 mL of a 0.06% (w/v)
solution of 2,4-dinitrochlorobenzene (2,4-DNCB) in ethanol;
these animals served as positive controls. The remaining
10 guinea pigs (group II) were treated with 500 mg simazine
moistened with 1.0 mL deionized water (50% w/v).

One day prior to the induction and challenge phases of the
definitive study, the back of the trunk of each guinea pig
was clipped free of hair to expose an area at least 8 cm x
10 cm; thereafter, hair was removed as required. During
the induction phase of the study, animals were treated on
days 1, 3, 6, 8, and 10 with either 0.5 mL 2,4-DNCB in
ethanol or the 50% (w/v) solution of the test material.
The 2,4-DNCB or test material was applied to a gauze pad,
which, in turn, was secured to an adhesive. The adhesive
cover/patch was then placed on the clipped skin, and the
trunk of each guinea pig was wrapped with clear plastic
film to hold the patch in place. Animals were kept in a
restrainer and exposed to the control or test materials for
6 hours/day. They were then taken from the restrainers;
their wrappings and patches were removed, and they were
returned to their cages until the next exposure. Animals
were treated again on days 13, 15, 17, 20, and 22 with a
100% (w/v) solution of simazine (the amount of water used
to moisten the test material was reduced to 0.5 mL prior to
application to the skin). The same test site was used on
each animal for all treatments. The challenge phase was conducted on day 36; animals were again treated at the previous test site and on a previously unexposed site with either 2,4-DNOCB or the 100% (v/v) solution of test material.

Test sites were examined 24 hours after each treatment; additional observations were made at 48 hours after treatments 1 and 10 and at 48 hours after the challenge application. Test sites were scored at each examination time using the scoring methods presented in Appendix A of this report; a 5-point method was used in which a score of zero (0) indicated no erythema or edema and a score of four (4) indicated severe erythema to slight eschar formation or severe edema. Animals were weighed on study days 0 and 35.

B. Skin treated with 2,4-DNOCB was characterized during the induction phase by moderate to severe erythema with eschar formation and slight to moderate edema; the pretreated, challenged test site of positive controls gave a similar but less severe reaction on day 36. Contrastingly, the virgin test site that was treated with 2,4-DNOCB on day 36 showed no reaction or, at most, very slight erythema and slight edema. The test material produced essentially no dermal irritation during either the initiation or challenge phases; the skin of one animal exhibited very slight erythema and very slight edema, and very slight edema was observed at the test site of a second guinea pig. The average dermal irritation scores at challenge for the positive controls were 3.7 (original test site) and 1.0 (virgin test site); both simazine-treated test sites had an average score of 0 at study initiation and at 24 and 48 hours after the challenge dose was applied. Simazine-treated animals gained weight during the study; some control animals had slightly low terminal body weights.

The study author concluded that 2,4-DNOCB (the positive control) acted as a dermal sensitizing agent and that simazine technical was not a dermal sensitizer in guinea pigs.

9. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

Modifications of the Buehler test (as described by Hayes; see Appendix B of this report) included the use of nine applications of the test material or 2,4-DNOCB on staggered days during a 3-week induction period rather than three applications (on days 0, 7, and 14) during a 2-week induction phase; use of a 5-point scoring method (scores 0-4) rather than 4 points (scores 0-3); and an increased concentration of test material during the second half of the induction phase. In addition, an
0.06% (w/v) solution (rather than 0.05%) of 2,4-DNCC was used to ensure adequate dermal irritation (study report p. 6). The rationale for the first three modifications was not discussed by the study author, although we expect these changes would increase sensitivity and improve quantitation of the results; the additional applications of test material during the induction phase, particularly in combination with the increased concentration of simazine, may have been included in an attempt to increase the chances for a definitive reaction from test animals. The data indicate that simazine technical did not produce a sensitizing reaction in guinea pigs.

A quality assurance statement, signed and dated May 22, 1989, and a statement of compliance with Good Laboratory Practices, signed but not dated, were provided.

10. CBI APPENDIX: No protocol was provided. Appendix A: Dermal Scoring Method (CBI p. 14); Appendix B: Protocol for the Buehler Test (from Hayes, A.W., ed., Principles and Methods of Toxicology, 1984, p. 214).
APPENDIX A

Dermal Scoring Method
(CBI p. 14)
SIMAZINE

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