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

AUG 1 0 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: 627. Fonofos (Dyfonate). Review of Dermal Sensitization Study.

Shaughnessy No. 041701
Tox. Chem. No. 454B
Project No. D193199
Submission No. S444660

TO: Judith Loranger, CRM Team # 73
Special Review and
Reregistration Division (H7508W)

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THRU: Roger L. Gardner, Section Head Roger Gardner 7/30/93 KA 8/2/93
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Background and Request:

Zeneca Ag Products has submitted a dermal sensitization study conducted on Technical Fonofos in response to FIFRA '88 requirements (MRID # 42842601). The Toxicology Branch (TB-I) has been requested to review the study.

Toxicology Branch Response:

TB-I has reviewed the dermal sensitization study and has found it to be acceptable for regulatory purposes. The following statements summarize the results of the study.

Fonofos was tested for skin sensitization potential using a version of the maximisation test of Magnusson and Kligman. Formaldehyde was used as a positive control and elicited a positive response. Fonofos is considered to be a weak to mild sensitizer under the conditions of the study.

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Reviewed By: Pamela Hurley, Toxicologist Pamela M. Hurley 7/30/93
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DATA EVALUATION RECORD

STUDY TYPE: Dermal sensitization (81-6) - Guinea pig

SHAUGHNESSY NO./TOX. CHEM. NO.: 041701/454B

ACCESSION NO./MRID NO.: 428426-01

DP BARCODE/SUBMISSION NO.: D193199

TEST MATERIAL: Fonofos

SYNONYMS: Dyfonate

STUDY NUMBER(S): GG5133, GG5071

REPORT NUMBER: CTL/P/3195

SPONSOR: ICI Americas, Inc., Agricultural Products, Wilmington, Delaware

TESTING FACILITY: ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK

TITLE OF REPORT: Fonofos: Skin Sensitization to the Guinea Pig

AUTHOR(S): N. J. Rattray and P. Robinson

REPORT ISSUED: 12/05/90

CONCLUSION: Fonofos was tested for skin sensitization potential using a version of the maximisation test of Magnusson and Kligman. Formaldehyde was used as a positive control and elicited a positive response. Fonofos is considered to be a weak to mild sensitizer under the conditions of the study.

Classification: Acceptable

Testing Guideline Satisfied: 81-6

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: o-ethyl s-phenyl ethylphosphonodithioate

Description: Amber liquid
Batch #(s), Other #(s): CTL Y02743/003; ref. 11825-25
Purity: 94.9%
Source: ICI Americas Inc., Western Research Center, Richmond, CA USA
Vehicle (if applicable): Corn oil
Positive Control(s): Formaldehyde (40% w/v aqueous solution)

2. Test Animals:

Species and Strain (sexes): Albino female guinea pigs (Alpk:Dunkin Hartley)
Age: Young adults
Weight(s): 339 - 473 g (main study); 310 - 392 g (positive control study)
Source(s): ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK.

3. Procedure: The sensitizing properties of the test material were assessed using a method based on the maximisation test of Magnusson and Kligman.

a. Basis For Selection of Dose Levels: The dose levels were selected on the basis of a sighting study in which groups of 2 animals were tested with up to 2 dose levels. Induction pretesting was conducted using both intradermal injection (test material in corn oil, up to 0.3% (w/v)) and topical application (3% or a 1% w/v preparation in corn oil in animals that had been injected with Freund's Complete Adjuvant at least 14 days previously). Higher dose levels were not tested because of the known toxicity of the test material. The sighting study also had a challenge phase in which preparations of the test sample were tested in corn oil to determine the highest concentration which did not produce irritation in animals that had been injected with Freund's Complete Adjuvant at least 14 days previously.

b. Animal Assignment and Dose Levels: Forty guinea pigs were used in the test, 20 test animals and two groups of 10 control animals. For the induction phase, a 0.3% w/v solution of the test sample was used for the intradermal induction segment and a 3% w/v preparation was used for the topical application segment. For the challenge phase, a 3% w/v preparation was applied to the left side and a 1% w/v preparation was applied to the right side.

c. Procedure: The induction phase was carried out in 2 segments, an intradermal segment and a topical segment. In the first segment, the hair was removed from the scapular region of each animal (approximately 5 cm x 5 cm area) and a row of 3 injections (0.05 - 0.1 mg each) was made on each side of the mid-line. These were:

1) Top: Freund's Complete Adjuvant plus corn oil in the ratio 1:1
2) Middle: a 0.3% w/v preparation of the test sample in corn oil.
3) Bottom: a 0.3% w/v preparation of the test sample in a 1:1 preparation of Freund's Complete Adjuvant plus corn oil.

The injections were checked for any adverse effects for up to 24 hours. After one week, the animals were reclipped and treated with the topical application of the test material (0.2 - 0.3 ml on filter paper). This was held in place by a piece of surgical tape and covered by a strip of adhesive bandage. This dressing was kept in place for 48 hours. The application sites were checked approximately 24 hours after removal of the dressings. The control animals were treated in an identical manner except that the test material was left out of each preparation.

The challenge phase was initiated 2 weeks after the topical inductions. A 15 cm x 5 cm area on both flanks of each animal was clipped and an occlusive dressing was prepared using 2 pieces of filter paper stitched to a piece of rubber sheeting. The 3% preparation in 0.05 - 0.1 ml was applied to 1 of the filter papers and the 1% preparation was applied to the other. The dressings were placed on each animal such that the 3% preparation was on the left shank and the 1% preparation was on the right shank. The dressings

were then covered with a strip of adhesive bandage. After 24 hours, the dressings were removed. Any erythematous reactions were quantified at 24 and 48 hours, using the following 4-point scale:

0 - no reaction
1 - scattered mild redness
2 - moderate diffuse redness
3 - intense redness and swelling

After scoring, the percentage of the control animals that responded was subtracted from the percentage of the test animals that responded and the net response was compared as follows:

% 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

Due to the high level of irritancy seen following the challenge with a 1% w/v preparation, a rechallenge was conducted 7 days later with 1% and 0.3% w/v preparations. The test samples were applied on different sites than those used previously. A fresh group of 10 control animals were used for the rechallenge.

The positive control group was tested with a 40% w/v aqueous preparation of formaldehyde. A 0.3% w/v dilution of the solution in corn oil was used for the intradermal injections and a 30% dilution of the solution in corn oil was used for the topical induction and challenge phases.

Individual bodyweight data were measured at the beginning and at the end of the study.

B. RESULTS:

Two animals were removed from the study (1 test and 1 control) because the bandages had slipped off early during the challenge phase. Scattered mild redness was observed in 1/19 of the test animals with the 3% preparation. No response was observed with the 9 control animals. The percentage response was calculated to be 5%. **The report concluded that the 3% preparation elicited a weak skin sensitization response. TB-I agrees with the authors of the report.**

With the 1% preparation, scattered mild redness to moderate diffuse redness was seen in 8/19 test animals and in 3/9 control animals. The net percentage response was calculated to be 9%. **The report concluded that the 1% preparation elicited a mild skin sensitization response. TB-I agrees with the authors of the report.**

During the rechallenge, the bandages slipped off of 3 test animals and 1 control animal. These animals were excluded from the analysis of the rechallenge results. During the rechallenge with the 1% preparation, no response was observed in any of the test or control animals. **For the rechallenge, the 1% preparation did not elicit a response.**

Following rechallenge with the 0.3% preparation, scattered mild redness was observed in 1/17 test animals and no response was observed in any of the controls. The net percentage response was calculated to be 5%. **The report concluded that the 0.3% preparation elicited a weak sensitization response. TB-I agrees with the authors of the report.**

The positive control induced scattered mild redness to intense redness and swelling in 20/20 test animals. No response was seen in any of the corresponding controls. The net percentage was calculated to be 100%.

In summary, fonofos was considered to be at most, a mild sensitizer under the conditions of the test.

The body weight data showed no differences between the control and treated groups.

Quality Assurance Measures: Signed Good Laboratory Practice and Quality Assurance statements were provided.

C. DISCUSSION: The study is acceptable for regulatory purposes. Fonofos is considered to be a weak to mild sensitizer under the conditions of the study.