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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM June 4, 2001

SUBJECT Fentinhydroxide (TPTH) *In vitro* dermal absorption studies

TO Maria Rodriguez PM 22
Fungicide Branch
Registration Div (7505C)

FROM Robert P Zendzian Ph.D. 6/4/01
Senior Pharmacologist
Science Analysis Br
Health Effects Division (7509C)

THROUGH Jess Rowland 6/4/01
Chief
Science Information Management Br
Health Effects Division (7509C)

DP Barcode # D261374 Case #048295 Submission #S569867

Chemical #083601 ID #00181`2-00244 Registrant L.L.C. Griffin

MRID #449409-01 and 449280-01

Action Request

Review the following nonguideline dermal absorption studies:

CITATION: Study 1

Fentin hydroxide: *In vitro* absorption from Supertin 4L Formulation through rabbit and human whole skin. R.J. Ward and B.H. Wollen. Zeneca Central Toxicology Laboratory. CTL Ref: 06564/003. CTL Study No. JV1448. October 24, 1995. MRID 44940901

EXECUTIVE SUMMARY:

In an *in vitro* dermal penetration study (MRID 44940901) Triphenyltin hydroxide as the Supertin 4L formulation was applied to isolated whole skin preparations from rabbit and human. Doses

were Concentrate formulation (4731 ug/cm^2), 1:358 v/v spray dilution (13.2 ug/cm^2) and 1:892 v/v spray dilution (5.30 ug/cm^2). The study was designed to determine the differences in dermal penetration between rabbit and human in order to show that the rabbit is not a valid quantitative model for human absorption.

The study procedure is considered **in valid** and was not reviewed for the following reasons:

1. It is well established that *in vitro* whole skin preparations significantly under estimate *in vivo* skin penetration of chemicals. Therefore any absolute values obtained with whole skin preparations would not accurately determine *in vivo* values of dermal penetration and would be of no value for risk assessment.

3. It is well established by *in vivo* studies that rabbit skin is significantly more permeable than human skin. Differences range from 10 to 16 fold. Because of these differences dermal penetration in the rabbit has never been proposed as a surrogate for human dermal penetration. In point of fact the use of the rabbit was specifically rejected in the development of the OPP guideline for *in vivo* dermal absorption.

3. The error of underestimation increases with the thickness of the whole skin preparation. Therefore the much thicker human whole skin will have a much greater proportional under estimate of dermal penetration than the thinner rabbit whole skin. Thus, the estimated difference between rabbit and human dermal penetration of test chemical will be indeterminately larger that which exists *in vivo*.

This study is classified as an **invalid dermal penetration/absorption study.** The experimental procedure can be expected to significantly underestimate *in vivo* dermal penetration.

CITATION: Study 2

Fentin hydroxide: *In vitro* absorption from Supertin 4L Formulation through human and rat epidermis. R.J. Ward and B.H. Wollen. Zeneca Central Toxicology Laboratory. Report No. CTL/E/129 Study No. JV1447. September 07, 1995. MRID 44928001

EXECUTIVE SUMMARY:

In an *in vitro* dermal penetration study (MRID 44940901) Triphenyltin hydroxide as the Supertin 4L formulation was applied to isolated epidermal membrane preparations from human and rat. Doses were Concentrate formulation (4731 ug/cm^2), 1:358 v/v spray dilution (13.2 ug/cm^2) and 1:892 v/v spray dilution (5.30 ug/cm^2). The study was designed to determine penetration of Fentin hydroxide through human skin at doses chosen "to simulate possible human dermal exposure to the formulation during normal use". The rat portion of the study was performed to show that the rat overestimates human dermal penetration of the test material.

The study procedure is considered **in valid** and was not reviewed for the following reasons:

1. The Office of Pesticide Programs has sufficient experimental data to show that the *in vitro* isolated epidermal membrane preparation significantly over estimates *in vivo* skin penetration of chemicals that have moderate to high solubility in water. It also can significantly under estimate *in vivo* dermal penetration of chemicals having a low solubility in water such as Fentin hydroxide (4.3 ppm). Therefore any absolute values obtained with these preparations would not accurately determine *in vivo* values of dermal penetration and would be of no value for risk assessment.

2. The error of estimation varies with the species from which the preparation is obtained. Thus, the estimated difference between rat and human *in vivo* dermal penetration of test chemical will be impossible to determine accurately with the isolated epidermal preparation..

3. It is well established by *in vivo* studies that rat skin is more permeable than human skin. Differences range from 3 to 5. The Office of Pesticide Programs guideline for *in vivo* dermal absorption does not use the rat as a surrogate for the human. Rather the values obtained from such studies are used to 'convert' oral toxicity values obtained in oral toxicity studies in the rat to relative dermal toxicity values in the absence of rat dermal toxicity studies.

Conclusion

These studies were not submitted to satisfy the subdivision F guidelines. They are nonguideline *in vitro* dermal absorption studies designed to simulate possible human dermal exposure and compare it with rat/rabbit absorption data. However, the procedures used cannot be expected to produce accurate, usable values for any species.

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6/4/01

EPA Reviewer: Robert P. Zendzian PhD
Science Information Br, HED (7509C)

6/4/01

EPA Secondary Reviewer:
/HED (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Absorption

OPPTS Number:

OPP Guideline Number:85.3

DP BARCODE: D261374

SUBMISSION CODE: S569867

P.C. CODE: 083601

TOX. CHEM. NO.: N/A

TEST MATERIAL (RADIOCHEMICAL PURITY): Triphenyltin Hydroxide (97.3% radio pure)

SYNONYMS: Fentin, TPTH, Supertin

CITATION:

Fentin hydroxide: *In vitro* absorption from Supertin 4L Formulation through human and rat epidermis. R.J. Ward and B.H. Wollen. Zeneca Central Toxicology Laboratory. Report No. CTL/E/129 Study No. JV1447. September 07, 1995. MRID 44928001

SPONSOR: L.L.C. Griffin

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In this study the experimental procedure can be expected to significantly misestimate *in vivo* dermal penetration in an unpredictable manner.

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SPONSOR: Griffin Europe. Sponsor Ref: C05615.

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In this study the experimental procedure can be expected to significantly underestimate *in vivo* dermal penetration.

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PC Code:	**083601**
HED File Code	**13000 Tox Reviews**
Memo Date:	**06/04/2001**
File ID:	**TX014581**
Accession Number:	**412-02-0006**

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