CASWELL FILE

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

009489

MAY 7 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id # 109701. Permethrin: Return of studies submitted to asses for dermal penetration of permethrin.

TOX CHEM No.: 652BB
PC No.: 109701
TOX PROJECT No.: 2-1500
Submission No.: S412104

FROM: John Doherty 4/27/91
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Christine Rice/Linda DeLuise
Product Manager #52
Special Review and Reregistration Division
(H7508C)

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C) Marion Copley 4/28/92

I. CONCLUSION

The studies submitted by the ICI Co. in a response to the Phase IV review for permethrin (refer to R. E. Hawk letter dated January 15, 1992) were previously submitted by the Fairfield American Co.. These studies were reviewed earlier and found not to be acceptable to satisfy the requirement for a dermal penetration study (series 85-3) for permethrin. A copy of the review of these studies prepared by Robert Zendzian, Ph.D of Science Analysis and Coordination Branch dated April 17, 1990 is attached.

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List of Studies Submitted.

MRID No.	Study Title/Author	TB-I Comment
421803-01	"Dermal Penetration and Distribution of ^{14}C-Labelled Permethrin Isomers." H.L. Snodgrass, Jr. and D. C. Nelson USAEHA, 1983	
412978-01	"Percutaneous absorption of topically applied ^{14}C permethrin in volunteers-Final medical report. Nora Bartelt and James Hubbell Burroughs Wellcome Company, 1983 THRS/86/0047	
413487-01	"The dermal absorption of permethrin and/or its metabolites by male rats following application of permethrin-isopropanol formulations, a 1% (w/w) permethrin creme rinse and a 5% (w/w) permethrin creme rinse" Burroughs-Wellcome #TYHK/83/0003 (1983)	
413487-01	"Comparative rates of dermal penetration of insecticides in Mice" P.V. Shah, R. J. Monroe and F.E. Guthrie Jour. Tox. Appl. Pharmacology 59:414-423 (1981)	
413487-01	"An investigation into the tolerance to and absorption of permethrin applied as a 1% shampoo or a 0.67% aerosol" Burroughs-Wellcome Document No.: BKPL/81/9	
413487-01	"The systemic exposure of volunteers to permethrin following application as a 1% permethrin creme rinse" Burroughs-Wellcome Document No.: TYHK/83/0004	
413487-01	"The systemic exposure of volunteers to permethrin following whole body applications of a 5% permethrin dermal cream." Burroughs-Wellcome Document No.: TBZZ/84/0002	

413487-01	"Estimation of the metabolites of permethrin in the urine of spray operatives handling this material during W.H.O. stage V evaluation of mosquito adulticides" Burroughs-Wellcome technical Report EB 14
41387-01	"Studies on the percutaneous absorption of four radioactive labelled pesticides" Wang Yi-Lan, Jin Xi-Peng, Jiang Xue-Zhi, Lin Hui Fen, Li Feng et al in Acta Academiae Medicinae Primaae Shanghai 8:(5) (1981).

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MEMORANDUM

April 17, 1990

SUBJECT: Permanone (Permethrin) Tick Repellent, Dermal Absorption Data

TO: Roger Gardner
Acting Section Head
Rev Sec I, Tox Br I
Health Effects Division (H7509C)

FROM: Robert P. Zendzian Ph.D. 4/17/90
Senior Pharmacologist
RSSR Sec, SACB
Health Effects Division (H7509C)

Compound; Permethrin — Tox Chem #652BB

Registration #4816-AVA — Registrant; Fairfield Am Corp.

Accession #412978- — Tox Project #0-0489

Action Requested

Review the data package submitted by the Registrant (Ltr 11/3/89 etc.) consisting of the documents listed below.

Conclusions

The contents of this package lead one to the conclusion that the Registrant has collected all the documents that could be found that appear to have any connection to dermal absorption of the proposed product and submitted them to the Agency. Most of the reports do not satisfy Agency and scientific criteria for reports and the only thing the materials tested have in common with the product is the active ingredient. The Registrant is advised to consider the points presented below and with the individual reports before submitting reports of scientific studies to the Agency. First, each study must be applicable to the product and its applicability must be made clear in writing. Second, each report must be complete in describing the study performed and reporting all data generated in the study. Third, each report must satisfy the Agency's data reporting requirements as included in PR Notice 86-5. An up to date copy of this notice should be obtained from Registration Division.

Individual documents

Percutaneous Absorption of Topically Applied ^{14}C-Permethrin in volunteers - Final Medical Report, N. Bartelt and J. Hubbell, Burrough Welcome Co. Nov 3, 1989, MRID 412978-01

The report as submitted is unacceptable as it lacks individual data. Analytical data must be supplied on all samples collected for all individuals in the study. Such tables should be included as appendices to the report.

The study reported is on the 'dermal penetration of permethrin 25:75/cis:trans in 5% Topical Cream for the treatment of scabies and 1% Creme Rinse (NIX™) for the treatment of head lice infestions." Since the dermal absorption of a pesticide is quantitatively effected by the vehicle, the data generated by this study may not be applicable to the Permanone® Tick Repellent.

Dermal Penetration and Distribution of ^{14}C-Labelled Permethrin Isomers, Study No. 75-51-0026-80 and 75-51-0351-82, US Army Enviromental Hygene Agency Aberdeen Proving Ground, Maryland 21010-5422

This "Report" has been submitted, in parts and whole, several times by the Army. The report appears to be a random collection of zergraphic copies of pages from laboratory notebooks attached to progress reports. It is unacceptable. If it were rewritten in an acceptable form, a laboratory audit would be required before this office would agree to review it.

The following reports are part of one package submitted under the title;

Permanone Tick Repellent, EPA File Symbol Number 4816-AUA, Volume 1, Supplimental Toxicity Data package, MRID 413487-01

Attachment I

The dermal absorption of permethrin and/or its metabolites by male rats following applications of permethrin-isopropanol formulations, a 1% (w/w) permethrin creme rinse, and a 5% (w/w) permethrin dermal cream, T.L. Allsup and J.P. Hubbell. Burroughs Wellcome Co. Doc. No. TYHK/83/0003, Feb 16, 1983

The report was not reviewed. Since dermal absorption of a pesticide is quantitatively effected by the vehicle, the data generated by this study may not be applicable to the Permanone® Tick Repellent. The Registrant must submit formulation data on their repellent product and the products tested in this study showing that they are essentially identical, qualitatively and quantitatively, to justify Agency review of the study.

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Attachment II

Comparative rates of dermal penetration of insecticides in mice, P.V. Shaw, R.J. Monroe & F.E. Guthrie, Toxicology and Applied Pharmacology, 59, 414-423 (1981).

As a published paper, the report lacks individual animal data and cannot be evaluated. Also, the test compounds were applied in acetone and since dermal absorption of a pesticide is quantitatively effected by the vehicle, the data generated by this study are not expected to be applicable to the Permanone® Tick Repellent.

Attachment III

An investigation of tolerance and absorption of permethfin applied as a 1% shampoo or a 0.67% aerosol, J.A. Farquhar, D.B.A. Hutchinson & R.G. Sparks, Wellcome Group Research and Development, Doc. No. BKL/81/9, 6/11/81

The report was not reviewed. The material(s) tested is a head louse shampoo. Since dermal absorption of a pesticide is quantitatively effected by the vehicle, the data generated by this study may not be applicable to the Permanone® Tick Repellent. The Registrant must submit formulation data on their repellent product and the products tested in this study showing that they are essentially identical, qualitatively and quantitatively, to justify Agency review of the study. Also note, the report lacks the certifications required by PR Notice 86-5 and as such is not considered acceptable by the Agency.

Attachment IV

The systemic exposure of volunteers to permethrin following application of a 1% permethrin creme rinse, T.L. Allusup & J.P. Hubbell, Burroughs Wellcome Co, Doc. No. TYHK/83-0004, Oct 26, 1983.

The report was not reviewed. The material(s) tested appears to be a head louse creme which was applied to the head and scalp of human volunteers. Since dermal absorption of a pesticide is quantitatively effected by the vehicle and the application site, the data generated by this study may not be applicable to the Permanone® Tick Repellent. The Registrant must submit formulation data on their repellent product and the products tested in this study showing that they are essentially identical, qualitatively and quantitatively, to justify Agency review of the study. Also note, the report lacks the certifications required by PR Notice 86-5 and as such is not considered acceptable by the Agency.

Attachment V

The systemic exposure of volunteers to permethrin following whole body application of a 5% permethrin dermal cream (Clinical protocol P31-02-01), T.L. Allsup & J.P. Hubbell, Burroughs Wellcome Co, Doc. No. TBZZ/84-0002 Mar 13, 1984.

The report was not reviewed. The material tested is a body creme. Since dermal absorption of a pesticide is quantitatively effected by the vehicle and the application site, the data generated by this study may not be applicable to the Permanone® Tick Repellent. The Registrant must submit formulation data on their repellent product and the products tested in this study showing that they are essentially identical, qualitatively and quantitatively, to justify Agency review of the study. Also note, the report lacks the certifications required by PR Notice 86-5 and as such is not considered acceptable by the Agency.

Attachment VI

Estimation of the metabolites of permethrin (OMS 1821) in the urine of spray operative handling this materal during W.H.O. Stage V evaluation of mosquito adulticides., J.S. Cridland & P. Skidmore, Welcome Research Laboratories, Berkhamsted, Hertfordshire, England, Technical Report EB 14, June 1978.

The report was not reviewed. Technically the report is incomplete, lacking sufficient detail in materials, methods and and results to allow evaluation. The vehicle used is a spray 'solution' for mosquito control. Since dermal absorption of a pesticide is quantitatively effected by the vehicle, the data generated by this study may not be applicable to the Permanone® Tick Repellent. The Registrant must submit formulation data on their repellent product and the material sprayed in this study showing that they are essentially identical, qualitatively and quantitatively, to justify Agency review of the study. Also note, the report lacks the certifications required by PR Notice 86-5 and as such is not considered acceptable by the Agency.

Attachment VII

Studies on the percutaneous absorption of four radioactive labelled pesticides, Wang Yi-Lan, Jin Xi-Peng, Jlang Xue-Zhi, Lin Hui-Fen, Li Feng, Jin Pi-Han, Yang Xi and Geng Jian-Bing, Acta Acedemiae Medicinea Primea Shjanghi, Vol 8, No, 5 1981

A translation of a published paper, the report lacks individual data and cannot be evaluated. Also, since the test compounds were studied in an in vitro test system which data

has been found to be not applicable to in vivo exposure the data generated by this study is not applicable to the Permanone® Tick Repellent.

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Part B US Army Toxicity Summaries

This consists of summaries of 16 reports subitted by the army to the EPA and and copies of three of the reports as noted below.

The summaries are not acceptable. The Registrant must submit copies of the reports. For each study the registrant must show the applicability of the study to the product which is being presented for registration.

The three reports are;

Neurotoxicity in rats following subchronic ingestion of permethrin-treated food, US Army Environmental Hygiene Agency, Study No. 75-51-0351-87, Mar 6, 1987

This report has been evaluated by the Agency and classified supplementary, since it lacks individual data and fails to satisfy the criteria of PR Notice 86-5. The registrant must show the applicability of the study to the product which is being presented for registration.

Skin sensitization of the insecticide permethrin in amn and the potential for nonimmunoligical cntact urticaria, US Army Environmental Hygiene Agency, Study No. 75-51-0351-86, June 13, 1986.

This report has been evaluated by the Agency and classified supplementary, since it lacks individual data and fails to satisfy the criteria of PR Notice 86-5. The registrant must show the applicability of the study to the product which is being presented for registration.

Fabric/skin contact from wearing the army battle dress uniform, US Army Environmental Hygiene Agency, Study No. 75-52-0687-88, Apr 12, 1988

The report lacks individual data and fails to satisfy the criteria of PR Notice 86-5. The registrant must show the applicability of the study to the product which is being presented for registration.

Additional reports

Migration of permethrin from impregnated military fabrics as measured in rabbits, H.L. Snodgrass, Toxicology Div, Directorate of Occuational and Environmental Health, US Army Environmental Hygiene Agency, Study No. 75-51-0351-87, Mar 1, 1988, MRID 406482-01

This report has been reviewed and the study accepted by the Agency. The Registrant must explain how the study supports their proposed product.

The effects of laundering on the permethrin content of impregnated military fabrics, H.L. Snodgrass. Toxicology Div, Directorate of Occuational and Environmental Health, US Army Environmental Hygiene Agency, Study No. 75-51-0687-88, Mar 15, 1988, MRID 406482-02

This study is not a toxicology study and will not be reviewed by Toxicology.