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

008997

JAN 7 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

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

Tox.Chem No.: 740
MRID No.: 411845-0
Submission No.: 0-0458

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-dinitrochlorobenzene (2,4-DNCB) in ethanol. Group II guinea pigs were treated with 500 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.

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EPA No.: 68D80056
DYNAMAC No.: 372-B
TASK No.: 3-72B
August 7, 1991

008997

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 (Unpublished study No. 6040-89 performed by Stillmeadow, Inc., Houston, TX, for Ciba-Geigy Corporation, Greensboro, NC; dated May 22, 1989.)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: William L. McLellan for

Date: Aug 7, 1991

0002

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. Amb 8/7/91

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

4. STUDY IDENTIFICATION: Kuhn, J.O. Dermal sensitization study in guinea pigs. EPA Guideline No. 81-6. (Unpublished study No. 6040-89 performed by Stillmeadow, Inc., Houston, TX, for Ciba-Geigy Corporation, Greensboro, NC; dated May 22, 1989.)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: William L. McLellan for
Date: Aug 7, 1991

Margaret E. Brower, Ph.D.
Independent Reviewer
Dynamac Corporation
Signature: margaret Brower
Date: August 7, 1991

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation
Signature: Nicolas P. Hajjar
Date: August 7, 1991

Henry Spencer, Ph.D.
EPA Reviewer, Section III
Toxicology Branch I
(H-7509C)
Signature: Henry Spencer
Date: Aug. 26/1991

Karl Baetcke, Ph.D.
EPA Branch Chief
Toxicology Branch I
(H-7509C)
Signature: Karl P. Baetcke
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 upgraded with submission of the test material purity. [illegible] 8/3/91

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 (Camm 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-DNCB or the 100% (w/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-DNCB 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-DNCB 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-DNCB (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-DNCB 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-DNCB 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

Page_____ is not included in this copy.

Pages 8 through 10 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__X__ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.