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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

PC 111801

SUBJECT: Polyhexamethylene biguanide (Baquacil): Review of a Dermal Sensitization Study Submitted by the Registrant.

Caswell No: 676
Shaugnessey: 111801
Submission: S444289
MRID No:426742-01
DP Barcode: D192976

FROM: Timothy F. McMahon, Ph.D., Toxicologist 8/12/93
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Kathryn Scanlon / PM 53
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Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) Marcia Van Gemert 8/16/93

Registrant: ZENECA , Inc. (formerly ICI)

Action Requested: Review of a dermal sensitization study conducted with baquacil, 20.2% a.i.

Data Summary:

In a letter to Kathryn Scanlon, SRRD, the registrant indicated that positive control data would be submitted in order to upgrade an existing dermal sensitization study (MRID # 71345). However, the positive control data did not meet the Agency's criteria for data submissions. Therefore, the registrant submitted a new study for review.

Conclusions:

In this study, polyhexamethylene biguanide (PHMB), applied as a 20.2% neat solution, caused a moderate sensitization in female guinea pigs. A 30% dilution of PHMB in deionized water produced a mild sensitization response in these same animals. Thus, the technical grade of PHMB produced moderate skin sensitization in female guinea pigs. This study is graded **core minimum** data and satisfies the guideline requirement (§ 81-6) for a dermal sensitization study.

Reviewed by: Timothy F. McMahon, Ph.D. 8/12/93
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 8/13/93
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Dermal sensitization-guinea pigs (81-6) Tox. Chem. No.: 676
P.C. Code: 111801

MRID number: 426742-01

Test material: Baquacil

Synonyms: Poly (hexamethylenebiguanide); PHMB

Study number(s): GG5741, GG5694

Testing Facility: ZENECA Central Toxicology Laboratory
Cheshire, UK

Sponsor: ZENECA Inc
Wilmington, Delaware

Title of report: Polyhexamethylene Biguanide: Skin Sensitization to the Guinea Pig of a 20% Aqueous Solution

Author(s): L Duerden

Report issued: February 10, 1993

Conclusions:

Moderate sensitization was observed in response to dermal application of 20.2% PHMB in female guinea pigs. A 30% dilution of PHMB in deionized water produced a mild sensitization response in these same animals. Thus, the technical grade of PHMB produced moderate skin sensitization in female guinea pigs.

Core Classification: minimum

This study satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

I. MATERIALS

A. Test Material: PHMB; description: faint yellow liquid; purity: 20.2 % active ingredient; Reference # Y00156/008. Test material was tested as supplied and as a solution in deionized water.

B. Positive Control Material: 2-mecaptobenzothiazole. Positive control material was used a: a preparation in corn oil.

C. Test Animals: Albino female guinea pigs (Alpk: Dunkin Hartley). Source: Barriered Anima Breeding Unit, ZENECA Pharmaceuticals, Cheshire, UK. Age: young adult; Weight (include: test **and** controls for each group): males, 371-660g (433.9±50.52g); females, 445-715g (611.2±60.29g). Males were used for the sighting study, while females were used for the main study.

II. METHODS

General:

Guinea pigs were acclimated to the laboratory environment for a minimum of 6 days prior to the start of the study. Animals had free access to food (RGP Guinea Pig Diet) and tap water. Animals were housed in a temperature (19 ± 2 ^{o}C) and humidity (55 ± 15%) controlled animal room. A 12 hour light/dark cycle was used. Guinea pigs were housed individually in suspended cages made of stainless steel with wire mesh fronts.

Sighting Study

Dose levels for the main study were determined by a sighting study in which groups of 2 or 4 guinea pigs were used and up to 4 dose levels tested on each group. Intradermal injection of test material diluted in deionized water (up to 10% w/v) was made to determine the highest concentration which could be tolerated locally and systemically; Neat test sample was also tested to determine the highest concentration which did not cause greater than a mild to moderate irritation response in animals injected for the previous 14 days with Freund's Complete Adjuvant. Topical challenge was also made with neat test material or preparations in deionized water to determine the highest non-sensitizing concentration.

Main Study

For the main study, a group of thirty female guinea pigs (20 test animals and 10 controls) was used.

Induction:

Skin on the scapular region of each guinea pig approximately 5 x 5 cm was clipped free of hair. After clipping, triplicate intradermal injections of 0.05-0.1ml of the appropriate test material were made on each side of the mid-line at three locations as follows:

Control guinea pigs: Site (i) was injected with Freund's complete Adjuvant + deionized water (1:1).

Site (ii) was injected with deionized water.

Site (iii) was the same as site (i) above.

Test guinea pigs: Site (i) was injected with Freund's complete Adjuvant + deionized water (1:1).

Site (ii) was injected with a 0.3% (w/v) preparation of test article in deionized water.

Site (iii) was injected with a 0.3% (w/v) preparation of test article in a 1:1 preparation of adjuvant + deionized water.

After induction, injections were checked for adverse effects up to 48 hours.

Optimization:

One week following induction, animals were clipped free of hair at the induction site and the site treated with a topical application of undiluted test article. Test article (0.2-0.3ml) was applied to filter paper (4 x 2 cm) and held in place by a piece of surgical tape. The tape was covered by a strip of adhesive bandage and secured by a piece of self-adhesive PVC tape. Control animals were treated similarly except that nothing was applied to the filter paper. Occlusive dressings were kept in place for 48 hours. Application sites were checked approximately 24 hours after removal of the dressings.

Challenge:

Two weeks following topical inductions (optimization), a new skin site (approximately 15cm x 5cm) was shaved on both flanks of test and control animals, and an occlusive patch prepared containing two pieces of filter paper stitched to rubber sheeting. Undiluted test article was applied to one piece of filter paper, and a 30% (w/v) preparation of test material in deionized water was applied to the second piece of filter paper. The occlusive

dressing was placed on the guinea pig so that undiluted test article was on the left shorn flank, and the 30% preparation on the right shorn flank. This was then covered by a strip of adhesive bandage which was secured by self-adhesive PVC tape. This preparation was left in place for 24 hours.

Erythematous reactions were quantified 24 and 48 hours after removal of the dressing according to a 4 point scale provided by the registrant (page 14 of report). Sensitization was quantified by subtracting the percentage of control animals responding from the percentage of test animals responding, and scaling the net response according to information provided by the registrant (page 14 of report).

To classify the sensitization response, the percentage of the control animals responding was subtracted from the percentage of test animals that responded. Based on the percent net response (page 15 of the report), a sensitization potential was derived, as summarized below:

% net response	description
0	not a sensitizer
1-8	weak sensitizer
9-28	mild sensitizer
29-64	moderate sensitizer
65-80	strong sensitizer
81-100	extreme sensitizer

The positive control phase of this study was performed in a similar manner as that used for application of test material, using a 3% w/v preparation in corn oil for intradermal injection and challenge, and a 75% w/v dilution for topical induction.

III. RESULTS

At 24 hours following challenge with undiluted (20.2% a.i.) test material, 18 of 20 test animals showed a response, ranging from scattered mild redness (9/20) to moderate and diffuse redness (8/20). One test animal showed intense redness and swelling at the application site. In controls, 4 of 10 animals showed a scattered mild redness at the test site. Based on these data, the registrant calculated a net frequency of response at 50% (moderate sensitizer according to the scale on page 15 of the report).

After challenge with a 30% preparation of test material in deionized water, scattered mild redness was observed in 5 of 20 test animals (25%) and in 1 of 10 controls (10%), resulting in a net frequency of response of 15% (mild sensitizer according to the scale on page 15 of the report).

In positive control guinea pigs (20 males), challenge with a 10% solution of 2-mercaptobenzothiazole produced a response in all 20 animals. Scattered mild redness was observed in 7/20 animals at 24 hours post-challenge, while moderate and diffuse redness was observed in 6/20 animals. Of the remaining 7 guinea pigs, 6 showed intense redness and swelling, and 1 showed no reaction to treatment.

In positive control guinea pigs treated with a 3% solution of 2-mercaptobenzothiazole, similar reactions were observed as for the group treated with the 10% solution. In control guinea pigs assigned to the positive control group, sensitization reactions were observed in 2 of 10 animals at 24 hours after application of the 10% 2-mercaptobenzothiazole solution, and also in 2 of 10 animals after application of the 3% solution. Thus, for positive control guinea pigs, the net frequency of response was approximately 80%, indicating that the test system (in this case, the guinea pigs) functioned properly for purposes of dermal sensitization.

IV. CONCLUSIONS

Moderate sensitization was observed in response to dermal application of 20.2% PHMB in female guinea pigs. A 30% dilution of PHMB in deionized water produced a mild sensitization response in these same animals. Thus, the technical grade of PHMB produced moderate skin sensitization in female guinea pigs.

V. CORE CLASSIFICATION

minimum

This study satisfies the guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.