011574

[81-6. Maximization test/permethrin/1989]

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DATA EVALUATION REPORT

STUDY TYPE: 81-6. Dermal sensitization study - guinea pig maximization test.

MRID NO.: 410311-06 **TOX. CHEM. NO.:** 652BB
PC No.: 109701

TEST MATERIAL: Technical permethrin, 95/6% purity.

STUDY NUMBER: CTL/P/2456

SPONSOR: ICI Agrochemicals

TESTING FACILITY: ICI Central Toxicology Laboratory, Cheshire, UK.

TITLE OF REPORT: "Permethrin: Skin Sensitization Study"

AUTHOR: A.M. Leah

REPORT ISSUED: February 21, 1989
[In-life phase: November and December 1988]

EXECUTIVE SUMMARY:

A group of 20 female guinea pigs (Dunkin Hartley) were inducted intradermally with 10% permethrin in corn oil and both neat and 30% solution of permethrin and later challenged with neat and 30% permethrin solutions in a guinea pig maximization test. (MRID #410311-06).

9 of 20 total guinea pigs produced indications of a positive response when none of the 10 total guinea pigs had definite scores for reaction. **Permethrin was demonstrated to be a moderate dermal sensitizer in the guinea pig maximization test,** but a weight of evidence evaluation of other sensitization study data do not indicate that permethrin should be regulated as a potential sensitizer in humans.

Classification: ACCEPTABLE. The guinea pig maximization study is one of several types of dermal sensitization studies run with permethrin and is considered to have a high rate of false positives. Thus, the determination that permethrin causes dermal sensitization should be based on the weight of the evidence for all sensitization studies and use history of the chemical. Other studies including some with humans do not indicate that permethrin should be regarded as a potential dermal sensitizer in humans.

Quality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.
Statement of Data Confidentiality Claims: No claim of confidentiality indicated.
Flagging Statement: Provided.

REVIEW

Experimental Constants:

Test Chemical:

Chemical:	Technical permethrin
Purity:	95.6% (as per certificate of analysis RS/38/F)
Reference:	P56
CTL Ref #:	Y00040/085/001
Description:	Brown liquid

Positive Control:

Chemical:	Formaldehyde (40% in water).

Test System:

Species/strain:	Guinea pigs-albino Alpk:Dunkin Hartley - females only.
Supplier:	Animal Breeding Units, ICI Pharmaceutical Cheshire, England.
Weight:	234-299 for main study, 262-385 for positive control study.
Housing:	Individually.
Diet:	Labsure RGP Guinea Pig Diet.

Basic Experimental Design:

This study was based on the maximization test of Magnusson and Kligman. In the main study, two groups of female guinea pigs consisting of 10 controls and 20 dosed with permethrin (10% w/v in corn oil for the intradermal induction phase, undiluted permethrin for the topical induction and challenge phases).

The test dose of permethrin was determined on the basis of a preliminary dose range finding study in which sets of two or more guinea pigs were assessed for their reaction to intradermal, topical applications at either induction or challenge

Induction. The induction phase consisted of removing the hair for the scapular region and a row of three injections (0.05-0.1 ml each) was made on each side of the mid-line. These injections were:

i. Top: Freund's Complete Adjuvant plus corn oil (1:1).
ii. Middle: Test sample in corn oil.
iii. Bottom: Freund's Complete Adjuvant plus test sample in corn oil (1:1) preparation .

One week later the scapular region was clipped again and treated with undiluted test samples (0.2-0.3 ml) applied on a

filter paper which was held in place by a piece of surgical tape for 48 hours.

Controls were treated similarly except that the bottom row was treated the same as the top row and the topical applications consisted of corn oil only.

Challenge. The challenge was made two weeks after the topical inductions. The pigs were prepared by having their hair again clipped and an occlusive dressing applied which consisted of two pieces of filter paper stitched to a piece of rubber sheeting. Undiluted test sample (0.05-0.1 ml was applied to one of the pieces of filter paper and a 30% (w/v) preparation in corn oil (0.05-0.1 ml) was applied to the second piece of filter paper. The dressing was placed on the guinea pig so that the undiluted test sample was on the left shorn flank and the 30% preparation was on the right short flank. The filter papers were then covered with adhesive bandage which was secured by adhesive PVC tape. The test material was kept in contact for 24 hours before removal. The position of the papers on the skin was identified using a black waterproof marker-pen. The guinea pigs were assessed for reactions after 24 and 48 hours following removal of the challenge dose.

Positive control. Formaldehyde as a 0.3% dilution in deionized water was used for the intradermal injections and a 30% (w/v) dilution was used for the topical induction and challenge applications.

Results

One test and one control animal died from causes reported to be unrelated to treatment although the cause of death or the conditions of morbidity were not described. Three animals were eliminated from further analysis: two permethrin treated animals and one control. The bandage was reported to have slipped form the control animal and the two permethrin treated guinea pigs were reported to have an "equivocal response" No explanation or description was provided for the "equivocal response".

The formaldehyde positive control treated guinea pigs were reported to have developed scattered mild to intense redness and swelling in all test animals with scores ranging from 1 to the maximum score of 3. The reaction to formaldehyde was described as extreme.

None of the 9 guinea pigs had reactions to challenge treatment with neat permethrin at either 24 or 48 hours. One guinea pig challenged with 30% permethrin had a score of 1 that was also classified as doubtful at 24 hours but the score for this animal was 0 at 48 hours.

The study report asserts that 9 of 19[1] guinea pigs challenged with permethrin developed redness that was scattered mild or moderate diffuse. Thus the study indicated that permethrin is a moderate skin sensitizer using the guinea pig maximization test. Table 1 (photocopied from the study report, attached) illustrates the results of the challenge doses with permethrin, It is noted, however, that although the text of the study report states that as many as three animals were not included in the assessment these animals are not indicated in this table or elsewhere in the study report.

Ten guinea pigs dosed with neat permethrin had scores of 0 for both time intervals. Five guinea pigs had a score of 1 at 24 hours only. Three had a score of 1 at both 24 and 48 hours. One guinea pig had a score of 2 at 24 hours and 1 at 48 hours.

DISCUSSION/CONCLUSION. This study is classified as ACCEPTABLE and to demonstrate that permethrin is a moderate sensitizer in the guinea pig maximization test. TB-I notes discrepancies in the study report with regard to the reporting of the animals for which were included in the analysis. The report results section of the report states that as many as three were not included, but the summary table attached reports results for all 20 animals in the test group without indicating which guinea pigs were not included in the assessment. Although, TB-I recognizes this discrepancy, providing and identifying the exact number of animals included in the assessment by the study author will not change the conclusions of the study that permethrin is a moderate sensitizer in the guinea pig maximization test.

The significance of the positive finding in this guinea pig maximization study does not require that permethrin be regarded a sensitizer to humans. This type of study which utilizes Freund's adjuvant tends to have a high rate of false positives. Thus, the actual determination that permethrin is a potential dermal sensitizer to humans should be made on a weight of evidence assessment of available data that includes all other series 81-6 sensitization studies and product incident history for products containing permethrin.

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[1]The exact number of permethrin treated animals that were included in the assessment is not clear from reading the study report. In the results section, three guinea pigs are said to be omitted from the analysis, one with an equivocal response, one that died and one from which the bandage slipped. This would give nine with indications of permethrin reaction out of 17 animals or 53%.

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