

US EPA ARCHIVE DOCUMENT

10-191

432-1132

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.:4816-688

From: Lucy D. Markarian, Biologist *y 9/11/91*
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

To: George LaRocca/T. LeMaster, PM 13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head *E 10/1/91*
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

Applicant: Fairfield American Corporation
809 Harrison Street
Frenchtown, NJ 08825

FORMULATION FROM LABEL:

<u>Active Ingredient(s)::</u>	<u>% by wt.</u>
Permethrin	10.0 %
<u>Inert Ingredient(s):</u>	
.....	90.0 %
Total:	100.0 %

1092

BACKGROUND

Six tests submitted by The Fairfield American Corporation under EPA 4816-688 were reviewed as of 10/22/90. The submitted sensitization test was considered supplementary data by the reviewer claiming that the test report did not include the data from the pre test screening for the determination of the highest non-irritating concentration. The performing laboratory claims that this was included and a copy of the report has been obtained and is reviewed for reconsideration.

RECOMMENDATION

The sensitization assay remains supplementary data. However not for the reason cited by the previous reviewer. The rationale for the rejection of the data is as follows:

1- Although a preliminary screening for the definition of the induction and elicitation concentrations, is made, the data from this assay is not used correctly. Buehler¹ states that "During the period of induction of sensitization, it is often necessary to determine the primary irritancy of the test substance so that a non irritating concentration may be chosen for the response elicitation" The emphasis is on response elicitation: the non irritating concentration is used for challenge only.

In the same publication Buehler has chosen four guinea pigs for the screening, and states that "From this study we determine the highest nonirritating concentration, which is defined as the concentration in the solvent used that induces responses in four guinea pigs no more severe than two grades of 0.5 and two grades of 0. If this is transposed to the Draize scoring system, which Stillmeadow insists on using to evaluate a Buehler test, 10 % solution with no irritation observed was not the ideal elicitation concentration and far from the correct concentration for induction. Grade 1 erythema could possibly be equivalent of a 0.5 reaction on the Buehler scale, and accordingly a much higher concentration than 10% would meet two scores of 0.5 and two grades of 0. Still in the same publication, under the heading of Choice of Induction Concentration he states that "It should be made clear that we generally do not check the primary irritation potential of a test material prior to the induction phase of the study, since we are not primarily concerned about irritation during the induction phase, unless the irritation is so severe as to cause frank necrosis. In the case of severe necrosis (which has been rare in our experience), we either move the exposure site, decrease the concentration applied, or both."

¹Ritz, H.L. and Buehler, E.V., Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests, Current Concepts in Cutaneous Toxicity, Academic Press 1980

3

Robinson et al² state that " In order to enhance its sensitivity, the Buehler test should be conducted at the highest possible test material concentrations. For induction, a dose should be chosen which produces mild to moderate irritation in primary irritation studies." All this means that induction was undertaken at a concentration where sensitization was not possible.

2- PRS has often objected to the grading of a Buehler test by the Draize scoring system. This test proves the unsuitability of the Draize scoring system for the evaluation of the Buehler test. According to the Draize system grade 1 erythema and edema are not remarkable and are not considered positive for primary irritation. The positive control animals were challenged at the induction site, which is of no value in a topical sensitization test, and at a naive site as Buehler has designed the test. All the naive sites in the positive control group showed grade 1 erythema and 3/10 showed grade 1 edema. These being unremarkable scores, the laboratory, in theory, proved that it was not capable of inducing sensitization.

3- PRS finds that the Draize scoring system in itself is not used correctly by the laboratory either. According to the included Draize evaluation system the presence of eschar would be graded as grade 4 erythema. Eschar is repeatedly included as part of edema and sites showing eschar are given erythema scores of 1, 2 or 3, but rarely 4. It is against Good Laboratory Practices to state that a certain procedure is to be followed and then make changes in the procedure at will. This nullifies the results.

4- There were no naive controls included in the study. Buehler³ states that" The significance of reactions in the experimental group is based on intensity and incidence relative to the reactions in the two control groups". By control groups Buehler means a naive control and a vehicle control group:" At the same time a control group of animals that have not received the previous induction patches is challenged on one flank. A third group of guinea pigs is tested throughout the experiment with vehicle alone." The positive control group is to show that the laboratory is capable of inducing sensitization. In this case this very ability is open to question.

5- The use of ethanol as vehicle for elicitation is not suitable as

²Robinson, M.K., Nusair, T.L., Fletcher, E.R., and Ritz, H.L., A Review of The Buehler Guinea Pig Skin Sensitization Test and Its Use in A Risk Assessment Process for human skin Sensitization, Toxicology, 61 (1990) 91-107, Elsevier Scientific Publishers Ireland Ltd.

³Buehler, E.V., and Griffith, J.F., Experimental Skin Sensitization in The Guinea Pig and Man, Animal Models in Dermatology (H.I. Maibach, ed) p56, Churchill Livingstone, Edinburgh, London, & New York, 1975.

4

it has been proven that ethanol has the ability to sensitize.⁴ Buehler¹ himself reiterates this: " Early in our studies, 80 % ethanol was used as a vehicle for both induction and challenge, but we eventually found out that when we started to do experiments involving re-challenges, responses could be obtained to 80 % alone on animals repetitively exposed to 80 % ethanol." The use of ethanol could have been the reason for the adhesive causing the irritation in the test group. The concentration of the ethanol used in the dilution of the test material was not specified; therefore it cannot be said with certainty that this had a definite bearing on the dissolution of the adhesive tape and causing dermal irritation.

LABELING

Labeling will have to remain as recommended previously until a definitive sensitization study is submitted.

⁴Stotts, J., and Ely, W.J. (1977) Induction of Human Skin Sensitization to Ethanol. Jour. Invest. Dermatol. 59:219

5

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager:13
MRID No.:416280-05
Testing Laboratory:Stillmeadow, Inc.
Author(s):Janice O. Kuhn
Species:Guinea Pig, Hartley
Weight:350 - 410 g
Source:Harlan Sprague Dawley, Houston Texas
Test Material:Permanone 10 % EC code FEN90-01-13A
Positive Control Material:DNCB
Quality Assurance (40 CFR §160.12): Included

Reviewer: L. Markarian
Report Date:9/11/91
Report No.:7111-90

Method:Modified Buehler

Summary:

1. This Product is / is not a dermal sensitizer.
2. Classification:Supplementary

Procedure (Deviation From §81-6):

A pre test assay was made to determine the induction and elicitation concentrations for the test by using two guinea pigs and four concentrations in ethanol (concentration of ETOH not specified). 100, 50, 10, and 1 % v/v concentrations were utilized. At 10 % no irritation was observed, and this concentration was used for both induction and elicitation. 0.06 % DNCB in ethanol was used as positive control material for induction and elicitation.

Two groups of ten animals were used for the test. One group was inducted with the test material and the other with the positive control. There were no naive controls.

For induction the respective materials in 0.5 ml aliquots were applied beneath gauze pad and adhesive coverlets (Beiersdorf) and the trunks of the animals were wrapped with polyethylene film. The animals were restrained for the 6 hr exposures. There were a total of ten inductions, made on alternate days over a three week period. Induction sites were moved after the sixth application due to apparent interreaction of the test material and adhesive. Reaction from induction applications were evaluated at 24 and 48 hour after the first and tenth treatment and at 24 hours only after all other treatments.

Challenge was two weeks after the last induction in the same concentrations and mode of application as the inductions at the induction site and at a naive site.

Challenge reactions were evaluated at 24 and 48 hours. All evaluations were according to Draize.

5

Results:

At the pre test screening the following reactions were observed:

	100 %		50 %		10 %		1 %	
	24hr	48hr	24hr	48hr	24hr	48hr	24hr	48hr
Erythema								
grade 1	2/2	1/2	2/2	2/2	0/2	0/2	0/2	0/2
grade 2		1/2						
Edema								
Grade 1	2/2	2/2	0/2	1/2	0/2	0/2	0/2	0/2

In the test group after the first three applications there was no irritation at any of the application sites. Severe irritation was observed (eschar) following the fourth through the sixth applications. After the application sites were moved, grade 1 erythema at all sites and edema at 9/10 sites at 24 hrs following the 9th application, and grade 1 erythema and edema at all sites after 24 and 48 hrs following the 10th application were observed. At challenge at the induction sites 3/10 showed grade 1 erythema at 24 hrs. All were negative at 48 hrs. There was no irritation at the naive challenge sites at any interval.

In the positive control group mild dermal irritation was observed following the third application, and became progressively worse. After the 10th application all sites showed severe dermal irritation (eschar) at 24 and 48 hour evaluations. At challenge all the induction sites showed positive reactions (grade 2 erythema and/or edema). At the naive sites at 24 hrs grade 1 erythema at all sites and grade 1 edema at 2/10 sites is recorded. At 48 hrs all sites show Grade 1 erythema and 3/10 show grade 1 edema. According to the Draize scoring system Grade 1 erythema and edema are not remarkable; therefore the positive control animals are not considered positive for sensitization.