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

JUN 4 1997

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id #0083118-010466. Tributyltin maleate: Review of a dermal sensitization (Buehler) study in guinea pigs.

PC No.: 083118
Barcode No.: D231467
Submission No.: S514480
Reregistration Case No.: 2620

FROM: John Doherty 6/3/97
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO[1]: Michael Metzger
Branch Chief
Risk Assessment and Analysis Branch
Health Effects Division 7509C

THROUGH: Marion Copley, DVM 6/3/97
Section Head, Section IV
Toxicology Branch I
Health Effects Division 7509C

I. CONCLUSION

The dermal sensitization study (Buehler method, MRID No.: 44142303) was reviewed and determined to be ACCEPTABLE and did not indicate that tributyltin maleate induced sensitization in the guinea pig. No additional dermal sensitization studies are required at this time for tributyltin maleate.

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[1]CC: Margaret Rice/Marie Boucher
Product Manager Team 53
Special Review and REregistration Division 7508W

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II. Background and Action Requested

Special Review and Reregistration Division has requested that Health Effects Division review a dermal sensitization study (MRID No.: 44142303) with tributyltin maleate. The study was reviewed and found to be ACCEPTABLE and is identified in the Table below.

Study Identification	Executive Summary
81-6. Dermal sensitization - guinea pigs. Nucro Technics Study No.: 28752, August 30, 1996, MRID No.: 44142303.	In a dermal sensitization study in guinea pigs using the Buehler method, three groups of guinea pigs were dosed with tributyltin maleate (98.5%, as 0.5% in methylcellulose, 20 pigs), positive control (2,4-dinitrochlorobenzene, 0.3%, 5 pigs) or methylcellulose only (10 pigs). Three induction applications were made at weekly intervals and a challenge application was made about 2 weeks after the last induction dose. Tributyltin maleate resulted in minimal irritation in response to induction but no increase in response to the challenge doe. The positive control produced a weak but clear positive response. **Tributyltin maleate was <u>not</u> demonstrated to be a sensitizer in the Buehler type guinea pig sensitization assay.** This dermal sensitization study is classified as ACCEPTABLE and satisfies the guideline requirement for a series 81-6 dermal sensitization study. No additional dermal sensitization studies are required at this time.

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[TBT maleate/1996] Dermal Sensitization Study (81-6)

EPA Reviewer: John Doherty 6/3/97
Toxicology Branch II (7509C)
EPA Secondary Reviewer: Marion Copley, DVM
Health Effects Division (7509C)

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DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - guinea pig
OPPTS 870.2600 [§81-6]

DP BARCODE: D231467
P.C. CODE: 083118

SUBMISSION CODE: S514480

TEST MATERIAL (PURITY): tributyltin maleate, 98.5% Lot # 206666.

CITATION: Pucaj, K. (study director). 1996 "Skin sensitization in guinea pigs (Buehler test) of tri-n-butyltin-maleate" Nucro Technics, Project No.: 28752. August 30, 1996. MRID No.: 44142303. Unpublished. Also Phase 4 Summary dated October 12, 1996 same MRID No.:.

SPONSOR: Thomson Research Associates

EXECUTIVE SUMMARY:

In a dermal sensitization study in guinea pigs using the Buehler method, three groups of guinea pigs were dosed with tributyltin maleate (98.5% in 0.5% in methylcellulose, 20 pigs), positive control (2,4-dinitrochlorobenzene, 0.3%, 5 pigs) or methylcellulose only (10 pigs). Three induction applications were made at weekly intervals and a challenge application was made about 2 weeks after the last induction dose.

Tributyltin maleate resulted in minimal irritation in response to induction but no increase in response to the challenge doe. The positive control produced a weak but clear positive response. **Tributyltin maleate was not demonstrated to be a sensitizer in the Buehler type guinea pig sensitization assay.**

This dermal sensitization study is classified as ACCEPTABLE and satisfies the guideline requirement for a series 81-6 dermal sensitization study. No additional dermal sensitization studies are required at this time.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: tributyltin maleate
   Description: white crystals
   Lot/Batch #: 206666
   Purity: 98.5% ai.
   CAS #: 14275-57-1
   Verification of concentration/homogeneity; **No data on the verification of the test dose solution was provided.**

2. Vehicle: 0.5% (w/v) suspension of the test material in 1% (w/v) methylcellulose (aqueous).

3. Positive control: 0.3% (w/v) 2,4-dinitrochlorobenzene (Lot# 41H08112 in 50/50 acetone/ethanol.

4. Test animals: Species: guinea pig.
   Strain: HA(BR)
   Source: Charles River, Quebec, Canada
   Age and weight at start of treatment: >300 gms
   Acclimation period: 14 days
   Diet: no information ad libitum
   Water: no information ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: June 18, 1996 end: August 8, 1996.

2. Animal assignment and treatment - The test method was based on the method of Buehler ("Experimental Skin Sensitization in the Guinea Pig and Man" in Animal Models in Dermatology. C. Livingston, Edinburgh London and New York, 1975).

Three groups of guinea comprised this study as follows:

→Treatment group - 20 pigs

→Negative control group - 10 pigs

→Positive control group - 5 pigs

The induction phrase consisted of applying 0.5 ml of the test material (0.5% w/v suspension in 1% methylcellulose) to an 4-6 cm^2 area that was prepared (shaved skin of the left flank). The test material was kept in place for 6 hours by means of rubber damning and bandages. The positive control was treated similarly with 2,4-dinitrochlorobenzene and the negative control group was treated with 1% methylcellulose in water. A total of three insults of 6 hours each were applied with applications being made approximately one week apart.

The dose level of tributyltin maleate was determined in a

preliminary study which indicated that dose levels higher than 1 % w/v resulted in necrosis. There was some irritation (score 1 for discrete or patchy erythema associated with 0.5% w/v tributyltin maleate but the study author determined that this level was appropriate for sensitization testing.

The challenge phrase consisted of application to the right flank (preshaven) of the test material or control articles at the same dosage as the induction phrase. The guinea pigs were assessed for sensitization 24 and 48 hours after the application of the challenge dose.

Scoring was assessed as follows. The average score of the overall product was calculated by subtracting the average score obtained by the 1st determination form the average score obtained by the challenge. If less than 15% of animals in the test group show average scores of 1 or more, the results is negative. If more than 15% of animals in the test group or control group show average scores of 1 or more the result is positive.

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration -

The average score for the first induction treatment for the three groups was 0.9±0.4 for the tributyltin maleate, 0.0±0.0 for the dinitrochlorobenzene and methylcellulose. Meaning that there was some local irritation resulting from the tributyltin maleate administration. Subsequent applications of the test material had lower scores for local irritation (i.e. 0.4±0.4 or 0.5).

B. Challenge reactions and duration -

The challenge reactions for the three treatment groups are illustrated in Table I

Based on the observation and calculation that there was no increase in the score following challenge relative to the first induction dose of tributyltin maleate, this chemical is not considered positive in this dermal sensitization study. The positive control indicated irritation in the challenge phrase of the study and not in the induction phrase. Thus, the positive control resulted in the expected positive response although the degree or severity of the response was weak.

Table I. Comparison of the induction (first insult) and

challenge insult in the guinea pig sensitization study with 012250 tributyltin maleate.

Group	Induction	Challenge	Difference
Tributyltin Maleate	0.9±0.4	0.6±0.5	[-0.3]
Dinitrochloro-benzene	0.0±0.0	0.8±0.6	0.8
Methylcell-ulos	0.0±0.0	0.0±0.0	0

C. Conclusion: This study is classified as ACCEPTABLE and satisfies the guideline requirement for a series 86-1 dermal sensitization study in guinea pigs.

D. Deficiencies -

There was no verification of the concentration of the test material in the dosing solution actually applied to the guinea pigs. This deficiency is noted and future studies from this laboratory may not be considered acceptable unless verification of the concentration in the test solution is provided. Although there is no verification of the test concentration, the study is still be accepted because the test material resulted in tell tale signs of dermal irritation to indicate its presence in the test solution. The erythema that resulted from the application of the test material was within an acceptable amount. In general, higher levels of erythema would be considered to interfere with the interpretation of the challenge response.

Note: No additional dermal sensitization studies are required for tributyltin maleate at this time. Tributyltin maleate, like other tributyltin congeners are corrosive to the skin and applying higher dose levels in attempts to demonstrate sensitization would be expected to result in irritation to the skin that would confound the interpretation of the sensitization study.