6

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

TXR NO. 0052775

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

OFFICE OF
PREVENTION, PESTICIDES,
AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: July 6, 2004

SUBJECT: **Permethrin**. Metabolism Assessment Review Committee Memorandum.

PC Code: 109701.
Barcode No.: D298310.

FROM: Sherrie L. Kinard, Chemist
Reregistration Branch II
Health Effects Division (7509C)
and
Yung Yang, Toxicologist
Toxicology Branch
Health Effects Division (7509C)
and
José Meléndez,
Environmental Risk Branch V
Environmental Fate and Effects Division (7507C)

THROUGH: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)
and
Chistine Olinger, Chairperson
Metabolism Assessment Review Committee
Health Effects Division (7509C)

TO: Yan Donovan, Executive Secretary
Health Effects Division (7509C)

1. INTRODUCTION

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a synthetic pyrethroid insecticide registered for use on numerous food/feed crops and for applications to livestock and livestock housing. Permethrin formulations registered by the

AUG 24 2004

basic producers for use on food/feed crops include emulsifiable concentrates (ECs), wettable powders (WPs), and a granular (G) formulation. These products may be applied to crop plants as broadcast and banded pre-emergence applications or foliar applications using ground or aerial equipment. Several of these formulations can also be applied as surface sprays to livestock housing.

With the exception of cottonseed, tolerances for permethrin residues in/on plant raw agricultural commodities (RACs) are currently expressed in terms of the insecticide permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] and the sum of its metabolites 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA) and (3-phenoxyphenyl)methanol (3-PBA) [40 CFR §180.378 (b) and (d)]. Tolerances for residues of permethrin in/on cottonseed (0.5 ppm) are expressed in terms of permethrin *per se* [40 CFR §180.378 (a)]. Tolerances for permethrin residues in/on animal RACs are currently expressed in terms of permethrin and the sum total of its metabolites 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA) and (3-phenoxyphenyl(methanol (3-PBA) and 3-phenoxybenzoic acid [40 CFR §180.378 (c)]. No food/feed additive tolerances have been established for residues of permethrin. Adequate methods are available for the enforcement of established tolerances, as currently defined.

The HED Metabolism Committee has previously determined tolerances will be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound (CBRS No. 16744, DP Barcode 222362, C. Olinger, 2/1/96). The chemical names and structures of the permethrin residues of concern are depicted in Figure 1.

2. MARC MEETING INFORMATION

Decision

Table 1. Residues of Concern for Plants, Livestock, and Water

Chemical: **Permethrin**		
Date: 15-January-2004		
Residues of Concern		
Matrix	Residues included in Tolerance Expression	Residues included in Risk Assessment
Plants	Parent only (both *cis*- and *trans*-)	Parent only (both *cis*- and *trans*-)
Livestock	Parent only (both *cis*- and *trans*-)	Parent only (both *cis*- and *trans*-)
Water	NA	Parent only (both *cis*- and *trans*-)

Meeting Date: January 15, 2004

MARC Rationale:

Plants:. Plant metabolism studies on cabbage, sweet corn, and soybean indicated that parent, DCVA, and MPBA are major residues (>10% TRR). MARC had previously concluded that tolerances will be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound. Since then, new toxicity data on DCVA have been submitted in associated with other pyrethroids such as cyfluthrin. MARC concluded based on the new toxicity studies and SAR considerations that DCVA will not likely cause the same neuro toxic effects as the parent pyrethriods. The ester linkage of a pyrethroid needs to remain intact for neurotoxicity. MARC concluded that for tolerance expression and risk assessment, parent only is the residue of concern. With regard to the potential carcinogenicity of DCVA, refer to the separate section below.

Livestock: Below is a summary of livestock metabolism studies:

- In orally and dermally dosed poultry and ruminants, the major residue in fat, muscle, milk, and eggs is permethrin.

- The major residues found in liver and kidney are DCVA and 3-PBA in orally and dermally dosed animals. Minimal permethrin is found in liver and kidney.

- DCVA and MPBA were found in the muscle of dermally treated hens at levels less than 20%TRR. DCVA was also found in the egg whites of orally treated hens at less than 11%TRR.

Drinking Water: Environmental fate studies indicated that Permethrin is immobile in five soils tested. Permethrin has a vapor pressure of 2.15×10^{-8} mm Hg=2.83×10^{-11} atm, water solubility of 0.07 ppm=1.8×10^{-4} mol/m^3, and an estimated Henry's Law constant of 1.6×10^{-7} atm•m^3/mol. Based upon its Henry's Law constant, permethrin is expected to have a relatively low potential for volatilization from water. Its potential for volatilization from soil should be lower due to its relatively high soil/water partitioning. Permethrin appears to dissipate primarily through binding to the soil, and by soil microbial degradation. It does not degrade through abiotic means (hydrolysis or photolysis). Aerobic and anaerobic soil metabolism studies indicated that DCVA and m-PBA are major degradates (DCVA:10-20% applied dose, m-PBA: 12-15% applied dose). Available data (K_d and K_{OC}) indicated that DCVA and m-PBA are more mobile than the parent, and therefore, they are more likely to reach drinking water than the parent. However, due to the low application rate, the absolute values of these degradates will be very small compared to exposures from food. As discussed above, DCVA and m-PBA are not likely to cause the same neuro toxic effects as the parent. MARC concluded that DCVA and m-PBA can be excluded as residues of concern. MARC concluded that parent only is the residue of concern to be included in the drinking water assessment.

Potential Carcinogencity of DCVA

Based on the weight of all the available evidence the MARC concluded there are not sufficient grounds to include DCVA in the cancer risk assessment at this time. The following points were considered in drawing this conclusion.

Based on the amount and nature of the radioactivity appearing in the urine of rats it is likely that the three pyrethroids permethrin, cypermethrin/zeta-cypermethrin, and cyfluthrin are metabolized to a significant extent by cleavage of the ester linkages with the resulting formation of DCVA. In the case of cypermethrin, similar metabolism and pharmacokinetics are observed in mice and dogs. The results of cancer studies in mice for the three pyrethroids were significantly different. Permethrin is classified as a likely human carcinogen with a q* based on lung adenomas and carcinomas plus liver adenomas in mice. Cypermethrin is a possible human carcinogen without a q* based on lung adenomas plus carcinomas also in mice. Cyfluthrin is classified as not likely to be carcinogenic to humans based on no evidence of carcinogenicity rat or mouse studies. Considering that cyfluthrin and permethrin are both metabolized to a significant extent in mammalian systems to DCVA and the different cancer classifications for the two insecticides, the weight of evidence suggests that DCVA per se does not contribute significantly to the carcinogenic effect.

Looking at the total human exposure to permethrin related residues from all possible sources, DCVA is expected to be a minor contributor compared to the parent. This conclusion is based on the wide array of residential uses of permethrin, the relative levels of parent and DCVA observed in crops and livestock, and the low absolute levels (ppb) of DCVA anticipated in drinking water.

It is noted that the above decision is consistent with those made for DCVA as a metabolite of the pyrethroid cyfluthrin (see 6/13/02 memo, D283553, PC code 128831) and for the November 1997 assessment to address expiring tolerances for most of the pyrethroids.

The salmonella reverse mutation assay (Ames assay) conducted with DCVA indicated that the compound was negative in the presence and absence of metabolic activation in all five tester strains.

Members Attended: Abdallah Khasawinah, Rick Loranger, Yan Donovan, Leung Cheng, John Doherty, Norman Birchfield, Leonard Keifer, Christine Olinger, and Pauline Wagner.

Members in Absentia: Alberto Protzel, PV Shah, Bill Wassell.

Non Members: Carol Christensen, Sherrie Kinard, Jose Melendez, and Yung Yang.

3. BRIEFING MATERIALS

- The major residue in plants when harvested within one day of treatment is the parent, permethrin.

- As the pre-harvest interval increases, hydrolysis of the ester bond occurs and the major residues are DCVA and MPBA (>15%TRR).

- In orally and dermally dosed poultry and ruminants, the major residue in fat, muscle, milk, and eggs is permethrin.

- The major residues found in liver and kidney are DCVA and 3-PBA in orally and dermally dosed animals. Minimal permethrin is found in liver and kidney.

- DCVA and MPBA were found in the muscle of dermally treated hens at levels less than 20%TRR. DCVA was also found in the egg whites of orally treated hens at less than 11%TRR.

Table 2: Metabolites Found in Peach, Potato, Tomato, Rotational Crops, and Water

Matrix	Major Metabolites/Degradates [1]	Minor Metabolites/Degradates [2]
Cabbage	permethrin, DCVA, MPBA	3-PBA, 4'OH MPBA, 2'OH MPBA
Corn, sweet	permethrin, *trans*-DCVA, MPBA	*cis*-DCVA, 4-OH PBA, 3-PBA
Soybean	permethrin, DCVA, MPBA	3-PBA, 4'OH MPBA, 2'OH MPBA
Poultry and Ruminants	permethrin, DCVA, OH-DCVA, DCVA-Glucuronide, 3PBA, 4'OH-3-PBA	OH-permethrin, DCVA-lactone
Water	permethrin, DCVA, 3PBA, 3PBalcohol	

[1] Major is defined as comprising >10% of the total radioactive residues in a plant metabolism study, or as >10% of the applied dose in an environmental fate study.
[2] Minor is defined as comprising <10% of the total radioactive residues in a plant metabolism study, or as <10% of the applied dose in an environmental fate study.

RESIDUE CHEMISTRY

Use Information:

A search of the Agency's Reference Files System (REFS) on 5/09/02 listed twelve permethrin end-use products (EPs) with food/feed uses registered to FMC Corporation (FMC; Company No. 279), AMVAC Chemical Corporation (AMVAC; Company No. 5481), and Syngenta Crop Protection (formerly Zeneca Ag Products; Syngenta; Company No. 100).

Plants:
Permethrin formulations registered by the basic producers for use on food/feed crops include emulsifiable concentrates (ECs), wettable powders (WPs), and a granular (G) formulation. These products may be applied to crop plants as broadcast and banded preemergence applications or foliar applications using ground or aerial equipment.

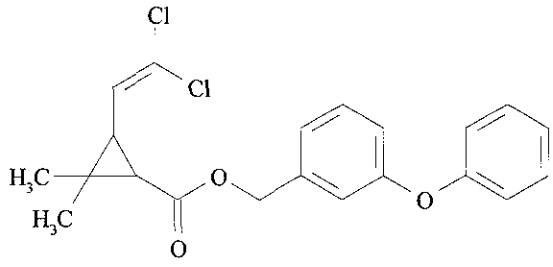
Livestock:
For direct application of permethrin to ruminants and their housing, the available residue data support repeated applications to livestock premises at a rate of 0.21 oz ai/1,000 ft^2 with a 14-day retreatment interval (RTI). The data also support direct applications to ruminants at 950 mg ai/animal (2 mg ai/kg body weight) with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 1-day preslaughter interval (PSI) should be specified for ruminants.

For direct application of permethrin to swine and their housing, the available residue data support repeated applications to swine housing at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to swine at 240 mg ai/animal with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 5-day PSI may be specified for swine.

For direct application of permethrin to poultry and their housing, the available residue data support repeated applications to poultry houses at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to hens at ~20 mg/bird with a 14-day RTI. A 1-day PSI should be specified for poultry.

Physical/Chemical Properties:

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a synthetic pyrethroid insecticide. Permethrin is a racemic mixture of the cis and trans isomers. Permethrin is a colorless crystal to a pale yellow viscous liquid with a melting point of 35°C and a boiling point of 220°C (0.05 mm Hg). Permethrin is soluble in water at less than 1 ppm, and is miscible in most organic solvents except ethylene glycol. Permethrin is soluble in acetone, ethanol, ether, and xylene.



Empirical Formula:	$C_{21}H_{20}Cl_2O_3$
Molecular Weight:	391.3
CAS Registry No.:	52645-53-1
PC Code:	109701

Summary of Plant Metabolism Studies:

- The major residue in plants when harvested within one day of treatment is the parent, permethrin.

- As the pre-harvest interval increases, hydrolysis of the ester bond occurs and the major residues are DCVA and MPBA (>15%TRR).

The qualitative nature of the residue in plants is adequately understood based on three adequate soybean, cabbage, and sweet corn metabolism studies. The HED Metabolism Committee (C. Olinger, 2/1/96) has concluded that the residues of concern in plant commodities are the *cis*- and *trans*-isomers of both permethrin and DCVA. Tolerances are to be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound.

In all studies permethrin was labeled in the cyclopropyl and phenyl rings (in separate tests). Results are presented in Tables 1 through 3. Structures of metabolites may be found in Figure 1 included in the back of this report.

Multiple applications were made to the sweet corn at a 5X rate. Forage was sampled one day after the third application while the grain was sampled one day after the fifth application. Product labels specify a one-day PHI.

Radiolabelled permethrin was added to an EC formulation and then diluted with water prior to application to cabbage and soybean plants. Cabbage leaves were harvested from the treated plants 0, 30, and 60 days after application. Whole soybean plants were harvested after 30, 50, and 78 days. A translocation study was also conducted with soybean plants where foliar and pod applications were made and samples of the plant parts were taken 15 and 45 days post-treatment.

Permethrin, *cis*- and *trans*-DCVA, and MPBA were the major metabolites in corn forage and fodder, cabbage, and soybean leaves. Hydroxylated MPBA and MPBAcid were also found in minor amounts (refer to tables 1 through 3).

All three studies demonstrate that the major residue is permethrin when the RAC is harvested soon after treatment (within one day). As the time between treatment and harvest increases, hydrolysis of the ester bond occurs, yielding DCVA and MPBA. Hydroxylation of the alcohol or conversion to the corresponding acid may then occur.

Table 1. Identification/characterization of ^{14}C-residues in sweet corn forage, fodder, grain, and cobs following repeated applications of [^{14}C]permethrin.

Metabolite/component	Forage		Fodder		Grain		Cobs	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
[^{14}C-Cyclopropyl] Permethrin								
Permethrin	21.2	0.375	63.9	23.52	-	-	0.7	0.001
trans-DCVA	15.5	0.274	3.3	1.22	-	-	-	-
cis-DCVA	2.5	0.043	1.2	0.474	-	-	-	-
Total identified	**39.2**	**0.692**	**68.4**	**25.21**	-	-	**0.7**	**0.001**
Organosoluble	45.8 (14; <9.5)	0.808	17.6 (11; ≤2.9)	6.42	42.1 (11; ≤7.6)	0.053	49.9 (9; ≤13.7)	0.049
Aqueous soluble	6.4	0.113	2.4	0.890	30.1	0.037	33.0	0.033
Unextracted	0.5	0.009	0.3	0.108	14.9	0.018	11.5	0.011
Total identified/ characterized	**91.9**	**1.622**	**88.7**	**32.63**	**87.1**	**0.108**	**95.1**	**0.094**
[^{14}C-Phenyl] Permethrin								
Permethrin	22.4	0.426	68.5	20.38	26.4	0.022	29.4	0.021
4-OH PBA	0.6	0.011	0.5	0.161	-	-	-	-
3-PBA	3.5	0.066	1.5	0.467	-	-	-	-
MPBA	9.9	0.189	3.3	1.006	-	-	-	-
4-OH-MPBA	-	-	0.3	0.104	-	-	-	-
Total identified	**36.4**	**0.692**	**74.1**	**22.12**	**26.4**	**0.022**	**29.4**	**0.021**
Organosoluble	51.4 (17; ≤2.5)	0.980	12.0 (8; ≤2.0)	3.47	24.3 (8; ≤14.1)	0.020	18.9 (3; ≤3.9)	0.013
Aqueous soluble	8.4	0.160	7.8	2.34	29.1	0.024	22.3	0.017
Unextracted	0.7	0.014	0.3	0.092	9.9	0.009	24.9	0.018
Total identified/ characterized	**96.9**	**1.846**	**94.2**	**28.12**	**89.7**	**0.075**	**95.5**	**0.069**

Table 2a. Summary of Characterization/Identification of ^{14}C Permethrin Residues in/on Cabbage Leaves Treated with [^{14}C-Cyclopropyl]Permethrin.

Compound	0-Day Samples		30-Day Samples		60-Day Samples	
	%TRR	PPM	%TRR	PPM	%TRR	PPM
Permethrin (cis/trans)	82.0	1.15	17.3	0.173	13.5	0.53
DCVA (cis/trans)	--	--	25.0	0.25	25.6	1.01
Characterized/Unknown	--	--	22.0	0.22	14.7	0.58
Total Char./ID	**82.00**	**1.15**	**64.30**	**0.64**	**53.80**	**2.12**
Unchar./Unknown	4.3	0.061	14.0	0.14	14.2	0.56
Total	86.30	1.21	78.30	0.78	68.00	2.68

Table 2b. Summary of Characterization/Identification of ^{14}C Permethrin Residues in/on Cabbage Leaves Treated with [^{14}C-Phenyl] Permethrin and Sampled at 0, 30 and 60 days Post-Treatment.

Compound	0-Day Samples		30-Day Samples		60-Day Samples	
	%TRR	PPM	%TRR	PPM	%TRR	PPM
Permethrin (cis/trans)	85.9	1.16	18.4	0.19	16.85	0.77
MPBA (alcohol)	--	--	15.2	0.17	13.3	0.61
3-PBA	--	--	0.40	0.004	0.40	0.018
4'OH MPBA (alcohol)	--	--	4.2	0.047	7.0	0.32
2'OH MPBA (alcohol)	--	--	1.25	0.014	2.62	0.12
4'OH MPBA (acid)	--	--	0.54	0.006	0.87	0.04
2'OH MPBA (acid)	--	--	0.18	0.002	0.33	0.015
Characterized/Unknown	--	--	7.2	0.081	8.1	0.37
Total Char./ID	**85.90**	**1.16**	**47.37**	**0.51**	**49.47**	**2.26**
Unchar./Unknown	3.0	0.041	57.1	0.64	10.1	0.46
Total	88.90	1.20	104.47	1.15	59.57	2.72

Table 3a. Summary of Characterization/Identification of ^{14}-C Residues from Application of [^{14}C-Cyclopropyl] Permethrin on Soybean Leaves

Compound	14-Day Samples		30-Day Samples		60-Day Samples	
	%TRR	PPM	%TRR	PPM	%TRR	PPM
Permethrin (cis/trans)	45.5	15.3	26.0	4.03	7.7	1.54
DCVA (cis/trans)	12.2	4.1	22.9	3.55	17.2	3.47
Characterized/Unknown	1.8	0.61	2.7	0.42	2.9	0.59
Total Char./ID	**59.50**	**20.01**	**51.60**	**8.00**	**27.80**	**5.60**
Unchar./Unknown	7.1	2.4	26.1	4.0	20.8	4.2
Total	66.60	22.41	77.70	12.00	48.60	9.80

Table 3b. Summary of Characterization/Identification of ^{14}C Permethrin Residues on Soybean Leaves Treated with [^{14}C-Phenyl] Permethrin.

Compound	14-Day Samples		30-Day Samples		60-Day Samples	
	%TRR	PPM	%TRR	PPM	%TRR	PPM
Permethrin (cis/trans)	46.6	13.2	26.6	7.73	14.0	3.4
MPBA (alcohol)	13.2	3.75	14.5	4.23	12.7	3.12
3-PBA	0.6	0.17	2.0	0.58	1.0	0.25
4'OH MPBA (alcohol)	3.7	1.05	5.2	1.5	5.4	1.33
2'OH MPBA (alcohol)	1.0	0.28	3.8	1.1	6.4	1.57
4'OH MPBAcid	1.7	0.48	1.6	0.47	1.6	0.39
2'OH MPBAcid	0.3	0.085	0.38	0.11	0.5	0.12
Characterized/Unknown	2.0	0.57	3.8	1.1	4.3	1.06
Total Char./ID	**69.10**	**19.59**	**57.88**	**16.82**	**45.90**	**11.24**
Unchar./Unknown	8.7	2.47	17.7	5.15	15.0	3.69
Total	77.80	22.06	75.58	21.97	60.90	14.93

Summary of Livestock Metabolism Studies:

- In orally and dermally dosed poultry and ruminants, the major residue in fat, muscle, milk, and eggs is permethrin.

- The major residues found in liver and kidney are DCVA and 3-PBA in orally and dermally dosed animals. Minimal permethrin is found in liver and kidney.

- DCVA and MPBA were found in the muscle of dermally treated hens at levels less than 20%TRR. DCVA was also found in the egg whites of orally treated hens at less than 11%TRR.

The qualitative nature of the residue in animals is adequately understood based upon acceptable poultry and ruminant metabolism studies using both oral and dermal dosing of [^{14}C]permethrin. The HED Metabolism Committee (C. Olinger, 2/1/96) has concluded that the residues of concern in animal commodities are the *cis*- and *trans*-isomers of both permethrin and DCVA. Tolerances are to be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound.

Oral and dermal metabolism studies have been conducted in ruminants and poultry. All studies were conducted with cyclopropyl- and phenyl-labeled permethrin in separate tests. The ruminant oral study was conducted at an approximately 1x rate, while the poultry oral study was conducted at a 116x rate. Dermal studies were conducted at a 1x rate per application, but with a much shorter retreatment interval. The poultry studies are considered adequate, but additional characterization of two organosoluble unknowns have been requested for the ruminant studies.

Results of the oral and dermal metabolism studies are presented in Tables 4 though 7. Permethrin was the major residue found in fat, muscle, milk, and eggs for orally and dermally dosed animals. Hydrolysis to DCVA and 3-PBA occurred in liver and kidney in the oral and dermal studies; minimal permethrin was found. MPBA was also found in the muscle of hens treated dermally.

Table 4. Summary of ^{14}-C Permethrin Residues in Goat Tissues and Milk Dosed Orally at a 1X Rate

	Liver[a)]				Kidney[a)]				Milk[b)]			
	Cyclo-label		Phenyl-label		Cyclo-label		Phenyl-label		Cyclo-label		Phenyl-label	
	TRR=1.18 ppm		TRR=0.91 ppm		TRR=1.04 ppm		TRR=0.78 ppm		TRR=0.17ppm		TRR=0.41 ppm	
Metabolite	%TRR	PPM	%TRR	PPM	%TRR	PPM	%TRR	PPM	%TRR	PPM	%TRR	PPM
Permethrin	--	--	2.0	0.018	--	--	--	--	46.5	0.08	55.5	0.23
Hydroxy-Permethrin	--	--	2.0	0.018	--	--	--	--	8.1	0.01	2.6	0.01
DCVA (cis+trans)	12.9	0.15	--	--	26.3	0.27	--	--	--	--	--	--
DCVA-Lactone	1.0	0.012	--	--	0.6	0.006	--	--	--	--	--	--
Hydroxy-DCVA[c)]	11.0	0.13	--	--	10.4	0.10	--	--	--	--	--	--
DCVA-Glucuronide	--	--	--	--	22.0	0.23	--	--	--	--	--	--
3-PBA	--	--	14.5	0.13	--	--	56.7	0.44	--	--	--	--
4'Hydroxy-3-PBA	--	--	10.7	0.097	--	--	--	--	--	--	--	--
Identified	**24.9**	**0.29**	**29.2**	**0.26**	**59.3**	**0.6**	**56.7**	**0.44**	**54.6**	**0.09**	**58.1**	**0.23**
Unknowns	63.4		58.9		37.1		30.4		29.9		25.3	
Total	88.3		96.4		85.4		87.1		84.5		83.4	

[a)] Goat #1 dosed with cyclopropyl-labelled permethrin and Goat #2 dosed with phenyl-labelled permethrin. [b)] Goat #2: day-4 milk samples. [c)] The peak corresponding to reference substance hydroxy-DCVA would on occasion split into two peaks; the amounts in the table given for hydroxy-DCVA represent theoretical maximums, only.

Radioactive residues in fat and muscle were too low for adequate quantification and are therefore not included in the table.

Table 5. Identification and Characterization of ^{14}C-Residues in Tissues and Eggs of Hens Dosed Orally with ^{14}C-Permethrin for Seven Days (ca. 116x)[1]

Metabolite	Day 6 Yolks		Day 6 Whites		Liver		Peritoneal Fat		Leg Muscle	
	Cyclo-label	Phenyl-label	Cyclo-label	Phenyl-label	Cyclo-label	Phenyl-label	Cyclo-label	Phenyl-label	Cyclo-label	Phenyl-label
TRR (ppm)	0.28	0.31	0.108	N/A[2]	0.16	0.28	0.37	0.31	0.026	0.025
Permethrin	57.6	56.7	51.9	-	-	-	78.4	77.4	30.7	33.7
4-OH-Permethrin	-	3.4	-	-	-	-	-	-	-	-
cis+*trans*-DCVA	<1	-	10.6	-	13.8	-	-	-	-	-
OH-Permethrin	-	-	-	-	-	-	5.4[3]	6.5[3]	-	-
Organosoluble	32.8	18.9	7.1	-	36.2	11.7	10.8	6.5	18.7	10.2
Aqueous Soluble	3.7	11.1	-	-	39.6	78.8	-	-	13.2	10.2
Unextracted	4.8	9.9	30.4	-	10.4	9.9	2.7	3.2	37.4	45.9

[1] All results are reported as %TRR unless otherwise noted. [2] N/A = not analyzed [3] Identity not confirmed by a second method.

Table 6a. Identification and characterization of ^{14}C-residues in tissues and eggs of hens treated dermally for 3 consecutive days with [^{14}C-cyclopropyl] permethrin at ~20 mg/hen/day (10.3 mg/kg body wt./day, 1x rate)

Metabolite/component	Liver (0.190 ppm) [a]		Leg Muscle (0.029 ppm)		Breast Muscle (0.014 ppm)		Subcutaneous Fat (0.216 ppm)		Mesenteric Fat (0.295 ppm)		Egg Yolk (0.089 ppm) [b]	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Permethrin	2.4	0.004	44.7	0.013	52.9	0.007	38.9	0.084	73.2	0.216	83.1	0.074
4-OH permethrin	4.1	0.008	6.6	0.002	3.8	0.001	-	-	-	-	-	-
trans/cis-DCVA	15.5	0.029	17.2	0.005	18.5	≤0.003	-	-	-	-	1.8	0.002
DCVA lactone	- [c]	-	-	-	-	-	-	-	-	-	0.8	0.001
Total Identified	**22.0**	**0.041**	**68.5**	**0.020**	**75.2**	**0.011**	**38.9**	**0.084**	**73.2**	**0.216**	**85.7**	**0.077**
Major Unknown(s) (>10% TRR)	36.3 [d]	0.069	-	-	-	-	13.9	0.030	-	-	-	-
Minor unknowns (<10% TRR)	18.9 (5; ≤8.3) [e]	0.036	3.5	0.001	7.1 (10; ≤7.1)	0.001	25.9 (4; ≤9.7)	0.056	10.8 (2; ≤7.1)	0.032	8.3 (5; ≤2.4)	0.008
Unresolved chromatographic radioactivity	6.6	0.012	17.3	0.005	1.9	<0.001	5.5	0.012	6.1	0.018	2.6	0.002
Organosoluble	1.4	0.003	-	-	-	-	2.8	0.006	7.3	0.022	0.7	<0.001
Aqueous soluble	10.3	0.020	10.5	0.003	20.5	0.003	11.0	0.024	<0.3	<0.001	0.6	<0.001
Total Identified/ Characterized	**95.3**	**0.181**	**99.8**	**0.029**	**104.7**	**0.015**	**98.0**	**0.212**	**97.4**	**0.288**	**97.9**	**0.087**
Unextracted	0.5	0.001	6.9	0.002	7.1	0.001	-	-	-	-	1.1	0.001

[a] TRR in each matrix; ppm values are expressed in [^{14}C]permethrin equivalents.
[b] Data from Day-3 egg yolk.
[c] "-" not detected.
[d] TLC analysis separated fraction into several minor polar components each accounting for ≤6.8% TRR (≤0.013 ppm).
[e] Values in parentheses are the total number of minor unknowns and the %TRR accounted for by each one.

Table 6b. Identification and characterization of ^{14}C-residues in tissues and eggs of hens treated dermally for 3 consecutive days with [^{14}C-phenyl] permethrin at ~20 mg/hen/day (10.3 mg/kg body wt./day, 1x rate)

	Liver (0.215 ppm) [a]		Leg Muscle (0.039 ppm)		Breast Muscle (0.011 ppm)		Subcutaneous Fat (0.277 ppm)		Mesenteric Fat (0.357 ppm)		Egg Yolk (0.076 ppm) [b]	
Metabolite/component	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Permethrin	0.9	0.002	59.9	0.023	51.9	0.006	59.0	0.163	78.5	0.280	72.4	0.055
4-OH permethrin	1.9	0.004	-	-	4.3	<0.001	-	-	-	-	-	-
MPBA	- [c]	-	6.6	0.003	3.8	<0.001	-	-	-	-	<1	<0.001
3-PBA	-	-	-	-	-	-	-	-	-	-	<1	<0.001
Total Identified	**2.8**	**0.006**	**66.5**	**0.026**	**60.0**	**0.006**	**59.0**	**0.163**	**78.5**	**0.280**	**72.4**	**0.055**
Major Unknown(s) (10% TRR)	26.1 [d]	0.056	-	-	-	-	-	-	-	-	-	-
Minor unknowns (<10% TRR)	33.5 (9; ≤9.8) [e]	0.072	-	-	7.4 (5)	<0.001	22.1 (5; ≤5.5)	0.061	6.8 (2, ≤3.9)	0.028	5.2 (5; ≤2.6)	0.004
Unresolved chromatographic radioactivity	8.0	0.017	5.1	0.002	2.5	<0.001	7.6	0.021	4.6	0.017	2.6	0.002
Organosoluble	1.5	0.003	-	-	-	-	4.0	0.011	3.9	0.014	1.3	0.001
Aqueous soluble	22.0 [f]	0.048	5.4	0.002	7717.8	0.002	2.3	0.006	0.7	0.002	1.2	0.001
Total Identified/ Characterized	**93.9**	**0.202**	**77.0**	**0.030**	**87.7**	**0.008**	**95.0**	**0.262**	**94.5**	**0.341**	**82.7**	**0.063**
Unextracted	1.9	0.004	23.1	0.009	18.2	0.002	-	-	-	-	-	-

[a] TRR in each matrix; ppm values are expressed in [^{14}C]permethrin equivalents.
[b] Data from Day-3 egg yolk.
[c] "-" not detected.
[d] TLC analysis separated fraction into 3 polar components each accounting for ≤8.8% TRR (≤0.019 ppm).
[e] Values in parentheses are the total number of minor unknowns and the %TRR accounted for by each one.
[f] Aqueous soluble residues from two fractions accounting for 12% and 10% of the TRR, respectively.

Table 7. Identification and characterization of ^{14}C-residues in milk and tissues of cows treated dermally for 3 consecutive days with either [^{14}C-cyclopropyl] or [^{14}C-phenyl]permethrin at 939-971 mg/cow/day (~2 mg/kg body wt./day, 1x rate)

	[^{14}C-cyclopropyl] Permethrin							
	Fat [a] (0.261 ppm) [b]		Kidney (0.133 ppm)		Liver (0.116 ppm)		Milk (0.061 ppm) [c]	
Metabolite/component	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Permethrin	67.8	0.177	0.8	0.001	5.2	0.006	90.6	0.055
trans/cis-DCVA	- [d]	-	6.0	0.008	10.4	0.012	-	-
Total Identified	**67.8**	**0.177**	**6.8**	**0.009**	**15.6**	**0.018**	**90.6**	**0.055**
Major Unknowns by R_t [e]:	-	-					-	-
39-42 min			-	-	19.5	0.023		
37-38 min			22.8	0.030	-	-		
31-33 min			27.8	0.037	-	-		
Minor unknowns [f] (each at <10% TRR)	14.2 (7; ≤6.9)	0.037	26.4 (6; ≤8.6)	0.036	14.7 (4; ≤6.9)	0.017	1.5	0.001
Unresolved chromatographic radioactivity	3.4	0.009	5.3	0.007	23.2	0.027	2.9	0.002
Aqueous soluble	0.4	0.001	<0.4	<0.001	4.3	0.005	2.8	0.002
Total Identified/ Characterized	**85.8**	**0.224**	**89.1**	**0.119**	**77.3**	**0.090**	**97.8**	**0.060**
Unextracted	1.5	0.004	4.5	0.006	6.9	0.008	0.6	<0.001
	[^{14}C-phenyl] Permethrin							
	Fat [a] (0.199 ppm) [b]		Kidney (0.169 ppm)		Liver (0.456 ppm)		Milk (0.053 ppm) [c]	
Metabolite/Component	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Permethrin	68.1	0.135	1.7	0.003	6.0	0.027	90.4	0.048
3-PBA	-	-	57.1	0.096	10.3	0.047	-	-
Total Identified	**68.1**	**0.135**	**58.8**	**0.099**	**16.3**	**0.074**	**90.4**	**0.048**
Major Unknowns by R_t [e]:	-	-	-	-			-	-
38-41 min					22.7	0.104		
30-33 min					16.2	0.074		
Minor unknowns [f] (each at <10% TRR)	15.6 (9; ≤3.5)	0.031	8.3 (4; ≤2.5)	0.014	15.0 (4; ≤5.8)	0.069	6.3 (2; ≤4.0)	0.003
Unresolved chromatographic radioactivity	7.0	0.014	5.4	0.009	2.1	0.010	2.2	0.001
Aqueous soluble	1.5	0.003	<0.6	<0.001	2.5	0.011	0.5	<0.001
Total Identified/ Characterized	**92.0**	**0.183**	**72.5**	**0.122**	**74.8**	**0.342**	**99.4**	**0.052**
Unextracted	0.5	0.001	1.8	0.003	2.4	0.011	0.07	<0.001

[a] Data presented are from analysis of renal fat; similar results were obtain from subcutaneous and omental fat.
[b] TRR in each matrix; ppm values are expressed in [^{14}C]permethrin equivalents.
[c] Data for milk are from Day-3 pm for [^{14}C-cyclopropyl] treatment and Day-2 pm for [^{14}C-phenyl] treatment.
[d] "-" not detected.
[e] Retention times are from HPLC analysis.
[f] Values in parentheses are the total number of minor unknowns and the %TRR accounted for by each one.

Rotational Crop Studies:

An adequate confined rotational crop study is available. These data indicate that residues of permethrin in rotational crops are qualitatively similar to the residues resulting from the direct application of permethrin to the primary crops. Based on this study and the label-specified 60-day plant-back interval, limited field rotational crop studies are required.

The registrants submitted protocols for limited field rotational crop studies and indicated their intent to support the 60-day plant-back interval that is currently specified on their labels. These protocols were reviewed and deemed acceptable by CBRS (CBRS No. 16869, DP Barcode, C. Eiden, 3/15/96).

FMC Corp. (1997; MRIDs 444028201, 44428202 and 44428203) submitted limited field studies of field accumulation of permethrin residues in rotational crops. Radishes (three trials, AZ, FL, and TX) and lettuce (two trials, AZ and FL) were planted 57-60 days following the last of 10 applications of the 3.2 lb/gal EC formulation at 0.2 lb ai/application (2.0 lb ai/A/season, 1x the maximum rate for any rotated crop). Spring wheat was planted 43-68 days following the last of five applications of the the 3.2 lb/gal EC formulation to winter wheat at 0.4 lb ai/application (2.0 lb ai/A/season); wheat trials were conducted in IN, KS, and WA. One control and two treated samples of lettuce, radish roots, and radish tops were harvested from each test. For wheat, forage samples were collected from all three tests, and grain and straw samples were collected from one test. Crop samples were stored frozen for up to 1 year prior to analysis. Adequate storage stability data are available from a variety of crops indicating that permethrin residues are stable for up to 19 months and that DCVA residues are stable for up to 36 months. The method is adequate for data collection.

Residues of *cis* and *trans* permethrin and DCVA were each <0.01 ppm (<LOD) in/on all crop samples tested; therefore, tolerances for residues of permethrin in/on rotated crops are not required, provided all labels specify a 60-day plant-back interval.

Residue Analytical Methods:

Adequate analytical methodology is available for data collection and enforcing tolerances of permethrin. One GLC/mass spectrometry (MS) method and six GLC/electron capture detection (ECD) methods are listed in PAM Vol. II (Section 180.378) for determining permethrin and its regulated metabolites in/on plant and animal commodities.

Method I is a GLC/ECD method for determining *cis*- and *trans*- permethrin in plant matrices that has undergone a successful EPA method validation on cottonseed. This method involves solvent extraction, partitioning into methylene chloride, and cleanup using Florisil chromatography prior to GLC/ECD analysis. Oil containing matrices are initially extracted with hexane and cleaned up by gel permeation chromatography prior to Florisil chromatography. The limit of quantitation (LOQ) is 0.05 ppm for each isomer.

Method II is a GLC/ECD method for determining *cis*- and *trans*- permethrin in animal matrices, and has undergone a successful EPA method validation on milk. This method involves acetone/hexane

extraction, partitioning into dimethylformamide and then hexane, followed by cleanup using Florisil chromatography. Residues are determined by GLC/ECD analysis. The LOQ is 0.01 ppm for each isomer.

Methods III and IIIa are similar GLC/ECD methods for determining MPBA and DCVA (*cis* and *trans*), respectively, in plant matrices, and have undergone a successful EPA method validation on soybeans. Residues are extracted into methanol/water, partitioned with methylene chloride, and acid hydrolyzed to release any conjugated metabolites. Free MPBA is partitioned into hexane, cleaned up using a Florisil column, derivatized with heptafluorobutyric anhydride, and further purified on a Florisil column prior to GLC/ECD analysis. Free DCVA is partitioned into hexane, derivatized to a butyl ester, and cleaned up on a Florisil column prior to GLC/ECD analysis. The LOQ is 0.01 ppm for MPBA and each isomer of DCVA.

Method IV is a GLC/MS and ECD method for determining 3-PBA and DCVA (*cis* and *trans*) in animal matrices that has undergone a successful EPA method validation on liver and milk. Residues are extracted into methanol/water, partitioned with organic solvent, and acid hydrolyzed to release any conjugated metabolites. Free 3-PBA is derivatized with heptafluorobutyric anhydride and determined by GLC/ECD analysis. Free DCVA isomers are derivatized to their methyl esters with diazomethane and determined by GLC/MS in the selected ion monitoring mode. The LOQ is 0.05 ppm for 3-PBA and each isomer of DCVA.

Method A is a GLC/ECD method for the analysis of permethrin in eggs that is essentially the same as Method II except that an additional clean up step is available for yolk samples following the Florisil column clean up. The LOQ is 0.01 ppm for each isomer of permethrin.

The Phase 4 Review noted that the enforcement method for determining DCVA residues in animal commodities (Method IV) utilized the hazardous reagent diazomethane and required the registrant provide justification for use of this reagent. In response, the registrant has proposed substituting (trimethylsilyl)diazomethane for diazomethane. Method validation data to show that residues of DCVA are adequately recovered from representative animal commodities when (trimethylsilyl)diazomethane as the derivatizing reagent and a revised method incorporating this reagent would be required. However, DCVA is not a regulated residue; therefore, these data are not required at this time.

Data on residues of permethrin and DCVA in/on plants and animals have been collected using adequate GLC/ECD and/or GLC/MSD methods that are similar to the above enforcement methods. Modifications to the above methods have included the use of different solvents for extraction and additional cleanup steps. The limits of quantitation for these methods range from 0.005-0.1 ppm for each isomer of permethrin and DCVA.

Multi-Residue Method:

The FDA PESTDATA database dated 1/94 (PAM, Vol. I, Appendix I) indicates that *cis*- and *trans*-permethrin are completely recovered using FDA Multiresidue Protocols D and E (fatty) (PAM I

Sections 232.4 and 212.1) and that recovery of permethrin through FDA Multiresidue Protocol E (nonfatty) (PAM I Section 211.1) is variable. Residues of DCVA are not recovered using FDA Multiresidue Protocols.

Crop Field Trials:

For purposes of reregistration, requirements for magnitude of the residue in plants are fulfilled for the following crops: alfalfa, almonds, apples, artichokes, asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cherries, corn (field and sweet), cucurbit vegetables, filberts, horseradish, lettuce, onions (dry bulb), peppers (bell), pistachios, potatoes, spinach, turnips (roots and tops) and walnuts. Adequate field trial data depicting permethrin residues following applications made according to the maximum or proposed use patterns have been submitted for these commodities. Geographical representation is adequate and a sufficient number of trials reflecting representative formulation classes were conducted. The adequate data from onion (dry bulb) will be translated to support the use on garlic, and data from bell peppers will be translated to support the use on eggplants.

Adequate data are available on soybeans, provided use directions for soybeans are amended to specify a minimum volume of 2 gal/A for aerial applications; otherwise, residue data supporting ULV applications to soybeans are required.

Additional residue data are required on avocados, collards, and grasses (rangeland) for purposes of reregistration. The requested residue data on avocados will be translated to support the use on papayas.

Additional information is required to upgrade the existing studies on mushrooms, peaches, pears, and tomatoes. Information on sample storage intervals and conditions is required to upgrade pear and tomato field studies. Adequate descriptions of the residue analytical methodology are required to upgrade the peach field studies. To upgrade the mushroom study, data are required depicting the stability of permethrin and DCVA in frozen mushroom stored for up to 1 year.

Outstanding requirements for residue data on avocado and collards are being fulfilled by IR-4.

Processed Food/Feed:

The reregistration requirements for magnitude of the residue in processed food/feed commodities are fulfilled for apple, corn (field and sweet), potatoes, soybeans, and tomatoes. The requested cottonseed processing study is no longer required as the registrants have deleted uses on cotton from all product labels. Based on the above processing studies, tolerances are not required on apple, corn (field or sweet), potato, soybean, and tomato processed commodities.

Residues of permethrin did not concentrate in plant processed commodities, with the following exceptions: apple pomaces (wet - 3x, dry - 10x), soybean hulls (1.4x), corn flour (1.3x), sweet corn cannery waste (~23x), and tomato pomaces (wet - 7x, dry - 5x). Dried apple pomace, sweet corn cannery waste, and tomato pomaces (wet and dry) are no longer regulated livestock feed items.

Although permethrin residues concentrated in wet apple pomace, corn flour, and soybean hulls, tolerances are not required as permethrin residues in these commodities are not likely to exceed the established Section 408 tolerances when processed from RACs treated at 1x the maximum use rate.

Data from the field corn processing study found permethrin residues in aspirated grain fractions at levels up to 1.47 ppm following a 2.7x exaggerated application rate. The registrant should propose a tolerance for aspirated grain fractions. Based upon the exaggerated application rate, an appropriate tolerance would be 1.0 ppm.

Magnitude of the Residue in Crops - Pending Petitions:

There are currently three active tolerance petitions from FMC or IR-4 pertaining to the use of permethrin on peas and beans (PP#4E2972), raspberries (PP#8E3675), and wheat (PP#7F3514). Toxicological considerations permitting, CBTS has recommended in favor of establishing a tolerance with regional registration at 1.0 ppm for residues of permethrin in/on raspberries grown only in OR or WA (CBTS No. 13200, DP Barcode D199077, M. Nelson, 5/13/94).

CBTS has also recommended in favor of establishing tolerances on wheat grain, forage, hay, and straw, provided a 45-day PHI is specified for wheat hay (CBTS No. 11089; DP Barcode D185941, G. Otakie, 3/18/94). However, a risk assessment by DRES determined that the addition of wheat tolerances would create an unacceptable cancer risk (J. Wintersteen, 6/29/94; B. Steinwand, 3/20/95). In response, FMC submitted a dietary exposure assessment to demonstrate that the dietary cancer risk is $<10^{-6}$ from all food/feed uses of permethrin, including the proposed wheat use. In its review of this assessment, CBRS reiterated its support for the wheat petition, provided toxicological considerations permit, and recommended that a DRES analysis for cancer risk be performed using anticipated residue data outlined in the review (CBRS No. 16813 and 16814, DP Barcode 222629, S. Funk, 6/28/96).

The petition for tolerances on pea and beans (PP#4E2972) is currently in reject status based upon deficiencies pertaining to analytical methodology and label directions (CBTS No. 12078, DP Barcode D192486, G. Kramer, 12/8/93).

Magnitude of the Residue in Meat, Milk, Poultry, and Eggs:

The reregistration requirements for magnitude of the residue in animal commodities are fulfilled provided acceptable data are submitted depicting the stability of permethrin and DCVA in representative animal commodities held in frozen storage for up to 1 year.

Adequate poultry and ruminant feeding studies are available provided storage stability issues are resolved. In addition, acceptable residue studies are available depicting permethrin residues resulting from direct applications to livestock and their housing. Although neither of the basic producers is supporting direct dermal applications of permethrin to livestock, numerous EPs currently exist for this use. The available residue data and the reassessed animal tolerances will support the following uses.

For direct application of permethrin to ruminants and their housing, the available residue data support repeated applications to livestock premises at a rate of 0.21 oz ai/1,000 ft^2 with a 14-day retreatment interval (RTI). The data also support direct applications to ruminants at 950 mg ai/animal (2 mg ai/kg body weight) with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 1-day preslaughter interval (PSI) should be specified for ruminants.

For direct application of permethrin to swine and their housing, the available residue data support repeated applications to swine housing at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to swine at 240 mg ai/animal with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 5-day PSI may be specified for swine.

For direct application of permethrin to poultry and their housing, the available residue data support repeated applications to poultry houses at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to hens at ~20 mg/bird with a 14-day RTI. A 1-day PSI should be specified for poultry.

Based upon residue data from feeding studies and studies involving direct applications to livestock and their housing, dietary exposure to permethrin residues is the route that can result in the highest potential residues in animal commodities. Therefore, data from the ruminant and poultry feeding studies were used as the basis for reassessing tolerances. As feeding studies are not available for swine, the ruminant feeding studies were used to reassess tolerances on hog commodities. The calculated theoretical dietary burdens for livestock that were used in calculating the reassessed tolerances are presented below:

Feed Commodity	% Dry Matter [a]	% Diet [a]	Reassessed Tolerance (ppm) [b]	Dietary Contribution (ppm) [c]
Beef Cattle				
corn forage, field	40	40	50.0	50
alfalfa meal	89	25	45.0	12.6
corn grain	88	35	0.05	0.02
TOTAL BURDEN		100		**62.6**
Dairy Cattle				
corn forage, field	40	50	50.0	62.5
alfalfa meal	89	15	45.0	7.5
alfalfa hay	89	35	45.0	17.7
TOTAL BURDEN		100		**87.7**
Poultry				
alfalfa meal	N/A	10	45.0	4.5
corn milled byproducts	N/A	60	0.05	0.03
corn grain	N/A	30	0.05	0.015
TOTAL BURDEN		100		**4.55**
Swine				
alfalfa meal	N/A	10	45.0	4.5
turnip roots	N/A	40	0.2	0.08
potato culls	N/A	50	0.05	0.025
TOTAL BURDEN		100		**4.61**

[a] Table 1 (August 1996).
[c] Reassessed tolerances from Table C.
[b] Contribution = [Reassessed tolerance / % DM (if cattle)] X % diet).

International Considerations:

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for permethrin residues in/on various plant and animal commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part A.1, 1995*). The Codex MRLs and U.S. tolerances are not compatible because the U.S. tolerance expression currently includes the parent permethrin and its DCVA and MPBA metabolites (also 3-PBA in animal commodities). However, the HED Metabolism Committee has recommended that the U.S. tolerance expression be amended to include only *cis*- and *trans*-permethrin (C. Olinger, 2/1/96). Once the U.S. tolerance definition is amended, it will be compatible with the definition for Codex MRLs.

TOXICOLOGY SECTION

Hazard Characterization

Permethrin, a racemic mixture of the cis and trans isomers, is a synthetic pyrethroid insecticide. It has been shown that increased content of cis isomer would increase its severity of clinical signs and toxicity. The current registered technical active product has a content of cis isomer ranging from 35% to 55%. The toxicology database of permethrin showed that studies of the test material has a content of cis isomer ranging from 25% to 50%.

Permethrin has a low acute toxicity (toxicity category 3 or 4) via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. Permethrin is a type I pyrethroid with the primary target organ of nervous system. The neurotoxic effects are consistently characterized by tremors, hyperactivity, and altered FOB observations. In studies where the liver is affected, it appears to be an adaptive response and is not considered an adverse effect. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted in urine and feces.

Developmental and reproductive toxicity studies demonstrated that there is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats. However, the HIARC determined that there is a concern for developmental neurotoxicity based on evidence of neurotoxicity and increased incidence of microscopic lesions associated with neurotoxic effects at high doses in a subchronic neurotoxicity study. A developmental neurotoxicity study (DNT) is required for permethrin.

The CARC classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route, with a Q_1^* of 9.567×10^{-3} $(mg/kg/day)^{-1}$. This classification was based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR information.

Summary of Toxicology Endpoint Selection for Permethrin

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	**Acute RfD** = No applicable	An appropriate endpoint attributable to a single dose was not identified.	
Acute Dietary (General population including infants and children	NOAEL = **25** mg/kg/day UF = **1000** **Acute RfD** = 0.025 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Chronic Dietary (All populations)	NOAEL= **25** mg/kg/day UF = **1000** **Chronic RfD** = 0.025 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.025 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Short-Term Incidental Oral (1 - 30 Days)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 1000	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Intermediate-Term Incidental Oral (1 - 6 Months)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 1000	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1 - 30 days)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Intermediate-Term Dermal (1 - 6 Months)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Long-Term Dermal (> 6 Months)	Oral NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Short-Term Inhalation (1 - 30 days)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Intermediate-Term Inhalation (1 - 6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Long-Term Inhalation (>6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" with Q_1^* (mg/kg/day)$^{-1}$ = 9.567 x 10^{-3}		

NOTE:* The Special FQPA Safety Factor recommended by the HIARC **assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

Critical Toxicity Studies

Acute Neurotoxicity

(1) In an acute neurotoxicity study (MRID 43046301), permethrin (95.3% a.i., Lot # PL90-269, cis:trans 50:50) was administered by gavage to Sprague-Dawley rats (4/sex/group) at dose levels of 0, 10, 150, or 300 mg/kg in corn oil. Following administration, the rats were assessed for clinical signs daily. FOB and motor activity assessments were made pre-test and at day 0, (at estimated time of peak effect) and days 7 and 14. After day 14, the rats were sacrificed and the nervous system assessed histopathologically.

Reactions to treatment were noted in the 300 mg/kg treated males and females only. The reactions attributed to treatment included one death (a female), tremors (all animals), staggered gait and gait impairment (8/sex), splayed hindlimbs (2 males, 6 females), decreased forelimb grip strength (21% decrease in males, 13.5% decrease in females) as well as other symptoms occurring in 2 or less animals but not in the controls (convulsion, ataxia, exaggerated hindlimb flexion, increased auditory response, uncoordinated landing). No evidence of compound related neurohistopathology was noted in tissues from animals perfused in vivo. **The LOAEL was 300 mg/kg based on tremors and gait impairment. The NOAEL was 150 mg/kg.**

This acute neurotoxicity study was classified **unacceptable/guideline** because the study was determined to have used inappropriate dose levels and dosing volume of corn oil. A pilot study was reported to indicate clinical signs due to treatment with 50 mg/kg of permethrin when administered as a 10% corn oil solution. The main study was assessed using a 1% corn oil solution and the LOAEL was determined to be 300 mg/kg or 4 times greater. The 1% corn oil solution required dosing the rats with 30 ml/kg for the control and high dose groups and 15 ml/kg for the mid-dose group and 1 ml/kg for the low-dose group. It is considered that dosing with volumes greater than 10 ml/kg results in confounding the interpretation of the study data because of potential effects on compound absorption.

However, the Toxicology Branch has determined that the requirement for an acute neurotoxicity screen study has been satisfied when taken together with another acute oral neurotoxicity study (MRID 45657401, McDaniel and Moser, Neurotoxicology and Teratology 15:71-83, 1993).

(2) In a published literature study (MRID 45657401), permethrin (95%, a.i., cis:trans 50:50) was administered by gavage to Long-Evans rats (8/sex/group) at dose levels of 0, 25, 75, or 150 mg/kg in corn oil. FOB and motor activity were assessed prior to dosing and at 2, 4, 24 and 48 hours after dosing.

At 75 mg/kg, the rats displayed a general pattern of increased excitability and aggressive behavior. Some of the more pronounced responses included abnormal motor movement (3/8, both sexes) decreased grip strength for forelimb (males) and hindlimb (males and females), motor activity (males), and increased body temperature (males). At 150 mg/kg, arousal score (males), righting reflex (males) and approach response score (females) were affected and 7/8 of both sexes had abnormal motor movement and motor activity was further decreased and body temperature was increased >2°C. Slight decreases in body weight (3-4%) were evident. Recovery from the symptoms was within 24 hours. **The LOAEL is 75 mg/kg based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature. The NOAEL is 25 mg/kg.**

The study is classified as **acceptable/nonguideline.** Study is in the form of a literature reprint and was not designed to meet a specific guideline protocol.

Subchronic Neurotoxicity

(1) In a subchronic neurotoxicity study (MRID 42933701), permethrin (95.3% a.i., Lot# PL90-269, cis:trans 50:50) was administered via diet to Sprague-Dawley rats (10/sex/group) at dose levels of 0, 250, 1500, or 2500 ppm (0, 15.49, 91.51, or 150.35 mg/kg/day for males and 0, 18.66, 111.37, or 189.63 mg/kg/day for females, respectively) for 13 weeks. Assessments for clinical signs were made daily and FOB and motor activity assessments were made at pretest, and 4, 8, and 13 weeks of the study. Following sacrifice, the control and high dose group rats were perfused and subjected to histopathological assessment.

Reactions to treatment noted in the 1500 ppm dose group included tremors (in 3 males and 5 females), staggered and/or impaired gait, splayed hindlimbs, increased landing feet splay and abnormal posture and decreased grip strength. Only splayed hindlimb and staggered gait were noted in the FOB battery at 1500 ppm. At 2500 ppm, all of the rats had tremors, staggered gait and splayed hindlimbs. Staggered gait and splayed hindlimbs started later. No effects on motor activity or neurohistopathological lesions were noted. Body weight in the high dose group males was 5% decreased and a corresponding slight decrease in food consumption was also noted for this group. **The LOAEL for neurotoxicity is 1500 ppm (91.51 mg/kg/day in males) based on clinical signs (tremors and staggered gait). The NOAEL is 250 ppm (15.49 mg/kg/day).**

This subchronic neurotoxicity study is classified **acceptable/guideline** and satisfied guideline requirement for a subchronic neurotoxicity study.

(2) In a preliminary subchronic oral neurotoxicity study (MRID 00071952), groups of 10 male Wistar rats were administered 2500, 3000, 3750, 4500, 5000, or 7500 ppm of permethrin (PP 557) in the diet for 14 days. The isomeric ratio of the test article (Batch No. P48; 90.4% a.i.) was 39.9% cis and 60.1% trans. Based on a food factor of 0.05 for the rat, doses for the treated groups were 125, 150, 187.5, 225, 250, and 375 mg/kg, respectively. Each treated group had a paired control group consisting of litter mates with similar body weights. Toxicity assessments were limited to clinical observations, measurements of body weights and food consumption, and light and electron microscopic evaluation of the sciatic nerve.

At 7500 ppm six rats were found dead on day 1 and the remainder were sacrificed *in extremis* on day 1 or 2. Prior to sacrifice the animals were observed with convulsive tremors and excessive salivation and those animals for which data were available showed marked weight loss and decreased food consumption. In the 5000-ppm group, two rats were found dead on day 1 and six were sacrificed on day 2; convulsive tremors were observed in one animal prior tc death.

Slight to moderate whole body tremors were observed initially in all animals in the 2500 and 3000 ppm groups but almost complete remission occurred by day 5. Moderate tremors were seen in most animals of the 3750 and 4500 ppm groups which lessened during the study but were still evident on day 14. Also at 3750 and 4500 ppm hyperactivity and hypersensitivity to noise were observed mainly during the first 7 days. In the two surviving 5000-ppm animals, slight to moderate tremors were observed until day 10.

Mean absolute body weights of the 3000-, 3750-, and 4500-ppm groups were significantly ($p \leq 0.05$ or 0.01) less than their paired control group weights beginning on day 1 and continuing until termination. Body weights of the surviving 5000-ppm animals were also clearly less than the control. Body weight gains by the 2500-, 3000-, 3750-, 4500-, and 5000-ppm groups were 81%, 60%, 61%, 28%, and 22%, respectively, of their control group level during the first week. However, during the second week body weight gains by all treated groups were 98-104% of the control levels with the exception of the 5000-ppm group which was 83% of the controls.

Food consumption for the first week was significantly ($p \leq 0.01$) reduced in all treated groups to 67-84% of their paired control group levels. Consequently, food utilization was increased in a dose-related manner for all treated groups as compared with the control groups.

The number of rats with degenerating nerve fragments in the treated and paired control groups was 5/10 each at 2500 ppm, 8/10 and 2/9, respectively, at 4500 ppm, and 6/10 and 2/10, respectively, at 5000 ppm. The number of fragments per nerve ranged from 1-5 for animals in the control, 2500-, and 4500-ppm groups and for animals in the 5000 ppm group that died or were killed intercurrently. In contrast, the two surviving rats in the 5000 ppm group had 19 and 44 fragments respectively.

Nerves from rats in the 2500- and 5000-ppm groups were also examined by electron microscopy. No treatment-related abnormalities were observed in the 2500-ppm group. At 5000 ppm, the ultrastructural changes observed were similar in animals that died and in the two rats that survived to scheduled termination. In the unmyelinated nerves, 7/7 rats given 5000 ppm had degenerative changes including axonal swelling, disorganization of the neurofilaments, an increase in multivesicular-type and vesicular structures, and vacuolation. Only a minimal increase in vesicular structures was observed in 3/7 paired controls. Mild to marked vacuolation of the Schwann cell cytoplasm was seen in 5/7 rats treated with 5000 ppm and mild vacuolation was seen in 2/7 controls. Also in the Schwann cells, dense bodies occurred in the cytoplasm of 6/7 treated rats vs. 0/7 controls and hypertrophy and increased nuclear chromatin with multiple nucleoli were seen in 5/7 treated and 1/7 control rats. Intercellular vacuolation was observed in 4/7 treated and 1/7 control rats.

Therefore, the systemic and neurotoxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neurotoxicity NOAEL was not identified for this preliminary study.

This study is classified **acceptable/nonguideline** and does not satisfy the requirements for a subchronic oral neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats.

(3) In a subchronic oral neurotoxicity study (MRID 40766807), Sprague-Dawley rats (10/sex/group) were administered Permethrin (98%, 40:60 cis/trans, Lot No. PL85-216) in acetone at concentrations of 0, 100, 200, or 400 mg/kg/day in the diet for 90 days (main study). Two control groups were included, one was an untreated control group and the other was a vehicle (acetone treated diet) control group. After the 90 days, the rats in the main study were sacrificed by a special procedure designed to allow for fixation of the nervous system *in situ*. The experiment also included a special recovery component that consisted of 10 male and 10 female rats in the 400 mg/kg/day and untreated control groups; these animals were sacrificed 6 weeks after the completion of dosing after being maintained on untreated control diet. Neurological tissues fromcontrol and high-dose animals were examined microscopically. Functional observational battery (FOB) and motor activity testing were not performed.

There were no treatment-related deaths. Clinical signs included hyperexcitability, intermittent tremors, and irritability in mid-dose males during the first 3 weeks of treatment and intermittent tremors in mid-dose females during the first week of treatment. High-dose rats exhibited hyperexcitability, intermittent and continuous tremors, twitching, nystagmus (males only) and combativeness (males only) throughout the treatment period. Body weight gain was decreased 6 to 13% in high-dose males from treatment week 11 to post-dosing week 2; and 5 to 9% in high-dose females compared to controls from weeks 3 to 13. No treatment-related food consumption effects were noted. There were no gross lesions associated with treatment and there were no microscopic observations indicative of a neurotoxic effect.

The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.

This study is classified **acceptable/nonguideline**. The data provide useful information suggesting no morphological or histological effects in rats fed 400 mg/kg/day for 90 days.

(4) In a nonguideline repeated dose oral neurotoxicity study (MRIDs 00059066 and 00070627), groups of 10-16 Sprague-Dawley rats/sex/dose were administered 700, 2000 or 6000 ppm of NRDC 143 (Lot No.: 60307, 93.3% a.i.; 45 *cis*:55 *trans*) in the diet for 8 days. Additional groups of 8-10 animals/sex served as controls. Doses for the treated groups were 57, 160 or 454 mg/kg/day, respectively, males and 58, 198 or 453 mg/kg/day, respectively, females. Toxicity assessments were limited to clinical observations, body weights, food consumption and microscopic evaluation of the brain, spinal cord and sciatic nerve. In addition, groups of 16 Sprague-Dawley rats/sex/dose group were treated with three other synthetic pyrethroids: NRDC 149 at 500, 1500 or 3000 ppm (average daily dose levels 42, 72 or 126 mg/kg/day, males and 37, 80 or 115 mg/kg/day, females); S3206 at 1000 ppm (77 mg/kg/day, males or 58 mg/kg/day, females) and S5602 at 3000 ppm (146 mg/kg/day, males or 142 mg/kg/day, females) and were similarly evaluated.

At 6000 ppm permethrin, a total of 3 males and 2 females died during the study; one each on day 5 and the remainder on day 6. In addition, 4 moribund high-dose rats of each sex were sacrificed on day 7 and again on day 8. Clinical signs of toxicity, including severe tremor and muscle twitch, were reported in high-dose males and females beginning on day 1, but the frequency of these signs was not given. Body weight gains by the high-dose males and females (taken on day 7) were -74% and -58% lower than their respective control group levels (mean body weights were about -8.4% below controls, both sexes). Food consumption was not affected at any dietary concentration. No clinical signs of toxicity or mortalities and no effects on body weight gains occurred in the low- and mid-dose groups. Very slight or slight swelling of the sciatic nerve fibers was seen in 5/5 high-dose males and females, but only very slight swelling was observed in 6/15 control males, 5/13 control females, 1/8 low-dose males and 1/9 mid-dose females. No abnormalities were noted in the brains or spinal cords from any high-dose or control animal. Findings in the brains and spinal cords from the low- and mid-dose groups were not reported. **The LOAEL is 6000 ppm (453 mg/kg/day, females; 454 mg/kg/day, males) based on mortality, clinical signs of toxicity, decreased body weight gain and microscopic lesions in the sciatic nerve. The NOAEL is 2000 ppm (160 mg/kg/day, males; 198 mg/kg/day, females).**

Similar clinical findings (mortality, clinical signs in addition to tremor including hindlimb ataxia, erratic jumping and hypersensitivity) and neuropathology (sciatic nerve swelling, fiber disintegration and/or occasional nodal demyelination) were observed at variable incidence with NRDC 149 (3000 ppm), S3206 (1000 ppm)and S5602 (3000 ppm). Body weight/weight gain decreases were observed in all groups. Effects at 1500 ppm NRDC 149 included slight hypersensitivity, decreased body weight/weight gain and in females, very slight sciatic nerve fiber swelling and disintegration. No findings were reported at 500 ppm NRDC 149. NOAELs were not established for S3206 or S5602 in these studies.

This study is classified **unacceptable/nonguideline (upgradable)** and does not satisfy the requirements for a subchronic oral neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats.

Metabolism

All submitted metabolism studies on permethrin were classified unacceptable/guideline based on deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article). However, consider all metabolism studies together, it provides information on absorption, distribution, and excretion. Executive summaries are as follows.

(1) In a series of metabolism and disposition experiments (MRID 00089006, 00054719), male and female Wistar-derived rats were placed on various oral treatment regimens with [^{14}C-alcohol]permethrin ([^{14}C-cyclopropyl]permethrin) or [^{14}C-acid]permethrin ([^{14}C-benzyl]permethrin). For MRID 00054719, [^{14}C-acid]permethrin (>98% purity, 53:47, cis trans ratio) or [^{14}C-alcohol]permethrin (99% purity, 40.5:59.5 cis:trans ratio) were diluted as needed with nonlabeled permethrin (93.6% purity, 40.5:59.5, cis:trans ratio) and given by gavage to two male and two female rats at a dose of 6.5 mg/kg for quantitative and qualitative assessment of excretion. In MRID 00089006, tissue distribution and blood kinetics were assessed in male and female Wistar-derived rats given repeated or single oral doses of [^{14}C-acid]permethrin (>98% purity; 53:47, cis:trans ratio) or [^{14}C-alcohol]permethrin (99% purity, 38:62 cis:trans ratio)

These studies provided information on the excretion and tissue burdens of permethrin in rats following single or multiple oral doses of either alcohol ([^{14}C-cyclopropyl]permethrin) or acid [^{14}C-benzyl]permethrin). Based upon a limited number of rats, overall recovery was 93.7% to 101% regardless of label position. Following a single oral dose of 6.5 mg/kg, most radioactivity (58-65%) from a single dose of the [^{14}C-alcohol] permethrin was eliminated via the urine over a 7-day period with much of the remainder (29-43%) being excreted in the feces. Urinary excretion of radioactivity following a single dose of [^{14} C-acid] permethrin was slightly less and fecal excretion correspondingly greater. Results of tissue distribution and autoradiographic experiments showed that most radioactivity was associated with adipose tissue and, initially, with the gastrointestinal tract and organs/tissue associated with excretory function. Following oral administration to rats, most permethrin-associated radioactivity appears to be excreted within 48 hours. Following multiple doses, radioactivity in adipose tissue appears to be greater for [^{14}C-alcohol] permethrin than for [^{14}C-acid] permethrin. This is also consistent with blood kinetics data showing lower radioactivity (C_{max}) in the blood of rats receiving [^{14}C-acid] permethrin. Upon cessation of dosing, radioactivity levels in adipose tissues declined. There was no attempt to identify the metabolites in these studies.

(2) In a metabolism study (MRID 00102185), male Wistar-derived rats were given a single low dose (2.0 mg/rat) or single high dose (20 mg/rat) of permethrin ([^{14}C-cyclopropane]permethrin, 40:60 cis-trans ratio and non-labeled permethrin, 38.2:59.3 cis-trans ratio; no purity or lot/batch nos. for either) intragastrically. Feces and urine collected one day prior to dosing and for three days postdose were analyzed for radioactivity and metabolites.

These experiments provided an initial and cursory effort at identification and quantitation of major metabolites in the urine and feces of rats following single oral doses (2 or 20 mg/rat) of [^{14}C-

cyclopropane]permethrin. Approximately 78.5% of the administered radioactivity was recovered over the 3-day experimental period (dose group not specified). A conjugated metabolite, 3-(2,2-dichlorovinyl)-1-methylcyclopropane-1,2-dicarboxylic acid, was identified in both the urine and feces that reportedly accounted for approximately 2.2% of the administered dose. No additional data were provided regarding characterization of the remaining recovered radioactivity.

(3) In a metabolism study (MRID 00065903), groups of rats were given oral doses (1.6-4.8 mg/kg) of radiolabeled isomers ([^{14}C-acid] or [^{14}C-alcohol] labeled) of permethrin (radiochemical purity >99%; no lot/batch nos.) in dimethylsulfoxide vehicle. Metabolism and disposition was assessed over a 4 to12-day period

Recovery of administered radioactivity was 97-100% at 12 days after administration of the test article. The test material appeared to be rapidly absorbed and excreted in the urine and feces. Quantitative differences in excretion profile were characterized by greater amounts of *trans*-permethrin in the urine suggesting greater metabolism of the *trans* isomer than the *cis* isomer. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates of these products. Qualitative differences in metabolite profiles were also noted for the two isomers. Excretion of radioactivity via expired air was negligible. Fat tissue, liver, and kidney contained the highest levels of radioactivity, although there did not appear to be potential for sequestration at the dose regimens studied. The study authors concluded that the metabolism in rats of the *cis* and *trans* isomers of permethrin was characterized by ester cleavage, oxidation at the *cis* or *trans* methyl group of the dimethyl moiety, and oxidation at the 2' or 4' position of the phenoxy group.

(4) Two metabolism studies were conducted using adult Beagle dogs. In MRID 0054721, groups of four male and four female beagle dogs were given [^{14}C-alcohol]permethrin (PP557; 59.7 mCi/mM; purity not reported) or [^{14}C-acid]permethrin (PP557; no lot/batch nos.; 1.87 mCi/mM; purity 99%) as a single oral dose (6.5 mg/kg and 6.2 mg/kg, respectively) in a gelatin capsule. Excreta were collected over a 7-day period and tissues collected and analyzed at termination. In MRID 00042160, two beagle dogs (gender not specified) were given 10 daily doses (1.0 mg/kg via gelatin capsules) of [^{14}C-alcohol]permethrin (PP557; 59.7 mCi/mM; purity not reported). Excreta were collected after seven days and adipose tissues analyzed at termination.

These experiments provided preliminary information regarding the metabolism and disposition of permethrin in dogs. Data were insufficient for determination of definitive mass balance for administered radioactivity. Following oral administration of a single dose of [^{14}C-alcohol]permethrin (6.5 mg/kg) or [^{14}C-acid]permethrin (6.2 mg/kg), approximately 84-87% of administered radioactivity was eliminated via the feces and urine in 24-48 hours (MRID 000054721). Fecal excretion (~45-56% of dose) was somewhat greater than urinary excretion (~30-38% of dose) and the rate of excretion was slightly less for the [^{14}C-alcohol]permethrin. At seven days postdose, radioactivity was detected in the tissues selected for analysis (peri-renal and subcutaneous fat, liver, kidney, lung, heart, blood, and brain). The highest tissue levels (0.5-0.7 µg eq./g) were found in the fat tissues. Although radioactivity was detected in all tissues seven days following the single oral dose, levels were minimal and there was no evidence for significant sequestration. Following a single oral dose, TLC analysis of organic solvent

extracts revealed up to four metabolites in the urine and six in the feces, none of which were characterized. The excretory pattern for dogs given multiple doses of [^{14}C-alcohol]permethrin (1.0 mg/kg/day for 10 days) (MRID 00042160) was similar to that observed for the single dose study. The repeat-dose study also provided preliminary data showing a shift in the cis:trans ratio (an increase in the cis isomer) of residues in peri-renal and subcutaneous fat, and noted that this shift was indicative of a preferential metabolism of the trans isomer.

Quantification of metabolites

No data on quantification of metabolites are available. Studies indicated that permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates.

A proposed metabolic pathway of permethrin in the rat is shown in Figure 2 (The best available copy).

ENVIRONMENTAL FATE

The name of the chemical is permethrin. This chemical is currently used in numerous crops such as apples, avocados, cherries, nectarines, peas, almonds, pistachios, filberts, walnuts, broccoli, brussel sprouts, cauliflower, collards, cabbage, cucurbits, leafy vegetables, eggplants, peppers, tomatoes, onions, garlic, potatoes, corn, and soybeans. Up to ten applications are permitted per season. The maximum seasonal application rate is 2.0 lb a.i./A.

Environmental Persistence

Permethrin appears to dissipate primarily through binding to the soil, and by soil microbial degradation. It does not degrade through abiotic means (hydrolysis or photolysis).

The moderately high reported half-life for permethrin by aerobic soil metabolism was 37 days. The major degradates reported were $^{14}CO_2$ (34-40% after 6 months), trans-DCVA and 3-(2,2-dichlorovinyl)-2-methylcyclopropane-1,2-dicarboxylic acid, and 3-PBA. In an acceptable aerobic aquatic metabolism study the reported half-life ranged from 38 to 42 days. The half-life in an anaerobic soil metabolism study was 204 days when applied at a rate of 3.2 lb ai/A. The major degradates were trans-DCVA and 3-PBA. The half-life reported for permethrin in an anaerobic aquatic study ranged from 113 days to 175 days which indicates that the degradation in soil is slower as the oxygen levels are reduced.

Selected Environmental Fate Parameters of Permethrin

Parameter	Value	Source
Hydrolysis Half-Life (pH 6-7.6)	Stable	102043, 112936
Aerobic Soil Metabolism Half-Life	37 days	42410002
Aerobic Aquatic Metabolism Half-life	43 days	43938201
Aqueous Photolysis Half-Life	80 days	40242801 and additional supplemental data

Expected Mobility

Permethrin was immobile in five soils tested (see table below).

Summary of Batch Equilibrium Adsorption/Desorption Studies for etoxazole:

MRID#	K_d range	K_{OC} range	mobility classification
41868001	344-1517	28,200-194,000	immobile*
45170102	1420-2420	139000-491000	immobile*
*immobile is K_{OC}>5000			

Permethrin has a vapor pressure of 2.15×10^{-8} mm Hg=2.83×10^{-11} atm, water solubility of 0.07 ppm=1.8×10^{-4} mol/m^3, and an estimated Henry's Law constant of 1.6×10^{-7} atm•m^3/mol. Based upon its Henry's Law constant, permethrin is expected to have a relatively low potential for volatilization from water. It's potential for volatilization from soil should be lower due to its relatively high soil/water partitioning.

Environmental Metabolites

The major degradates observed in the laboratory studies were 3-PBA, trans-DCVA, and 3-PB-alcohol. Of these degradates, the later was observed only in the hydrolysis study at pH 9 only, since at neutral pH's, the solutions were relatively stable. Metabolism degradates were 3-PBA and trans-DCVA. They were shown to be highly mobile as they were weakly sorbed to various soils tested (see summary table below).

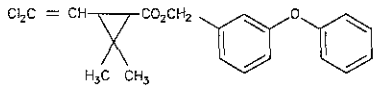
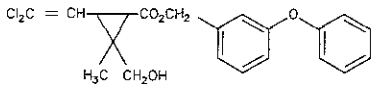
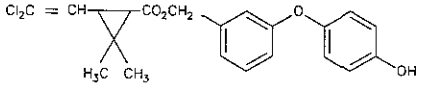
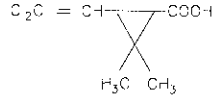
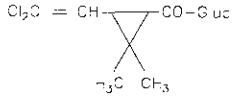
Summary of Batch Equilibrium Adsorption/Desorption Studies:				
Compound	**MRID#**	**K_d**	**K_{OC} range**	**mobility classification**
trans-DCVA	43424901	0.16-0.54	18-48	very mobile
mPBAcid		0.98-3.11	118-215	

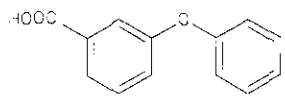
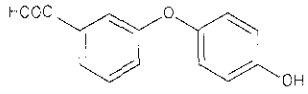
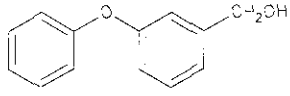
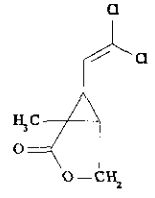
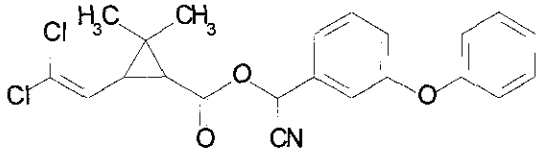
Summary table of results of laboratory studies for *Permethrin* and its major transformation products.		
Parent and Degradate Short Names:	**Study Name:**	**Results (calculated or observed half-life, degradates, and quantities in % of the applied):**
Permethrin	Hydrolysis (pH~7)	stable
	Photolysis in Water	$t_{½}$ = 80 days
	Photolysis on Soil	relatively stable
	Aerobic Soil Metabolism	$t_{½}$ = 37 days (trans isomer degraded slower)
	Anaerobic Soil Metabolism	$t_{½}$ =204 days (extrapolated)
	Aerobic Aquatic Metabolism	$t_{½}$ = 41 days
	Anaerobic Aquatic Metabolism	$t_{½}$ = 113-175 days
m-PBA	Aerobic Soil Metabolism	maximum 12-15% on day 30 of 365
	Anaerobic Soil Metabolism	maximum 12% on day 60 of 60 of anaerobic incubation
m-PB-alcohol	Hydrolysis	maximum 15.5% of the applied (in the pH 9 solution only)
cis/trans-DCVA	Hydrolysis	maximum 6.5% (total of two isomers) of the applied
	Aerobic Soil Metabolism	maximum 10% on day 14 of 365
	Anaerobic Soil Metabolism	trans-DCVA maximum 13% on day 60 of 60 of anaerobic incubation
	Aerobic Aquatic Metabolism	trans-DCVA maximum 20.0% on day 21 of 30
	Anaerobic Aquatic Metabolism	trans-DCVA maximum 20.8% on day 90 of 367

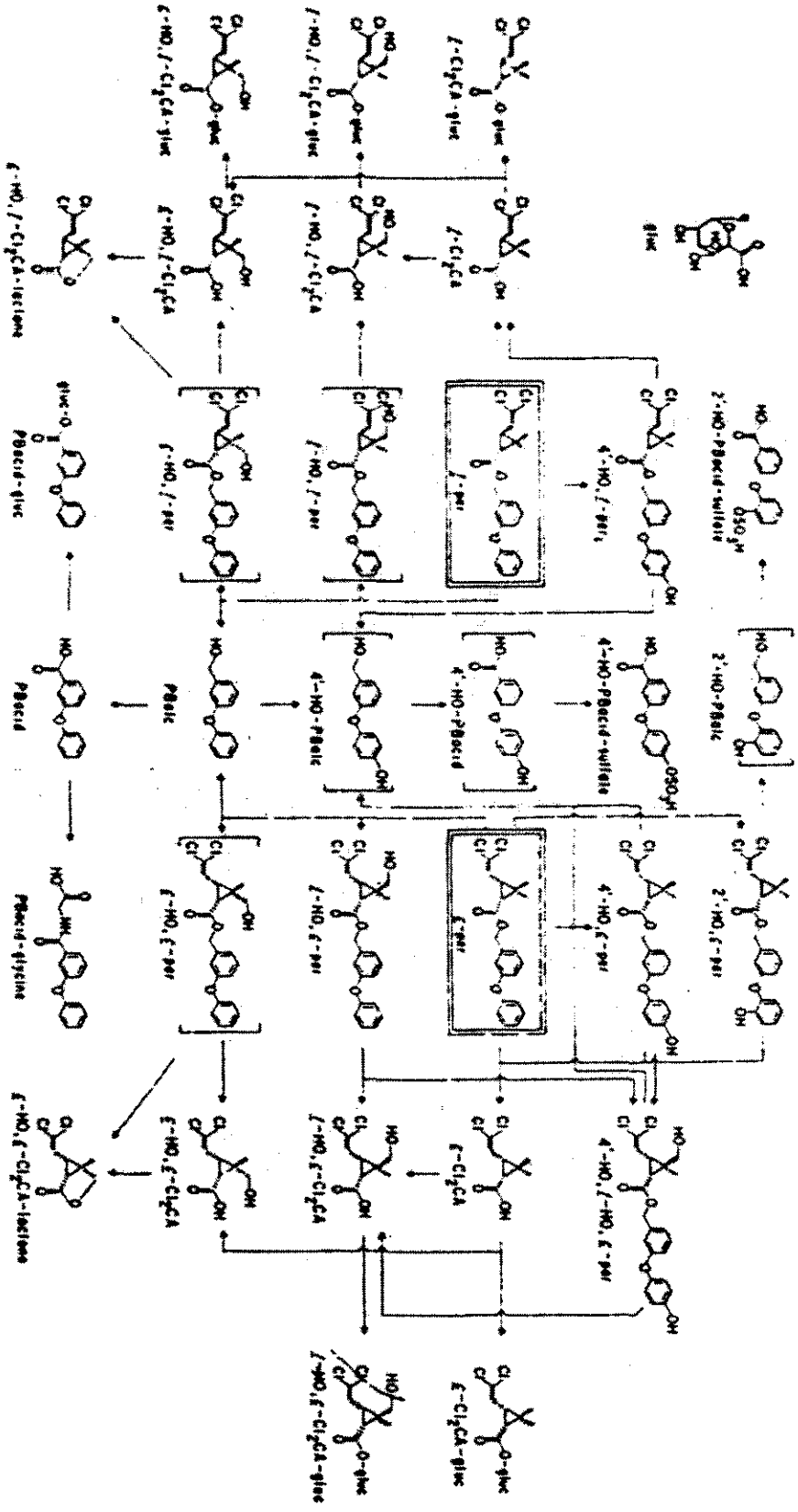
The fact that permethrin is very strongly adsorbed to soils (as evidenced by the very high K_{oc} values >>5,000), suggests that it could be mitigated in water treatment systems (e.g., by flocculation).

Refer to the above table and narrative, as well as the summary table of physicochemical and environmental fate properties of permethrin below.

Figure 1. Chemical names and structures of permethrin and its regulated and identified metabolites in poultry tissues and eggs[a].

Common Name/Chemical Name	Chemical Structure	Matrices
Permethrin 3-phenoxybenzyl(1RS)-*cis-trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate		Corn forage and fodder; cabbage leaves; soybean leaves Poultry: liver, fat, muscle, and egg yolk Ruminant: muscle, liver, kidney, fat, and milk
Hydroxypermethrin 3-phenoxybenzyl 1-(*RS*)-*cis-trans*-3-(2,2-dichlorovinyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylate		milk
4′-Hydroxypermethrin[b]		Poultry: liver and muscle
DCVA (*cis*- and *trans*-) 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid		Corn forage and fodder; cabbage leaves; soybean leaves. Poultry: liver, muscle, and egg yolk Ruminant: liver and kidney
***Trans*-DCVA-glucuronide** (Glu = glucuronic acid)		kidney urine

Common Name/Chemical Name	Chemical Structure	Matrices
3-PBA 3-phenoxybenzoic acid		cabbage, soybean leaves, and sweet corn forage and fodder egg yolk kidney and liver
4′-Hydroxy-3-PBA 4′-hydroxy-phenoxybenzoic acid		liver cabbage, soybean leaves, and sweet corn forage and fodder
MPBA (3-phenoxyphenyl)methanol 3-phenoxybenzyl alcohol		cabbage, soybean leaves, and sweet corn forage and fodder
DCVA lactone 3-(2,2-dichlorovinyl)cyclopropane-1,2-carbolactone		Poultry: egg yolk (tentative)
Cypermethrin		Related chemical



Attachment A.	**Nomenclature of Permethrin and its Degradation Products**
permethrin	3-phenoxybenzyl(1RS)-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate 3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester m-phenoxybenzyl (+/-)cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate Cyclopropanecarboxylic acid, 3-(2,2-dichlorovinyl)-2,2-dimethyl-, 3-phenoxybenzyl ester, (+-)-, (cis,trans)- 3-Phenoxybenzyl 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropanecarboxylate 3-Phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate 3-phenoxy benzyl (1RS)-cis,trans-3-(2,2 dichlorovinyl)-2,2 dimethyl-cyclopropane carboxylate
3-PBA or m-PBA	3- phenoxybenzyl acetic acid
3-PB-alcohol	3-phenoxybenzyl alcohol
cis/trans-DCVA	cis/trans 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid

Attachment B. Summary of Physicochemical and Fate Properties of Permethrin

Parameter	Value	Reference/Comments *
	Selected Physical/Chemical Parameters	
Molecular Weight	391.30 g/mol	ChemIndustry.com Database
Chemical Formula	$C_{21}H_{20}Cl_2O_3$	Various Sources
CAS No.	52645-53-1	Various Sources
Appearance	Colorless, odorless crystalline solid	Various Sources
Melting Poing	34-35°C	Various Sources
Boiling Point	200-220°C at 0.05 mm Hg	Various Sources
Density	1.19	Various Sources
Specific Gravity	1.190-1.272	Various Sources
Water Solubility (25°C)	0.07 mg/L	Reported by EFED
(20°C)	0.2 mg/L	Various Source
	0.220 mg/L 0.130 mg/L	MRID# 42109801
	0.0055 mg/L (average of 3 values)	Wollerton, C. 1987. Zeneca Summary September 2, 1987
Solubility in Organic Solvents	Soluble in most organic solvents except ethylene glycol	Various Sources
Vapor pressure (25°C)	$1.5x10^{-8}$ mm Hg (average of 2 values)	MRID# 42109801
	$2.15x10^{-8}$ mm Hg	Reported by EFED
Henry's Law Constant	$1.4x10^{-6}$ Atm m^3/mol	Calculated using s=0.0055 ppm, and a VP= $1.5x10^{-8}$ mm Hg
	$1.6x10^{-7}$ Atm m^3/mol	Calculated using s=0.07 ppm, and a VP=$2.15x10^{-8}$ mm Hg
Octanol/Water Partition, K_{ow}	$1.26x10^6$	Wollerton, C. 1987. Zeneca Summary September 2, 1987
log K_{ow}	6.1	Calculated

Attachment B. Summary of Physicochemical and Fate Properties of Permethrin

Parameter		Value	Reference/Comments *
		Persistence	
Hydrolysis $t_{1/2}$ 25°C	pH 3	stable	MRID# 102043 (c)
	pH 6	stable	
	pH 9	125-350 days (relatively stable)	
		Degradates m-PB alcohol (15.5%) and cis/trans-DCVA (6.5%)	
25°C	pH 5.7	stable	MRID# 112936 (s)
	pH 7.6	stable	
	pH 9.6	60 days for cis isomer,	
		40 days for trans isomer (Same degradates observed, samples contained 20% acetonitrile)	
Photolysis $t_{1/2}$	in water	80 days	MRID# 40242801 (s); Additional information reviewed 2/24/89: Tett. Lett. 35, 3045, 1976; J. Ag. Food Chem. 26, #3, 590, 1978
	on soil	L 106 days (estimated by extrapolation; relatively stable)	MRID# 40190101 (c)
		Several minor degradates.	
Soil metabolism	Aerobic $t_{1/2}$	CL 17 days	Williams, I.H. and Brown, M.J. 1979. J. Agric. Food Chem. 27:130-132
		SiL 16 days	
		Application rate had a greater effect than soil moisture on the rate of aerobic soil metabolism of permethrin in a SL. The cause was attributed to microbial inhibition and/or pesticide solubility.	MRID# 41970602 (s)
		SL 37 days	MRID# 42410002 (c)
		Major degradate CO_2, trans-DCVA, and m-PBA	
Soil metabolism	Anaerobic $t_{1/2}$	SL 204 days	MRID# 41970601(c)
Aquatic metabolism	Aerobic $t_{1/2}$	acid label 38 days	MRID# 43938201(c)
		alcohol label 43 days	
		Degs. trans-DCVA, (cis-DCVA and m-PBA were minor degradates ≤10%)	
Aquatic metabolism	Anaerobic $t_{1/2}$	acid label 175 days	MRID# 43982001(c)
		alcohol label 113 days	
		Degs. cis and trans-DCVA, m-PBA	

Attachment B. Summary of Physicochemical and Fate Properties of Permethrin

Parameter	Value	Reference/Comments *
	Mobility/Adsorption-Desorption	
Batch Equilibrium - Unaged	Soil $K_{d,f}$ $K_{OC,f}$ S 446 194,000 SL 355 341,000 SiL 344 28,200 CL 378 31,500 SL 1520 96,600 1/n= (1.09-1.32)	MRID# 41868001(p)
	Soil $K_{d,f}$ $K_{OC,f}$ SL 1420 491000 LS 2420 139000 SL 2100 190000 SL 1970 170000 1/n= (0.97-1.03)	MRID# 45170102(p)
	Soil K_d K_{OC} SL 1400-3100 280,000-480,000 LS 1800-2300 110,000-140.000 1/n is NA because measurements were made only at one concentration.	Hand, L.H. 2000. Zeneca Technical Letter 00JH0051 (Interim Report)
Batch Equilibrium - Degradates	Degradates: m-PBA S, SiCl, SL#1, SL#2 $K_{d,f}$ $K_{OC,f}$ 0.98 to 3.11 118-215 trans-DCVA S, SiCl, SL#1, SL#2 $K_{d,f}$ $K_{OC,f}$ 0.16 to 0.54 18 to 48	MRID# 43424901(p)
Aged Soil Column Leaching	Aged soil column study: parent permethrin did not leach in a SL column, but the degradate trans-DCVA appears to leach.	MRID# 42196701(p)
	Terrestrial Field Dissipation	
Terrestrial Field Dissipation	NC 17 days; IL 43 days; degradates observed were trans-DCVA and m-PBA	MRID# 42359109(c)

Attachment B. Summary of Physicochemical and Fate Properties of Permethrin

Parameter	Value	Reference/Comments *
	Aquatic Field Dissipation	
Aquatic Field Dissipation	CA: cis/trans-permethrin dissipated from the pond water with half-lives of 1.8 and 1.4 days, respectively; in the sediment (0-2") the half-lives were 118 and 18 days, respectively; cis/trans-DCVA and m-PBA detected in the water but not in the sediment. NC: cis/trans-permethrin dissipated from the pond water with half-lives of 3.1 and 1.9 days, respectively; in the sediment (0-2") the half-lives were 256 and 62 days, respectively; cis/trans-DCVA and m-PBA detected in the water but not in the sediment.	MRID#'s 44030501(p) and 44157101(p)
	Bioaccumulation	
Accumulation in Fish, max. BCF	180-230X for edible portion 570-610X for whole fish 950-1000X for non-edible	MRID# 41300401(p), 41300402(p), and 41300403(p)

* (c) = core study that fulfills guideline requirement; (s) = supplemental study; (u) = unacceptable study; (p) = partially fulfills the data requirement; NA=Not Available; N/A=Not Applicable

cc: Sherrie L. Kinard (RRB2), Yung Yang (Toxicology Branch), Jose Memendez (Environmental Risk Branch V), Carol Christensen (RRB2), Permethrin Subject File, RF, LAN. RD/I: Permethrin Team Review (2/23/04), A. Nielsen (7/6/04).

7509C: RRB2: S. Kinard: CM#2:Rm 722B: 703-305-0563:7/6/04.

13544

R101371

Chemical:	**Permethrin**
PC Code:	**109701**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/06/2004**
File ID:	**TX0052775**
Accession Number:	**412-05-1000**

HED Records Reference Center
09/07/2004