7603 /linuron R.D. 7-17-85

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

004563

JUL 17 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dermal sensitization test for linuron in guinea pigs; Identifying No. 353-326; Accession No. 257620

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C)

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D. James N. Rowe 7/12/85
Section V, Toxicology Branch
Hazard Evaluation Division(HED) (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. Dennis Teeters for L.D.C. 7-12-85
Section Head, Section V
Toxicology Branch/HED (TS-769C)

and

Theodore M. Farber, Ph.D. for WBS 7/17/85
Chief, Toxicology Branch/HED (TS-769C)

ACTION REQUESTED: Review dermal sensitization study in guinea pigs; linuron reregistration; Caswell No.528; Accession No. 257620; I.D. 352-326

RECOMMENDATIONS: Under the conditions of this test linuron does not appear to be a skin sensitizer. However, the sensitizing potential may not have been adequately evaluated. See sections on Experimental Methods and Discussion. It is recommended that another test be conducted using one of the more sensitive procedures in the 1982 Guidelines. This study is classified as a Core Supplementary since negative results were obtained using a procedure which is well-recognized as sensitive only for severe skin sensitizers. Furthermore, fewer induction injections than called for by the procedure were used, thereby probably making it an even less sensitive test.

Excerpts of data submitted by duPont on linuron were included in this review. (4 pages). These pages may be requested by writing Freedom of Information (A-101), EPA, Washington, D.C. 20460. Requesters will be asked to sign an Affirmation of Non-multinational Status.
See D-7604B for excerpts.

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DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization

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

TEST MATERIAL: Haskell No. 15,556 (INZ-326-118; N.B. 7673-8) described as an off-white powder. Dimethyl phthalate, described as a clear colorless liquid obtained from Fisher Scientific Company, was used as the vehicle and control material.

STUDY IDENTIFICATION:

a. Dermal sensitization study in young male albino guinea pigs of the Hartley strain received from Hazleton Dutchland, Inc., Denver, Pennsylvania.

b. Laboratory: Hazleton Laboratories America, Inc.
9200 Leesburg Turnpike,
Vienna, Virginia 22180

c. Study #: Project No. 201-778; Haskell Laboratory Report No. HLO-83- 85, MR No. 4581-219

d. Date of report: 1/18/85

e. Study director: James L. Gargus, M. S.
Life Sciences Division

f. Caswell # 528; Accession # 257620; EPA # 035506-5

CONCLUSIONS: Under the conditions of the test linuron was not a skin sensitizer. Linuron when applied dermally(7.5 and 75% suspensions in dimethyl phthalate) to the back area of guinea pigs produced no irritation (erythema, necrosis) at 24 and 48 hours post-administration. In the same animals, at some unspecified time after the dermal test, intradermal injections (0.1 ml aliquots of a 1% suspension; 4 injections,one/week) in the sacral/hip region followed by a challenge dose(0.05 ml at 7.5, 75% suspension) at 14 days to the skin gave negative results for skin sensitization. Although the results were negative, due to the recognized low sensitivity of the method used in the study, the sensitizing potential of linuron has not been adequately established. It is requested that a new test be performed using one of the seven test procedures recommended in the 1982 Guidelines. This study is classified as Core Supplementary.

EXPERIMENTAL METHODS:

A copy of the methods section is appended to this review. Comments on the methods are as follows:

1. The test method used is not one of the seven different test procedures recommended by the 1982 Guidelines. 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 (Test Code 71). 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 Guidelines . The use of only 4 injections would probably make the test even less sensitive. Furthermore, the animals used in the sensitization study had been previously exposed(dermally) for a dermal irritation study where the animals received 7.5 and 75% concentrations on the skin for an unspecified time period and the dermal response read at 24 and 48 hours. No time is stated as to when the guinea pigs used in the dermal irritation test were injected intradermally for the induction period although the time between the sensitizing(induction) doses and the challenge dose is stated as 14 days.

2. The vehicle control, dimethyl phthalate, is a dermal irritant(intradermally) in its own right as evidenced by the results reported in Table 2 of the study and summarized below in a table. Dimethyl phthalate is known from the open literature to produce a marked inflammatory response in rabbits when injected intradermally(Calley et al. 1966. J. Pharm. Sci., 55:158 as cited in Casarett and Doull. 1975, p. 610). On what basis was dimethyl pthalate selected as a vehicle control? Is it intended to maximize the potential sensitization response?

3. A positive control, as recommended by the 1982 Guidelines, was not used.

4. The initial and terminal body weights as requested in the 1982 Guidelines were apparently not recorded nor reported.

5. For accuracy's sake, the report should have included a correction for the dosage calculation based on the actual concentration of linuron used (96.21%) as opposed to the assumed dosage of 100% (p. 2 of report).

6. Based on the statement on page 4 of the methods, "The same 20 animals were used in the primary irritation phase that were treated during the induction phase.", it is unclear as to when the irritation and the induction phases were performed.

RESULTS:

No effects were reported in the range finding study with 3 animals at concentrations of 25, 50 and 75% test material. No erythema or necrosis was reported in any animal in the primary irritation phase of the study at 24 and 48 hours after administration of 7.5% or 75% concentrations to the skin.

Erythema, from very slight(1) to well-defined(2), was reported during the induction phase in all the test animals and the controls(see table below) when 0.1 ml aliquots of the test material suspension(1% in vehicle) were injected intradermally(a total of four injections, one/week). There appeared to be a somewhat stronger reaction in test animals than in the controls, i.e., 33 grade 2 responses(well-defined erythema)in the treated animals as opposed to 25 grade 2 responses in the controls during the induction period. No necrosis was reported for any animal.

Induction Period

Animal Number	Week 1/lt sd Injection 1		Week 2/rt sd Injection 2		Week 3/lt sd Injection 3		Week 4/rt sd Injection 4	
	Erythema	Necrosis	Erythema	Necrosis	Erythema	Necrosis	Erythema	Necrosis
Test								
H06553	2B[a]	0	2B	0	2B	0	2B	0
H06554	1B	0	2B	0	2B	0	1B	0
H06555	2B	0	2B	0	2B	0	2B	0
H06556	2B	0	2B	0	2B	0	2B	0
H06557	2B	0	2B	0	1B	0	2B	0
H06558	2B	0	1B	0	1B	0	2B	0
H06559	2B	0	2B	0	2B	0	1B	0
H06560	2B	0	2B	0	2B	0	2B	0
H06561	2B	0	2B	0	2B	0	2B	0
H06562	2B	0	2B	0	1B	0	2B	0
Control								
H06563	1B	0	2B	0	1B	0	1B	0
H06564	2B	0	2B	0	2B	0	1B	0
H06565	2B	0	1B	0	1B	0	2B	0
H06566	1B	0	2B	0	2B	0	2B	0
H06567	1B	0	1B	0	1B	0	1B	0
H06568	2B	0	2B	0	1B	0	1B	0
H06569	1B	0	2B	0	2B	0	2B	0
H06570	2B	0	2B	0	2B	0	2B	0
H06571	2B	0	2B	0	2B	0	1B	0
H06572	2B	0	2B	0	2B	0	2B	0

[a] B notation not explained in report; may refer to site of application

No effects were reported for any animal in the challenge phase when 0.05 ml aliquots of the test material(7.5 and 75% suspensions) were applied dermally to the test sites.

No deaths were reported during the study.

DISCUSSION

The test material does not appear to be a dermal sensitizer. However, the use of an apparently insensitive method which does not appear to provide adequate ability to detect a skin sensitizer makes any firm conclusion untenable. Other shortcomings are discussed in the methods section and need not be reiterated here. A retest using one of the more accepted methods cited in the 1982 Guidelines appears appropriate.