CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dermal sensitization test for linuron in guinea pigs; EPA ID No. 352-326; Accession No. 401876-01; Caswell No. 528; Project No. 7-1082

TO: Mark Boodee, Review Manager
Special Review Branch (TS-767C)
and
Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
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James N. Rowe 11/24/87

THRU: Quang Q. Bui, Ph.D.
Quang Q Bui 11/24/87
Section Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)
11/25/87

ACTION REQUESTED: Review dermal sensitization study in guinea pigs; linuron reregistration; Caswell No.528; Accession No. 401876-01; EPA I.D. 352-326; Project No. 7-1082

RECOMMENDATIONS:

Based on the development in the linuron treatment group (50% or 5% suspensions) of mild to moderate erythema with one animal having erythema associated with edema (grade 4), linuron was considered as a dermal sensitizer in guinea pigs.

This study is designated as Core Minimum data and fulfills the registration data gap for a dermal sensitization test.

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization (guinea pigs)

CHEMICAL: Linuron; 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea; CAS Registry # 330-55-2; Caswell # 528

TEST MATERIAL: Haskell No. 16,398 (INZ-326-118; N.B. 7673-8) described as an off-white crystal, 96.2% purity; dimethyl phthalate was used as the vehicle and control material; 1,4-benzenediamine (Fisher Scientific Co. Certified Grade; Lot # 855213) was used as positive control

STUDY IDENTIFICATION:

a. Title: Dermal sensitization study with INZ-326-118 in guinea pigs

b. Laboratory: E.I. du Pont de Nemours and Company, Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P.O. Box 50, Newark, DE 19714

c. Study #: Haskell Laboratory Report No. 152-87, MR No. 4581-444

d. Date of report: 4/23/87

e. Study director: John E. Henry, Technologist
Acute and Developmental Toxicology Section

f. Caswell # 528; Accession # 401876-01; EPA I.D. No. 352-326

CONCLUSIONS:

Based on the development in the linuron treatment group (50 or 5% suspensions) of mild to moderate erythema with one animal having erythema associated with edema, linuron was considered as a dermal sensitizer in guinea pigs.

This study is designated as Core Minimum data and fulfills the registration data gap for a dermal sensitization test.

MATERIALS AND METHODS:

A photocopy of the materials and methods section is attached. The following comment is noted:

The test method used was discussed in a previous study submission (Accession No. 257620; I.D. No. 352-326; 7/85). As noted in that review, the methods recommended by EPA are considered to maximize the ability of the tester to detect chemically-induced skin sensitization. The origin of the method used is not stated except to note that it is a Haskell Laboratory SOP for primary irritation and sensitization. If it is intended to mimic the Draize Test(1959) it should be noted that this test requires 10 intradermal injections every other day or 3/week. rather than the 4 injections(1/week) stated in this study. The Draize test is considered less sensitive than the other tests recommended by the 1982 EPA Guidelines . The use of only 4 injections would probably make the test even less sensitive. However, since a response is noted in the animals treated with the positive control and the test compound, this method is viewed as adequate to evoke a sensitization response.

RESULTS/DISCUSSION:

Primary irritation phase

Topical application of the vehicle [dimethyl phthalate: 1 drop(.05 ml)] did not produce any evidence of dermal irritation at either 24 or 48 hours (reported only for left front shoulder). Application of an equal volume (50% or 5% suspensions of linuron) induced mild to moderate response (grade 1 or 2) in 3/10 or 1/10 guinea pigs at 24 or 48 hours, respectively, and 1/10 animals (grade 2) at either 24 or 48 hours (5% suspension; same animal). Topical application of the positive control (p-phenylenediamine) as 30% or 3% suspensions produced no evidence of dermal irritation at either time or concentration.

Induction Phase

During the period the animals received the four intradermal injections, all three treatments (vehicle, linuron or p-phenylenediamine) produced varying degrees of moderate to strong erythema, erythema and edema associated with blanching and sometimes associated with necrotic centers. There did not appear to be any significant differences in the overall dermal responses.

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SUMMARY TABLE: DERMAL RESPONSES/CHALLENGE PHASE(from data presented on pg. 11 of report)

	Concurrent control				Test Material			
	50%		5%		50%		5%	
Response§	24 hr	48 hr	24hr	48 hr	24 hr	48 hr	24hr	48 hr
erythema & edema	0/10	0/10	0/10	0/10	0/10	1/10	0/10	0/10
moderate erythema	0/10	0/10	0/10	0/10	5/10	2/10	2/10	1/10
mild erythema	1/10	0/10	0/10	0/10	0/10	2/10	0/10	1/10
no erythema or edema	9/10	10/10	10/10	10/10	5/10	5/10	8/10	8/10

	Positive control			
	30%		3%	
Response	24 hr	48 hr	24hr	48 hr
erythema & edema	2/10	2/10	1/10	0/10
strong erythema	8/10	0/10	7/10	0/10
moderate erythema	0/10	4/10	0/10	4/10
mild erythema	0/10	4/10	2/10	5/10
no erythema or edema	0/10	0/10	0/10	1/10

§ Scoring system used is as follows:

Skin reaction	Score
no erythema or edema	0
mild erythema	1
moderate erythema	2
strong erythema	3
erythema and edema	4
necrosis or vesicles	5

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Challenge Phase

A summary table of the skin responses (14 days after last intradermal injection) is presented above.

The concurrent control (linuron in dimethyl phthalate) produced essentially no dermal response with only 1/10 guinea pigs responding with mild erythema.

A dermal sensitization response for the test material was observed with the development of moderate erythema in 5/10 animals at 24 hours after topical application of the 50% suspension. Two of ten animals in this same group had moderate erythema at 48 hours, 2/10 had mild erythema and 1/10 was reported with erythema and edema. In the 5% linuron suspension, 2/10 guinea pigs had moderate erythema at 24 hours while 1/10 had mild and 1/10 had moderate erythema at 48 hours post-challenge.

The positive control had 8/10 animals responding with a strong erythema and 2/10 with both erythema and edema in the 30% suspension at 24 hours. The response was somewhat lessened at 48 hours with 2/10 still having erythema associated with edema, 4/10 with moderate erythema and 4/10 with only mild erythema. For the 3% p-phenylenediamine suspension, 1/10 had erythema and edema, 7/10 strong erythema and 2/10 had mild erythema at 24 hours post-challenge. At 48 hours post-challenge, 4/10 had moderate erythema and 5/10 had mild erythema.

Body weights were reported for the treatment groups. Average body weight gains (% of initial body weights) were 34.5, 36.7 and 45% for the concurrent control, test material and positive control groups, respectively.

Based on the development in the linuron treatment group (50 or 5% suspensions) of mild to moderate erythema with one animal having erythema associated with edema (grade 4), linuron was considered as a dermal sensitizer in guinea pigs.

This study is designated as Core Minimum data and fulfills the registration data gap for a dermal sensitization test.

Accession # 401876-01

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Pages 6 through 4 are not included.

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