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

FEB 24 1992

FEB 10 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Registration of the Product "Insectkiller Cockroach Carpet"

TO: Linda Arrington/George LaRocca, PM-13
Registration Division (H7505C)

FROM: Flora Chow, Chemical Manager J. Chow 10Feb92
Reregistration Section
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: William Burnam, Acting Chief
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

HED Project No.: 1-2567
Caswell No.: 652BB, 25
Action: 165 New Product

Please find, attached to this memo, the TB-I review of the new product "Insectkiller Cockroach Carpet". According to the review, no new toxicity studies are required to support the proposed use of permethrin; however, data gaps for the indoor use of allethrin, the co-active ingredient, were identified.

The exposure review by OREB has been previously forwarded to you.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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JAN 30 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id #050654-U. Permethrin: Registration of the product INSECTKILLER COCKROACH CARPET.

TOX CHEM No.: 652BB (permethrin)
25 (allethrin)
PC No.: 109701 (permethrin)
004001 (allethrin)
HED PROJECT No.: INTRA-0304
and 1-2567
Submission No.: S403119

FROM: John Doherty John Doherty 1/29/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Flora Chow
Chemical Manager for Permethrin
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: Marion Copley, DVM, Section Head Marion Copley DVM 1/30/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

I. CONCLUSION

No additional toxicity data are required to support this proposed use of permethrin. A decision on use of allethrin in this proposed product will have to be made depending on the incremental increase in exposure to this chemical because of the deficiencies in studies which meet current acceptability guidleines.

The usage pattern should be reviewed by Occupational Residential Expsoure Branch to determine the extent of exposure to applicators and occupants of rooms to both permethrin and allethrin where the product is placed. Consistent with current Agency policy, carcinogenicity risk asssessment should be generated to support this proposed use of permethrin.

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II. ACTION REQUESTED

The Perrycut-Chemie AG Company of Switzerland (through their consultant Federal Regulatory Consultants, Inc. (refer to letter from A.E> Castillo dated July 22, 1991) is seeking to register their product Insectkiller Cockroach Carpet containing permethrin and allethrin. This product is a treated cardboard mat which is placed in a variety of rooms except where food is prepared, processed or served. Toxicology Branch I (TB-I) has been requested to provide an appropriate Toxicology Profile for permethrin and provide any comments.

III. TOXICOLOGY BRANCH COMMENTS

1. Copies of the Free Standing Toxicology Summary for permethrin and allethrin are attached.

2. The product Insectkiller Cockroach Carpet currently has the signal work CAUTION (Toxicity Category III) but no data supporting this signal word were submitted to TB-I.

TB-I considers that acute toxicity studies to support the labelling of this product can be waived. There is sufficient data currently available to indicate that products containing < 1% permethrin and allethrin would be toxicity category III for both oral and dermal toxicity and dermal irritation. The physical nature of this product (insecticide impregnated into large pieces of cardboard) preclude ocular and acute inhalation exposure.

3. The use of this product should, however, be reviewed by Occupation and Residential Exposure Branch to determine the potential exposure to applicators and occupants of rooms where the product is to be used. In particular, the potential atmospheric concentrations should be determined for permethrin. An estimate of the exposure to allethrin is also considered necessary (refer to point 5 below).

4. No new toxicity studies are required to support this proposed new use pf permethrin.

5. The toxicity data base for allethrin is currently being updated by the registrants and not all studies to support an indoor use of the product meet current standards for aceptability. Since allethrin is currently registred for use indoors, a decision based on incremental increase in exposure will have to be made regarding registering this product for additional indoor uses as propsed for this product.

The data gaps for the indoor use of allethrin are listed as follows:

81-6.	Dermal sensitization.
*82-1a.	Subchronic oral (rodent)
*82-1b.	Subchronic oral (nonrodent)
*82-2.	21-day dermal
*82-4.	21 or 90 day inhalation
*83-1a.	Chronic oral (rodent, or 83-5)
*83-1b.	Chronic oral (nonrodent)
*83-2a.	Oncogenicity (rat, or 83-5)
*83-2b.	Oncogenicity (mouse)
*83-4.	Multi-generation reproduction
*83-5.	Combined chronic feeding/oncogenicity
84-2.	Mutagenicity data base
*85-1.	Metabolism

*Conditionally required for indoor use depending upon potential exposure.

FREE STANDING TOXICITY SUMMARY - PERMETHRIN

Toxicity Data Base: Permethrin [Data provided jointly from the FMC and ICI Corporations, the Burroughs-Wellcome Co and/or the US Army.]

Tox Chem Number: 652BB
PC Number: 109701

Edition: October 22, 1991

Series. Study Type	Study Available	Comment on study or significant finding[2]	Document Number[3]
81-1. Acute oral - rats	A	Tox. Cat. III-IV	1570
81-2. Acute Dermal - rabbits	A	Tox. Cat. IV	1570
81-3. Acute inhalation - rats	A	Tox. Cat. IV	5/10/76
81-4. Primary eye - rabbits	A	Tox. Cat. IV	1570
81-5. Primary dermal - rabbits	A	Tox. Cat. IV	1570
81-6. Dermal sensitization - guinea pig	A	Not a sensitizer (U.S.Army study).	7624
81-7. Delayed neurotoxicity - hen	No	Not applicable	
81-8. Special neurotoxicity - rat	No	Requirement pending. See also 82-7.	
82-1a. Subchronic oral - rodent	3	NOEL/LEL = 100/500 ppm. Liver effects. NOEL = 20/100 ppm. Liver effects. NOEL/LEL = 20/100 ppm. Liver effects.	
82-1b. Subchronic oral - nonrodent	A	NOEL/LEL = 50/364 mg/kg/day (capsule). CNS activity, liver and body weight effects.	
82-2. 21-day dermal	A	NOEL = 1.0 gm/kg/day (HDT). U.S. Army study.	1570
82-3. 90-day dermal	No		

82-4. 90-day inhalation - guinea pig 90-day inhalation - dogs 90-day inhalation - rat	S S S	NOEL > 500 ug/l/day (HDT) NOEL > 500 ug/l/day (HDT) NOEL/LEL = 250/500 ug/l/day. Tremors, convulsions, liver effects. All are U.S. Army studies.	1570
82-5. 90-day neurotoxicity - hen	No	Not applicable.	
82-6			
82-7. Neurotoxicity screen rats Special study to assess for particular pyrethroid neurotoxicity. Note: new Guidelines require additional study types.	S	NOEL/LEL 100/200 mg/kg/day. Increased irritability. Possible morphological changes at 400 mg/kg/day. No morphological lesions at 600 ppm (21 days feeding). NOEL < 4000 ppm for tremors, deaths at 9000 ppm.	5946 8163
83-1a. Chronic feeding - rat		See 83-5.	
83-1b. Chronic feeding - nonrodent	2	NOEL/LEL = 5/100 mg/kg/day (capsule). Liver effects. NOEL > 250 mg/kg/ay (HDT).	3403
82-2a. Oncogenicity - rat		See 83-5.	
82-2b. Oncogenicity - mouse [3 studies considered acceptable, one considered invalid]	A	NOEL/LEL = 100/250 ppm. Liver effects. NOEL/LEL = 20/500 (males) and 2500/5000 ppm (females). Liver effects. Positive for lung and liver tumors. NOEL ≥ 250 mg/kg/day (HDT). Considered positive for lung tumors at 250 mg/kg/day.	8163
83-3a. Developmental toxicity - rat	A	NOEL/LEL = 50/150 mg/kg/day for both maternal and developmental toxicity (decreased fetal weight).	8344

83-3b. Developmental toxicity - rabbit	A	Maternal toxicity LEL < 600 mg/kg/day (equivocal body weight gain). NOEL/LEL for developmental toxicity 600/1200 mg/kg/day.	8344
83-4. Multi generation reproduction - rat	2	NOEL < 500 ppm. Liver effects in pups. BOdy tremors in parents at 1000 and 2500 ppm and in pups at 2500 ppm. NOEL > 180 mg/kg/day (HDT).	 8163
83-5. Combined chronic/onco - rat	3	NOEL < 500 ppm. Liver effects. NOEL/LEL = 20/100 ppm. Liver effects. Equivocal for lung adenomas. NOEL/LEL = 10/50 mg/kg/day. Liver effects.	 8163
84-2. Gene mutation	A	Ames test: Not mutagenic	
84-2. Chromosome aberration	No		
84-2. Other mechanism genetic toxicity.	No	Unscheduled DNA systhesis: Not mutagenic	8761
85-1. Metabolism - rata and dogs.	A	Several studies define absorption, excretion and retention of labelled permethrin.	1660 7524
85-2. Domestic animal safety		See formulations.	
85-3. Dermal Absorption - rabbits	S	[U.S. Army study indicates 30-70% absorption.]	
85-. Nerve function/operant behavior	No	Requirement pending	

[1] A = Acceptable study satisfies the data requirement. S = a SUPPLEMENTARY study containing useful information is available but additional data are required. Number = more than one ACCEPTABLE study containing useful information has been presented. No = no acceptable or useful study has been provided.

[2] Consult DER for additional details. Only significant toxicity at the LEL is presented.

[3] The document number for the DER is given but in some cases when no document number is available the date of the review is given. If no date or document number, consult the one liners for further study identification.

Special Toxicology Issues and Problems.

1. Labelling. There are no specific labelling and precautionary statements required based on the toxicity of technical permethrin. The label signal word and precautionary statements should be governed by the toxicity studies with the formulations.

2. Carcinogenicity.

The HED Peer Review Committee classified permethrin (as of September 18, 1989) as a Group C carcinogen (possible human carcinogen) and recommended that quantitative risk assessments be performed based on the FMC mouse study using the dose-related increase in combined lung adenomas and/or carcinomas observed in females.

The Q_1* based on the FMC mouse study for lung and liver tumors is 1.84 x 10 -2 (mg/kg/day).

3. RfD.

The RfD approved by the Agency RfD Committee is 0.05 mg/kg/day based on the FMC 2-year rat feeding study with a NOEL of 5 mg/kg/day and a safety factor of 100.

4. Non carcinogenic risk assessment.

There are no other specific toxicity endpoints besides carcinogenicity and RfD as indicated above.

5. Mutagenicity/genetic toxicity comments.

The mutagenicity/genetic toxicity data base is considered incomplete and is being revised and updated.

6. Dermal penetration.

The U.S. Army has submitted a study which indicates 30 - 70% of permethrin may be absorbed through rabbit skin. This study is considered SUPPLEMENTARY and additional data are required to better establish the rate of permethrin through the

skin. According to Robert Zendzian, pharmacologist HED, the dermal penetration factor of 3 to 7% is currently recommended for estimating human absorption of permethrin. This is based on human skin being about 1/10 as permeable as rabbit skin.

Free Standing Toxicity Summary

Toxicity Data Base: Allethrin
Edition: January, 1992

Tox Chem Number: 25
PC. No.: 00401

Series. Study Type	Study Available	Results/Comments	Document Number
81-1. Acute oral - rats	G	Toxicity Category III	242
81-2. Acute Dermal - rabbits	G	Toxicity Category III or IV	242
81-3. Acute inhalation - rats	G	Toxicity Category III or IV	2783 3222
81-4. Primary eye - rabbits	G	Toxicity Category IV	242
81-5. Primary dermal - rabbits	G	Toxicity Category III	242
81-6. Dermal sensitization - g. pig		Study Required	
81-7. Delayed neurotoxicity - hen		Not Applicable	
81-8. Special neurotoxicity - rat		Requirement pending	
82-1a. Subchronic oral - rodent	NC	[1972 study reports NOEL/LEL 1500/5000 ppm.]	2780
82-1b. Subchronic oral - nonrodent		No study. See 83-1(b).	
82-2. 21-day dermal		Study required.	
82-3. 90-day dermal		Requirement pending on usage patterns.	
82-4. 90-day inhalation		Requirement pending on usage patterns.	
82-5. 90-day neurotoxicity		Not applicable.	
82-6			
82-7. Neurotoxicity screen		Requirement pending.	
83-1a. Chronic feeding - rat		Study required.	
83-1b. Chronic feeding - nonrodent	NC	[Old study, undated, reports NOEL/LEL = 50/100 mg/kg/day.	2784

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82-2a. Oncogenicity - rat		Study required.	
82-2b. Oncogenicity - mouse		Study required.	
83-3a. Developmental toxicity - rat	G	NOEL/LEL = 25/125 mg/kg/day for maternal toxicity (deaths, clinical signs). NOEL > 125 mg/kg/day for developmental toxicity. Doses tested = 0, 5, 25, 125 mg/kg/day.	8466
83-3b. Developmental toxicity -rabbit	G	NOEL/LEL = 100/300 mg/kg/day maternal deaths, tremors, ataxia). NOEL > 300 mg/kg/day for developmental toxicity. Dose levels tested 0, 30, 100 and 300 mg/kg/day.	
83-4. Multi generation reproduction		Study required.	
83-5. Combined chronic/onco		Study required.	
84-2. Gene mutation		A host mediated assay circa 1975 did not indicate allethrin was mutagenic. Study type is no longer considered useful by HED.	6386
84-2. Chromosome aberration		Study required.	
84-2. Other mechanism genetic tox		Study required.	
85-1. Metabolism	NC	Earlier data has been submitted but needs but needs to be rereviewed to determine acceptability in terms of current standards.	
85-2. Domestic animal safety		See Formulations.	
85-3. Dermal Absorption		No data.	
85-. Nerve function/operant behavior		Requirement pending.	

G = A Guideline study exists and the requirement is considered fulfilled.
A = An acceptable study exists and the requirement is considered fulfilled.

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M = A Minimum study has been submitted and the requirement is considered fulfilled under most circumstances. NC = Not classified. A study exists that has some useful information but an earlier review did not classify according to current acceptance criteria. S = A study exists that contains useful information but cannot be used to meet the data requirement. I = the study has been determined to be INVALID. Any result must be considered temporary and subjected to confirmation by a valid study.

Special Toxicology Issues and Problems.

1. **Labelling.**

There is no acceptable dermal sensitization study (81-6) to determine if a dermal sensitization warning is required on the label.

The labelling of all products containing allethrin does not otherwise require special labelling instructions based on the toxicity of this active ingredient. The label signal word and precautionary statements should be governed by the toxicity tests for the individual formulations.

2. **Carcinogenicity.**

There are no rat and mouse carcinogenicity studies in Toxicology Branch files. Allethrin has not been reviewed by the HED Carcinogenicity Peer Review Committee.

3. **RfD.**

The HED RfD committee has concluded that there is insufficient data for RfD determination as per the Ad Hoc Meeting 7/25/89. Refer to 9/6/91 RfD tracking report.

4. **Non carcinogenic risk assessment.**

Insufficient data for determination.

5. **Mutagenicity/genetic toxicity comments.**

There are no acceptable studies for any category of mutagenicity/genetic toxicity. [Note: The host mediated assay is no longer considered an acceptable study type].

The office of Pesticide Programs is in the process of revising guidelines for mutagenicity studies. The registrant may choose either to submit data according to the current guidelines or the revised guidelines, which are not yet in effect.

Under the revised guidelines, the following will be required for the first tier of studies: 1) Salmonella reverse gene mutation; 2) mammalian cells in culture forward gene mutation assay, using either the mouse lymphoma L5178Y cells (thymidine kinase locus), CHO or hamster V79 cells (HGPRT gene locus plus an appropriate in vitro test for clastogenicity), or CHO strain AS52 (XPRT locus); and 3) in vivo cytogenetics assay, rodent bone marrow, either metaphase analysis or micronucleus assay. If the registrant elects to follow the revised guidelines, reformatted older studies may also be submitted but additional studies may also be required as indicated above.

The registrant is also requested to submit a complete bibliography of mutagenicity studies on cypermethrin, since this will be required for all chemicals under the revised guidelines.

6. **Dermal Penetration.**

No data.