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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. Nos: 50404-L and 50404-A. PERMETHRIN ARTHROPOD REPELLENT (50504-L) for use on military uniforms and fabrics and COULSTON'S PERMANONE TICK REPELLENT (50404-A) for use by general consumers.

TOX CHEM No.: 652BB
TOX Project No.: 8-1077
Record No.: 230038
228522

FROM: Edwin Budd
Section Head
Section I, Toxicology Branch-I, (IRS)
Health Effects Division (H7509C)

Budd 10/23/89

TO: George LaRocca
Product Manager #15
Registration Division (H7505C)

THROUGH: Karl Baetcke
Chief
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Karl Baetcke 10/27/89

Requested Action

The Coulston International Corporation is requesting registration of the products "COULSTON'S PERMANONE TICK REPELLENT" (EPA Reg. No.: 50404-A) and "PERMETHRIN ARTHROPOD REPELLENT" (EPA Reg. No.: 50504-L). The latter of these products, [redacted] will be used by the various military branches to treat uniforms and other fabrics to protect personnel from arthropods and the diseases which they may transmit. The former product is proposed for use by general consumers.

cc. J. Doherty, Toxicology Branch I, Health Effects Division

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

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Toxicology Branch Comments

1. The carcinogenic potential of permethrin was reevaluated by the Carcinogenicity Peer Review Committee of the Health Effects Division on December 12, 1988. The conclusions of this committee were that permethrin should be classified as a Category C carcinogen and that registrations and tolerances should be supported by quantitative risk assessments (refer to report titled "Peer Review of Permethrin" prepared by Dr. Esther Rinde and dated March 8, 1989).

The recommendations of the Peer Review Committee were subsequently commented on by the Science Advisory Panel (SAP) and although they concurred with the carcinogenic classification of permethrin as Category C they did not concur that quantitative oncogenic risk assessment was appropriate (refer to memo from R.B. Jaeger titled "Transmittal of the final FIFRA Science Advisory Panel Report on the May 9, 1989 Meeting", memo dated May 16, 1989).

A second Carcinogenicity Peer Review Meeting was held on June 1, 1989 to discuss the recommendations of the SAP. At this meeting the Peer Review Group again confirmed its recommendations that quantitative carcinogenic risk assessments should be generated to support the various uses and tolerances for permethrin.

The Agency as of this date has not formally made a decision as to whether or not quantitative carcinogenic risk assessments should be made to accompany registrations and tolerances for permethrin.

2. The proposed use of permethrin to treat clothing to protect against insects and ticks has previously been reviewed by Toxicology Branch I (TB-I) and has been determined to represent a chronic exposure (refer to memo by J. Doherty dated May 5, 1987).

3. The toxicity studies submitted with this submission by the Coulston International Corporation have been reviewed and Data Evaluation Records (DERs) prepared for those studies not previously reviewed. Refer to the study list below and the DERs attached.

4. A study designed to assess ^{14}C permethrin migration from treated fabrics to skin and its subsequent penetration through the skin was submitted, reviewed by TB-I and found to be acceptable (refer to the DER attached for study titled "Migration of Permethrin from Impregnated Military Fabrics as Measured in Rabbits, USAEHA Study #75:51--0351-87). The study demonstrated that an average of 3.36 +/-0.73% of the permethrin applied to the fabric migrated to the skin. Of the amount applied to the fabric, 1.94 +/-0.90% was recovered in the urine. This

information can be used to help assess the potential exposure to humans resulting from the treatment of fabrics with permethrin. The study, however, is regarded as being inappropriate for assessing the hazard associated with direct dermal exposure.

5. Data related to human exposure resulting from treatment of military uniforms with permethrin was evaluated by NonDietary Exposure Branch (NDEB). Refer to memos by Linda Kutney dated September 23, 1988 and by Curt Lunchick dated July 31, 1989 (attached). The overall conclusion as indicated in the July 31, 1989 memo is that the total dermal exposure to permethrin resulting from humans wearing battle dress uniforms 24 hours per day and for 365 days per year will average 0.0056 mg/kg/day.

6. Quantitative Carcinogenic Risk Assessment for military uniforms treated with Coulston's Permethrin Arthropod Repellent.

Although the Agency has not formally made a decision to require quantitative carcinogenic risk assessments, in the interim in order to assist Registration Division in evaluating the hypothetical risk associated with this specific use of permethrin, Dr. Robert Zendzian of Health Effects Division (HED) has performed a quantitative carcinogenic risk assessment for the use of PERMETHRIN ARTHROPOD REPELLENT on military uniforms. Dr. Zendzian's report (dated September 1, 1989) is attached. In summary, Dr. Zendzian concludes:

Worst case lifetime risk (exposure: 30 years, 12 months per year, 24 hours per day, 31-73% absorption of permethrin):

$$\text{Carcinogenic Risk} = 1.3 \text{ to } 3.2 \times 10^{-5}$$

More practical lifetime case (exposure: 20 years, 3 months per year, 16 hours per day, 3.1-7.3% absorption of permethrin):

$$\text{Carcinogenic Risk} = 1.4 \text{ to } 3.5 \times 10^{-7}$$

TB-I believes that the factors of years, months of the year, hours of the day and percentage absorption will vary widely in actual usage. Only in the most extreme of these combinations would the risk exceed 1×10^{-6}.

7. Since the product COULSTON'S PERMANONE TICK REPELLENT is likely to result in at least some direct dermal exposure to general consumers (including children), TB-I has requested an additional human exposure estimate from NDEB for this specific use.

8. The composition of the products "COULSTON'S PERMANONE TICK REPELLENT" and "PERMETHRIN ARTHROPOD REPELLENT" were indicated by the PM (refer to EPA Form 8579-13 (green sheet) sent to HED

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[redacted]

The studies supporting the label signal word and precautionary statements for the [redacted] product were reviewed previously (refer to B. Backus review dated December 21, 1981). The products have the signal word CAUTION consistent with the acute toxicity data.

As per discussion with Ms. Theresa Lemaster (PM Team #15, September 19, 1989) [redacted] TB-I does not consider the change in the formulation to be sufficient to warrant new toxicity studies for labelling purposes.

PERMETHRIN ARTHROPOD REPELLENT and COULSTON'S PERMANONE TICK REPELLENT have the signal word CAUTION which is considered appropriate based on acute toxicity. The precautionary statements are also considered appropriate.

OVERALL CONCLUSION

The worst case and more practical risks associated with the military use of the product PERMETHRIN ARTHROPOD REPELLENT are presented above. TB-I believes that only in the most extreme and unlikey combinations of exposure would the carcinogenic risk be greater than 10^{-6}. More practical usage and even frequent use would result in the risk being well below 10^{-6}.

Studies Submitted

Study	Review Status
Permethrin Interim Report-Preliminary Assessment of Relative Toxicity of Candidate Insect Repellent A13-29158 (Permethrin). USAEHA. #51-031-76. April, 1976.	Summary document.
Permethrin Toxicological Evaluation of Permethrin. #51-0831-78. April 1977.	Summary document.
Permethrin. Prepared by Coulston International Corporation dated July 27, 1988.	Summary document.
Permethrin Neurotoxicity in Rats Following Subchronic Ingestion of Permethrin Treated Food. USAEHA #75-51-0351-87. November 1986.	Study previously reviewed by J. Doherty June 17, 1987.
Permethrin Subchronic Inhalation Toxicity of Permethrin. USAEHA #75-51-0026-80, December 1978.	Study previously reviewed by J. Doherty March 8, 1982.
Permethrin Dermal Penetration and distribution of ^{14}C-Labelled Permethrin isomers. USAEHA, #75-51-0351-83, December, 1982.	Reviewed By R. Zendzian Feb. 3, 1985.
Migration of Permethrin from Impregnated Military Fabrics as Measured in Rabbits. U.S. Army Environmental Hygiene Agency, # 75:51-0351-87, March 1, 1988.	3.26+/-0.74% permethrin applied to fabric migrates to skin in 7 days, 1.94+/-0.90% is recovered in the urine. Refer to DER attached.
Permethrin Percutaneous Absorption of cis and trans permethrin in rhesus monkeys and rats: Anatomic Site and Interspecies Variation. As published in J. Toxicol. and Environmental Health 23:207-216 (1988).	Refer to DER attached.

Permethrin Skin Sensitization of the Insecticide Permethrin in Man and the Potential for Nonimmunological Contact Urticaria. USAEHA, #75-51-0351-86. December, 1985.	Refer to DER attached.
Permethrin Preliminary Assessment of Habituation to the Insecticide Permethrin. USAEHA, 75-51-0026-79. October, 1978.	Screening review of this study by Dr. William Sette determined that study would not meet any existing or planned neurotoxicity guidelines.
Permethrin Determination of Urine Metabolite Levels Following Inhalation of the Insecticide Permethrin in Rats. USAEHA, #75-53-0053-79. August, 1978.	Refer to Der attached.
Permethrin Pyrethrins and Pyrethroids for the Treatment of Scabies and Pediculosis. USAEHA #0278-145x/87/0602. 1987.	Not reviewed by Toxicology Branch-I. Data are efficacy.
Shimkin Mouse Lung Bioassay. BIOCON, Inc. Rockville, Md. #DAAD05-84-C-0234, September 13, 1989.	No evidence of increased incidence of lung tumors in male or female strain A/J mice. Doses tested: 0, 285, 475, 713.5 and 1435 mg/kg/treatment. SUPPLEMENTARY. Refer to DER attached.

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Reviewed By: John Doherty 11/30/88
Section I, Toxicology Branch I, - IRS (TS-769C)
Secondary Reviewer: Robert Zendzian 11/30/88
Science Analysis and Coordination Branch (TS-769)

DATA EVALUATION REPORT

Study Type: Special Study - Dermal Absorption from Fabric - Rabbits

Accession or MRID No.: 407668-13 TOX Chem No.: 652BB

Test Material: ^{14}C Permethrin (both cis and trans) and POUNCE 3.2 EC (from the FMC Corporation)

Synonyms:

Study Number(s): 75:51-0351-87

SPONSOR: U.S. Army

Testing Facility: U.S. Army Environmental Hygiene Agency
Aberdeen Proving Ground

Title of Report: Migration of Permethrin from Impregnated Military Fabrics as Measured in Rabbits.

Author(s): H.L. Snodgrass

Report Issued: March 1, 1988

Conclusions:

This study demonstrates that an average of 3.26 ± 0.74 percent of permethrin applied as a diluted formulation of POUNCE 3.2 EC applied to either cotton (100%) or NYCO blend (50% cotton, 50% nylon) migrates from the fabric to the skin over a 7-day period. Of this amount, 1.94 ± 0.90 percent, is actually absorbed such that it was recovered in the urine.

Classification: ACCEPTABLE

Special Review Criteria (40 CFR 154.7): N/A

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Quality Assurance Statement:

A statement signed by T. Fisher, Chief, Analytical Quality Assurance Office, attested that the report and the original raw data and the protocol for this study have been reviewed.

Review

Methods:

In this study, four groups of five or six New Zealand White rabbits (5 to 6 lb, obtained from the Hazleton Research Products, Inc., Denver, PA) were prepared by clipping the dorsal lumbar area of their backs (care was taken not to abrade the skin). These rabbits were assigned to treatment groups as follows:

Experimental Design:

Group	Animal Nos. (N)	Fabric Type	Treatment Rate*	Environ	Sweat	Exposure Period
A	1 - 6(6)	Cotton	0.125 mg/cm2	Temperate	No	7 Days
B	33 - 37(5)	Cotton	0.125 mg/cm2	Subtrop	Yes	7 Days
C	7 - 12(6)	NYCO	0.125 mg/cm2	Temperate	No	7 Days
D	38 - 42(5)	NYCO	0.125 mg/cm2	Subtrop	Yes	7 Days

*To each 50 cm^2 fabric swatch.

The cotton fabric used was identified as Battle Dress Uniform (BDU), camouflage pattern military specification MIL-C-43469D and generally worn by military personnel in hot weather climates.

The NYCO fabric was identified as a 50:50 nylon-cotton blend of BDU fabric military specification MIL-C-44031B and generally worn by military personnel in temperate environments.

The test material used was a mixture of ^{14}C cis and trans permethrin (with the specific activities being 57.1 and 57.3 mCi/mM, respectively). The radioactive permethrin was mixed with POUNCE 3.2 EC, a 38.4 percent formulation of permethrin used for

agricultural applications and registered by the FMC Corporation. (The product contains besides permethrin with a cis/trans ratio of [redacted] xylene and [redacted] inerts.) The radiolabeled permethrin isomers were obtained from the DuPont NEN Co., Boston, MA.

Prior to application of the fabrics to the rabbits, the fabric was cut into 50 cm^2 swatches and weighed. Each 50 cm^2 swatch was treated by dispensing 0.65 mL of the mixture of POUNCE 3.2 EC (diluted with water) and ^{14}C permethrin mixture of isomers by dropping at uniform intervals. The swatches were air dried under a hood for about 4 hours and then stored in a freezer until used. The nominal permethrin total ^{14}C per swatch was reported to be 4.724 uCi for the cotton material and 4.73 uCi for the NYCO material.

The swatches were applied to the rabbits by placing the swatch on the skin, covering with a 4-ply gauze pad and further covering with a larger section of screen. The edges of the screen were taped to prevent abrasion of the rabbits skin and the fabric, gauze and screen were stapled together and finally the combination was taped to the backs of the rabbits. Only the edges of the screen were taped to the rabbits' backs. This system was designed to allow normal convection but to prevent surface loss of the test material from the fabric and the presence of the screen controlled the probing of the rabbit's snout about the treated area. The test fabrics were kept in place for a 7-day period.

Groups B and D were designed to simulate testing under tropical conditions by application of 2 mL of artificial sweat through the screen and into the gauze and test swatch three times a day but once a day on the weekend. These rabbits were also housed in a room with a temperature of 89.6 $\pm$ 1.5 'F and relative humidity of 60 percent. The rabbits in Groups A and C were housed in a room with a temperature of 78.8 $\pm$ 1.5 'F and relative humidity of 40 percent.

Assessment of migration of the permethrin in the fabric to the skin and adsorption by the rabbit consisted of collecting the urine daily through the 7 days and determining the ^{14}C content. Feces were also collected and analyzed. The rabbits were sacrificed after the 7-day period and the skin from the application site (directly under the fabric) was sampled, extracted with methanol and analyzed for ^{14}C. The swatch, binding, gauze, and screen were all also assessed for ^{14}C activity.

Results:

Table 1 (attached), photocopied from the study report summarizes the results of the study. This table indicates and the individual animal data support the conclusion that the mean daily excretion of ^{14}C in the urine was 0.14 and 0.23 percent for

the cotton and NYCO fabrics, respectively, when exposed at temperate environment (lower temperature, no artificial sweat). The rabbits exposed to the "subtropical" environment excreted mean percentages of approximately 0.44 and 0.26 percent for the cotton and NYCO uniforms, respectively. [Note: Copies of Appendix A and C showing representative individual animal data are attached.] Graphical analyses of the ^{14}C in the urine vs. time (in days) indicated that the urinary content was roughly constant after about the second day and continuing out to the seventh day.

Less than 0.1 percent was recovered in the feces. The balance of the ^{14}C was recovered in the test fabric (76 to 86%), bindings (11.4 to 13.7%), and at the site of application on the skin (0.7 to 2.08%).

On this basis, it was concluded that 2.7449 to as much as 4.3583 percent of the permethrin migrated from the fabric to the skin.

[Note: The internal organs of the rabbits were not assessed for ^{14}C content. Since other data available on the pharmacokinetics of permethrin indicate that once permethrin is absorbed it is metabolized and excreted leaving only trace levels of isotope in the tissues, TB-I does not consider it necessary to assess the internal organs for this study.]

The high value for urinary excretion for the rabbits dosed under subtropical conditions and tested for cotton (3.1145%) was attributed to a single rabbit which had higher urinary counts than the other in the same group. It should be noted here that this rabbit was not noted to have ingested (orally) ^{14}C. Some rabbits for which there was evidence of oral ingestion as evidenced by the condition of the screen, had daily urinary radioactivity with noticeably higher counts. The counts for these days were not included in the mean determination.

Overall, there were no major differences in the percent migrating to the skin from the different test groups.

Conclusion:

This study is ACCEPTABLE. The study provides sufficient data demonstrating that 3.25 $\pm$ 0.73 percent (average of groups A, B, C, and D) of permethrin migrates to the skin and can be potentially absorbed when applied to fabric that is worn over the skin for a 7-day period.

TB-I notes that the test material used (POUNCE 3.2 EC formulation) is not the same product which will be used to treat fabrics. In this regard, TB-I considers that this study is representative of potential transfer from cloth to skin when

applied to the fabric in formulations similar to POUNCE 3.2 EC. Other formulations may contain chemicals that would promote the adhesion of permethrin to the fabric resulting in less migration to the skin. Other chemicals which may be present in other formulations may prevent the adhesion of permethrin to the fabric possibly resulting in more permethrin migrating to the skin.

[Note: The value 3.26 $\pm$ 0.73 percent migration is the average for 7 days of exposure. This value will have to be adjusted to daily exposure when determining the human risk assessment for this proposed use of permethrin.]

Attachments

Migration of Permethrin from Impregnated Military Fabrics as Measured in Rabbits. Study No. 75-51-0351-87.

TABLE 1.

MEAN TOTAL 14C RECOVERY (% OF DOSE) IN RABBITS WEARING PERMETHRIN-TREATED* COTTON OR NYCO FABRIC FOR 7 DAYS.

Group	A	B	C	D
Rabbit Nos.	1-6	33-37	7-12	38-42
Fabric Type	Cotton	Cotton	NYCO	NYCO
Environment	Temperate	Subtrop.	Temperate	Subtrop.
Sweat	No	Yes	No	Yes
URINE	0.9288	3.1145	1.7334	1.9996
FECES	0.0000	0.0715	0.0000	0.0339
SKIN-APPL SITE	2.0815	1.1723	1.2039	0.7114
TEST FABRIC	82.7193	85.7943	75.7454	80.5629
BINDINGS	13.5164	11.3715	13.7246	11.6462
Total	101.2460	101.5241	92.4073	94.9540
% MIGRA TO SKIN	3.0103	4.3583	2.9373	2.7449

* 0.125 mg permethrin/cm2 fabric X 50 cm2.

SKIN-APPL SITE - Skin section from under the test fabric.

TEST FABRIC - 14C remaining in test swatch after 7 days of wear.

BINDINGS - Tape binding including gauze and screen.

% MIGRA TO SKIN - % 14C recovered from excreta plus that remaining on the skin surface after 7 days.

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APPENDIX A

URINARY EXCRETION OF 14C IN RABBITS WEARING PERMETHRIN-IMPREGNATED COTTON FABRIC IN A TEMPERATE ENVIRONMENT

FABRIC: COTTON (50 cm2 SWATCH)
ENVIRONMENTAL CONDITIONS: TEMPERATE
TEST LENGTH: 7 DAYS

RADIOCARBON CONTENT-uCi	4.724
PERMETHRIN CONTENT-mg	6.24
mg/uCi	1.3209

ANIMAL NO.		DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	TOTAL
1	DPM/ML	87	185	225	190	185	120	125	
	URINE VOL	173	146	115	78	122	136	128	
	TOTAL uCi	0.0068	0.0122	0.0117	0.0067	0.0102	0.0074	0.0072	
	TOTAL MG	0.0090	0.0161	0.0154	0.0088	0.0134	0.0097	0.0095	
	% RECOVERY	0.1435	0.2576	0.2467	0.1413	0.2152	0.1556	0.1526	1.3125
2	DPM/ML	260	220	150	150	90	50	80	
	URINE VOL	62	150	136	148	100	116	88	
	TOTAL uCi	0.0073	0.0149	0.0092	0.0100	0.0041	0.0026	0.0032	
	TOTAL MG	0.0096	0.0196	0.0121	0.0132	0.0054	0.0035	0.0042	
	% RECOVERY	0.1537	0.3147	0.1945	0.2117	0.0858	0.0553	0.0671	1.0828
3	DPM/ML	195	290	230	150	130	160	95	
	URINE VOL	130	62	126	63	74	70	90	
	TOTAL uCi	0.0114	0.0081	0.0131	0.0043	0.0043	0.0050	0.0039	
	TOTAL MG	0.0151	0.0107	0.0172	0.0056	0.0057	0.0067	0.0051	
	% RECOVERY	0.2417	0.1714	0.2763	0.0901	0.0917	0.1068	0.0815	1.0597
4	DPM/ML	275	680 *	580 *	435 *	310 *	280	160	
	URINE VOL	76	78	92	92	120	124	173	
	TOTAL uCi	0.0094	0.0239	0.0240	0.0180	0.0168	0.0156	0.0125	
	TOTAL MG	0.0124	0.0316	0.0317	0.0238	0.0221	0.0207	0.0165	
	% RECOVERY	0.1993	0.5058	0.5088	0.3816	0.3547	0.3311	0.2639	2.5452 *
5	DPM/ML	110	100	130	90	30	40	60	
	URINE VOL	166	124	130	166	116	110	158	
	TOTAL uCi	0.0082	0.0056	0.0076	0.0067	0.0016	0.0020	0.0043	
	TOTAL MG	0.0109	0.0074	0.0101	0.0089	0.0021	0.0026	0.0056	
	% RECOVERY	0.1741	0.1182	0.1611	0.1425	0.0332	0.0420	0.0904	0.7615
6	DPM/ML	- 45	50	70	60	55	65	105	
	URINE VOL	224	123	90	82	100	112	44	
	TOTAL uCi	0.0045	0.0028	0.0028	0.0022	0.0025	0.0033	0.0021	
	TOTAL MG	0.0060	0.0037	0.0037	0.0029	0.0033	0.0043	0.0027	
	% RECOVERY	0.0961	0.0586	0.0601	0.0469	0.0524	0.0694	0.0441	0.4277
MEAN % RECOVERY		0.1681	0.1841	0.1878	0.1265	0.0957	0.1267	0.1166	0.9288
STNDRD DEVIATION		0.0455	0.0924	0.0753	0.0555	0.0635	0.0988	0.0737	0.3057

* Values omitted from computation of MEAN % RECOVERY. Artificially high recoveries resulted from the animal probing the patch and ingesting a portion of the test material.

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APPENDIX C

TOTAL 14C RECOVERY IN RABBITS WEARING 14C-PERMETHRIN-TREATED COTTON FABRIC IN A TEMPERATE ENVIRONMENT

FABRIC: COTTON (50 cm2 SWATCH)
ENVIRONMENTAL CONDITIONS: TEMPERATE
TEST LENGTH: 7 DAYS

RADIOCARBON CONTENT-uCi	4.724
PERMETHRIN CONTENT-mg	6.24
mg/uCi	1.3209

GRP	ANIMAL NO.		URINE	FECES	SKIN-APP SITE	TEST FABRIC	BINDINGS	% MIGRA TO SKIN*	TOTAL % RECOVERY
A	1	DPM/ML			3680	173385	16450		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.0829	3.9051	0.7410		
		TOTAL MG			0.1095	5.1582	0.9788		
		% OF APPL	1.3125	0.0000	1.7545	82.6644	15.6857	3.0670	101.4171
A	2	DPM/ML			4020	172570	16580		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.0905	3.8867	0.7468		
		TOTAL MG			0.1196	5.1340	0.9865		
		% OF APPL	1.0828	0.0000	1.9166	82.2759	15.8096	2.9994	101.0849
A	3	DPM/ML			4445	176925	13355		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.1001	3.9848	0.6016		
		TOTAL MG			0.1322	5.2635	0.7946		
		% OF APPL	1.0596	0.0000	2.1192	84.3522	12.7345	3.1788	100.2655
A	4	DPM/ML			2365	172695	16680		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.0533	3.8895	0.7514		
		TOTAL MG			0.0704	5.1377	0.9925		
		% OF APPL	(2.5452)	0.0000	1.1276	82.3355	15.9050		101.9100
A	5	DPM/ML			5040	190760	12155		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.1135	4.2964	0.5475		
		TOTAL MG			0.1499	5.6751	0.7232		
		% OF APPL	0.7615	0.0000	2.4029	90.9483	11.5902	3.1644	105.7029
A	6	DPM/ML			6645	179835	9830		
		VOL (ML)			50	50	100		
		TOTAL uCi			0.1497	4.0503	0.4428		
		TOTAL MG			0.1977	5.3501	0.5849		
		% OF APPL	0.4277	0.0000	3.1681	85.7396	9.3733	3.5958	98.7087
MEAN % RECOVERY			0.9288	0.0000	2.0815	84.7193	13.5164	3.2011	101.5148
STND DEVIATION			0.3057	0.0000	0.6231	3.0510	2.4885	0.2080	2.1341

* Total 14C appearing in excreta plus that remaining on the skin surface at test end.
Values in parentheses used only for accountability (TOTAL % RECOV). See Appendix A for explanation.

Reviewed By: John Doherty 12/14/88
Review Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Edwin Budd 5/1/89
Review Section I, Toxicology Branch I - IRS (TS-769C)

DATA EVALUATION REPORT

Study Type: Dermal Absorption

MRID Number: 407668-15 TOX Chem. No.: 652BB

Test Material: ^{14}C-Labeled Permethrin (cis and trans isomers and both alcohol and acid moieties labeled)

Synonyms:

Study Number: None

Sponsor: Health and Welfare Department of Canada

Testing Facility: Environmental Health Center
Tunney's Pasture, Canada

Title of Report: Percutaneous Absorption of cis and trans Permethrin in Rhesus Monkeys and Rats: Anatomic Site and Interspecies Variation.

Authors: E.W. Sidan, R.P. Moody, and C.A. Franklin

Report Issued: 1988 (as published in J. Toxicol. Environ. Health 23:207-216)

Conclusions:

Attached is the abstract of this paper as it appeared in the publication. Note: Publications from the open literature are not used to meet data requirements since these studies do not include the raw data and individual animal responses.

Classification: CORE-SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

No Quality Assurance information provided. Study is a published report from the open literature.

Attachment

PERCUTANEOUS ABSORPTION OF *cis*- AND *trans*-PERMETHRIN IN RHESUS MONKEYS AND RATS: ANATOMIC SITE AND INTERSPECIES VARIATION

Edward W. Sidon, Richard P. Moody, Claire A. Franklin

Environmental Health Directorate, Health and Welfare Canada, Ottawa, Ontario

Dermal absorption of cis- and trans-permethrin isomers was determined in rhesus monkeys and Sprague-Dawley rats. Four ^{14}C radiolabels were used (cis alcohol, cis cyclopropyl, trans alcohol, and trans cyclopropyl). One microcurie of each radiolabel was applied to either the forehead or forearm of rhesus monkeys or to the mid-lumbosacral region of the rat. Urine was collected for 7 or 14 d. Correction factors for incomplete urine excretion were derived from measurements of radiolael in the urine following im injection of an equivalent dose. It was noted that the total im dose recovered in the urine of both species was lower for the cis isomer than for the trans isomer. There was no significant difference between the dermal absorption of the cis isomer and that of the trans isomer in monkeys. The forehead, however, was more permeable for both isomers than the forearm (alcohol- and cyclopropyl-labeled cis and trans isomers, respectively, showed permeation in forehead, cis 28 ± 6%, 24 ± 6%, trans 21 ± 3%, 14 ± 4%, forearm, cis 9 ± 3%, 9 ± 3%, trans 12 ± 3%, and 5 ± 2%). There was no difference between absorption of the isomers (cis 46 ± 4%, trans 43 ± 5%) in rats, but absorption was significantly greater than in monkeys. The IM urinary t½ values in monkeys and rats were similar for both isomers (0.8-1.1 d).

INTRODUCTION

Permethrin is a synthetic pyrethroid insecticide that has been used extensively in Canada for mosquito and spruce budworm control (National Research Council of Canada, 1986). Although dermal exposure of spray personnel to pesticides is well documented, estimation of the potential health risk is usually derived from animal oral dose studies (Franklin et al., 1986). Previous reports have described permethrin metabolism in mammals following oral ingestion (Miyamoto, 1976; Elliott et al., 1976; Gaughan et al., 1977; Ivie and Hunt, 1980) and skin absorption in hens after spray applications (Hunt et al., 1979); however, there are

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007624

Reviewed By: John Doherty 12/14/88
Review Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Edwin Budd 5/25/89
Review Section I, Toxicology Branch I - IRS (TS-769C)

DATA EVALUATION REPORT

Study Type: 81-6 - Sensitization: Humans and Guinea Pigs

MRID Number: 407668-11 TOX Chem. No.: 642BB

Test Material: Permethrin (92.5%), supplier not specified

Synonyms:

Study Number: 75-51-0351-86

Sponsor: U.S. Army

Testing Facility: U.S. Army Environmental Hygiene Agency
Aberdeen Proving Ground, Aberdeen, Md.

Title of Report: Skin Sensitization of the Insecticide Permethrin in Man and the Potential for Nonimmunological Contact Urticaria.

Author: Report prepared by Herbert L. Snodgrass.

Report Issued: December 1985

Conclusions:

No evidence that permethrin treatment resulted in dermal sensitization in humans using the prophetic patch test or in guinea pigs using the nonimmunological contact urticaria test as predictive models.

Classification: CORE-SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

No Quality Assurance statement was provided.

Review

Part 1. Prophetic Patch Test (Humans)

In this study, 184 adult subjects (males and females, ranging in age from 18 to 80) were prescreened to qualify for the study and were treated with permethrin by means of a Werbil patch containing 0.2 mL of a 40% solution of permethrin in ethanol. These patches were applied to the upper arms and kept in place by means of an occlusive bandage. These patches were applied thrice weekly for 3 weeks. Two weeks after this sensitization period, the challenge application was made to previously unpatched sites. The challenge patches (apparently also 0.2 mL of permethrin) were removed 72 hours later and the area was scored after 96 hours.

There was no evidence that permethrin treatment resulted in sensitization. The only reactions reported were in "several" subjects that had transient burning, stinging and/or itching.

Part 2. Nonimmunological Contact Urticaria (NICU) Test (Guinea Pigs)

In this study, 10 guinea pigs were dosed with 0.1 mL of a 25% solution of permethrin (in acetone) to the ear lobes (0.05 mL to each site.) Acetone alone was applied to the left earlobe. A string micrometer was used to measure earlobe thickness, before application and at timed intervals (between 0 and 180 minutes) after application of the test material. An increase in lobe thickness compared to the left (vehicle control treated) ear lobe was the index for allergic response.

No evidence of increased lobe thickness was evident at any of the 12 time intervals at which the ear lobes were measured. Thus, there was no evidence presented that permethrin produced an NICU.

Conclusion:

These studies are SUPPLEMENTARY. These studies provide useful information to indicate the permethrin does not cause contact sensitization in humans or NICU in guinea pigs. It is of interest to note that the dose levels used according to the report corresponded to the approximate amount a human might be exposed to when wearing a 16 x 16 and a 10 x 10 inch patch of permethrin-impregrated uniform (80 and 31 mg) for the human patch test and guinea pig study, respectively.

007624

Reviewed By: John Doherty 12/14/88
Review Section I, Toxicology Branch I - IRS (TS-769C)
Secondary Reviewer: Edwin Budd 5/15/89
Review Section I, Toxicology Branch I - IRS (TS-769C)

DATA EVALUATION REPORT

Study Type: Special Study - Uninary Levels of Permethrin Following Inhalation (Multidosing) Exposure

MRID Number: 407668-06 TOX Chem. No.: 652BB

Test Material: Permethrin

Synonyms:

Study Number: 75-53-0053-79

Sponsor: U.S. Army

Testing Facility: U.S. Army Environmental Hygiene Agency Aberdeen Proving Ground, Aberdeen, Md.

Title of Report: Determination of Urinary Metabolite Levels Following Inhalation of the Insecticide in Rats.

Authors: J.A. Gere and R.E. Boldt

Report Issued: May-August 1978

Conclusions:

Urinary levels of the principal metabolite of permethrin were measured and found to be highest after 3 to 4 days of exposure and to drop after cessation of exposure indicating the rat can metabolize and excrete inhaled permethrin. Study has unusual finding that high levels of exposure to permethrin had apparent increase in urinary lipids.

Classification: CORE-SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

No Quality Assurance statement was provided.

Review

In this study, four groups of our male rats (Sprague-Dawley) were exposed to aerosol concentrations of permethrin of 0, 125, 250, and 500 mg/m^3 for 6 hours per day, 5 days per week for 13 weeks. The conditions of the chamber, method of generation of the test atmosphere, and information on the quantitation of the chamber atmospheres were not provided. Following removal of the rats from the exposure chambers, they were placed in individual metabolism chambers and their urine collected. The volume of the urine was determined and the urinary content of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (CIVA) was determined. The method of analysis for CIVA was not fully described, but was said to include enzymatic hydrolysis, esterification, and analysis by gas chromatography. Assay for CIVA was regarded as an index of the quantity of inhaled permethrin.

The results of the analyses showed that the concentration of CIVA in the urine increased during the week reaching a maximum on Thursday and Friday. As shown in the attached copy of a figure presented in the study report, there was a steep drop in CIVA content when measured on Saturday and Sunday when the rats were not exposed to permethrin. These data were interpreted by the investigators to indicate that the rats have an efficient mechanism for detoxification and excretion of permethrin.

One interesting aspect of the results reported by the investigators was that there were some difficulties encountered in analyzing the urine for CIVA because of an "apparent increase in lipid content of the rat urine." This apparent increase in lipid content was reported to affect the analysis of the rats exposed to the high-dose level of permethrin and in particular for the samples collected within 24 hours after exposure of the rats in the high-dose group. No further investigations were made to determine if exposure to permethrin resulted in increases in lipid content of the urine.

Conclusion:

This study is SUPPLEMENTARY. The report was in summary form only. The information is, however, considered limited because no quantitive assessment of the amount of permethrin inhaled versus what was excreted in the urine was provided (or attempted). The study also raises the question of the possibility that permethrin results in increased lipid levels in the urine.

Attachment

HSE-LR-B/WP
Study No. 75-53-0053-79, May-August 1978

Note: Urine was collected from the time inhalation was discontinued each afternoon until 8AM the following morning, ie the designation "Mon" represents collection from Monday afternoon thru Tuesday morning.

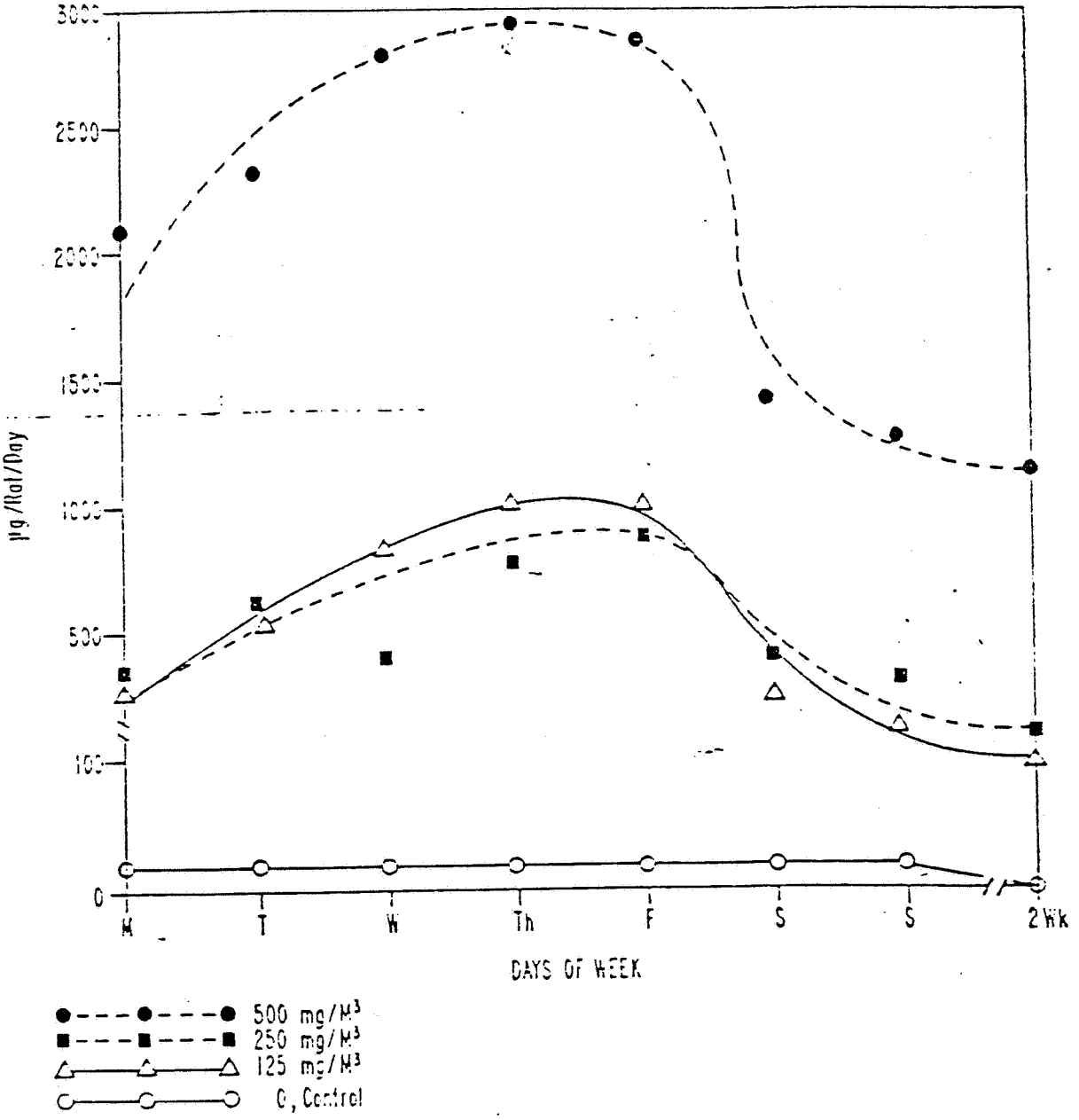

FIGURE I: PERMETHRIN CONTENT OF RAT URINE, µg/RAT/DAY

007624

Reviewed by: John Doherty
Section I, Tox. Br., Insecticide, Rodenticide Support (TS-769C)
Secondary reviewer: Edwin Budd Budd 10/3/88
Section I, Tox. Br., Insecticide, Rodenticide Support (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Special Study: Shimkin Mouse Lung Bioassay.

ACC.No.: 407668-17 TOX. CHEM. NO.: 652BB

TEST MATERIAL: Technical permethrin (92.5% pure, [redacted] cis/trans ratio, Lot #8599-RA, Penick Corp.)

SYNONYMS:

STUDY NUMBER(S): DAAD05-84-C-0234

SPONSOR: U.S. Army

TESTING FACILITY: BIOCON, Inc. 649 Lofstrand Ln. Rockville, Md.

TITLE OF REPORT: Shimkin Mouse Lung Bioassay.

AUTHOR(S): Lawrence E. Cunnick

REPORT ISSUED: September 13, 1985

CONCLUSIONS:

No evidence that permethrin treated mice (285 mg/kg/treatment, highest level of assessment) developed significant differences in adenoma formation relative to the control groups. The positive control (urethane) produced the expected positive result. Levels tested: 285, 475, 713.5 and 1425 mg/kg/treatment, death rate at 475 mg/kg and above precluded assessment.

Classification: SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7): N/A

Quality Assurance Statement:

A Quality Assurance Statement signed by Judith T. Snow indicated that inspections were made on five occasions.

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REVIEW

The Shimkin Mouse Lung Bioassay is a novel method to assess for the potential for suspect chemicals to produce or accelerate the formation or development of mouse lung adenomas in a strain of mice known to be especially susceptible to chemical induced and/or spontaneous lung tumor formation.

In this study, ten groups of 16 male and female A/J strain mice obtained from the Jackson Laboratory in Bar Harbor, Maine were dosed as shown in Table 1. The mice were injected with the test material (it is not clear if gavage or intraperitoneal injections were made) three days a week (Monday, Wednesday and Friday) for eight weeks except that the mice treated with urethane were injected on day one only. After 24 weeks the mice were sacrificed and their lungs removed and fixed in Tellyesniczky's fluid. When fixed in this fluid, the lung tumors appear as "pearly white nodules that can be counted on the surface of the lungs". Only the mice surviving the 24 week test period were evaluated for tumor production. The frequency of lung tumors in the treated mice were compared with the vehicle controls by the standard students t test. Table 1 shows the results of the study.

Group	Treatment		Survivors		Total Tumors		Tumors/Mouse	
			M	F	M	F	M	F
1	Permethrin	1425*	0	0	-	-	-	-
2	"	713.5	6	1	1	0	<1	<1
3	"	475**	N/A	4	N/A	2	N/A	<1
4	"	285	14	16	2	2	<1	<1
5	N,N-DP***	596	16	16	4	0	<1	<1
6	"	298	14	15	2	1	<1	<1
7	"	119	15	15	4	2	<1	<1
8	Urethane	1000****	9	10	231	217	25.7	21.7
9	Corn Oil	-	13	14	2	2	<1	<1
10	Untreated	-	16	16	0	1	<1	<1

* Dose level in mg/kg/treatment.

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** Only females were treated.
*** N,N-dipropylcyclohexanecarboxamide (the reason for including this chemical in the study was not stated, it is assumed by TB that the sponsor was interested in this chemical for unspecified reasons).
**** Only 10 mice per sex were used for this group.

The above table shows that neither permethrin or N,N-dipropylcyclohexanecarboxamide treatment resulted in lung tumors in excess of the corn oil and untreated control groups. The positive control (urethane) resulted in the expected positive response.

CONCLUSION. This study is SUPPLEMENTARY. There are no guidelines for this study type. The data are of interest but of limited usefulness since this type of assay is not recognized as a definitive mouse oncogenicity assay. The negative finding in this study may, however, be taken into consideration in the overall evaluation of the oncogenic potential of permethrin.