7-1-92

[FSTS-Cypermethrin, July, 1992]

Free Standing Toxicology Summary

Toxicity Data Base: Cypermethrin

Tox Chem No.: 271DD
PC No.: 109702

Series	Study Type	Study Available	Date requested/ Classification	Document Number
81-1	Acute oral - rats	AM	Tox. Cat. II	4825
81-2	Acute Dermal-	AM	Tox. Cat. III	4825
81-3	Acute inhalation - rats	UA		
81-4	Primary eye - rabbits	AG	Tox. Cat. IV	4825
81-5	Primary dermal - rabbits	AM	Tox. Cat. IV	4825
81-6	Dermal sensitization - g. pig	AM	Mod. Sensitizer	2391
81-7	Delayed neurotoxicity - hen	AG	Not neurotoxic NOEL > 10 gm/kg	2391
81-8	Special neurotoxicity - rat	UA		
82-1a	Subchronic oral - rodent	AM	NOEL = 150 ppm (but inc. liver enzyme act); LEL = 1500 ppm: body wt and poss. nerve damage.	4825
82-1b	Subchronic oral - nonrodent	AM	NOEL = 500 ppm, LEL = 1500 ppm: Diarrhoea, anorexia and nerve stim.	4825
82-2	21-day dermal-rabbit	AM	NOEL = 20 mg/kg, LEL = 200 mg/kg: liver pathology.	2391
82-3	90-day dermal	UA		
82-4	90-day inhalation	UA		
82-5	90-day neurotoxicity - hen	NR		
82-6				
82-7	Neurotoxicity screen	UA		
83-1a	Chronic feeding - rat		see 83-5	
83-1b	Chronic feeding -nonrodent	AG	NOEL = 1 mg/kg. LEL = 5.0 mg/kg: GI tract disturbance.	3249 5159 3647

82-2a	Oncogenicity - rat		see 83-5	
82-2b	Oncogenicity - mouse	AG	Positive for lung tumors	3249 3647
83-3a	Developmental toxicity - rat	AM	NOEL (maternal) = 17.5 mg/kg, LEL = 70 mg/kg. Body wt. NOEL (feto)= 70 mg/kg (HDT).	4825
83-3b	Developmental toxicity - rabbit	AM	NOEL > 30 mg/kg (HDT) for maternal and fetotoxicity	4825
83-4	Multi generation reproduction	AG	NOEL = 50 ppm, LEL = 150 ppm: dec. body wt gain in pups.	3249
83-5	Combined chronic/onco	AG	NOEL = 150 ppm, LEL = 1500 ppm: body wt. loss.	3249
84-2	Gene mutation-Ames test	NC	Not mutagenic in two separate studies	2391
84-2	chromosome aberration-Chinese Hamster bone marrow	NC	No chromosome aberrations	2391
84-2	Other mechanism genetic tox	UA		
85-1	Metabolism	AM	12 studies	2391
85-2	Domestic animal safety		see formulations	
85-3	Dermal Absorption	UA		
85-	Nerve function/operant behav	UA		

Status: AG = Acceptable with Guideline classification, AM = Acceptable with Minimum classification, UA = no study currently available, I = Invalid, NR = Not required for this chemical class, S = Supplementary, NC = Not classified.

Studies not currently available.

81-3**	Acute inhalation
81-8*	Special neurotoxicity
82-3**	90-day dermal
82-4**	90-day inhalation
82-7*	Neurotoxicity screen
84-2***	Other mechanism of mutagenicity
85-3**	Dermal absorption
85 **	Nerve function/operant behavior

*New requirement for pyrethroids. ** Required only for defined needs and registration purposes. *** Should be fulfilled.
Note: Cypermethrin has been reviewed for reregistration as a Group A chemical.

Special Toxicology Issues and Problems

1. **Labelling**

Cypermethrin is a type II pyrethroid. Dermal contact (especially to the face) may result in a tingling sensation and reddening of the skin (the pyrethroid reaction). The label precautionary statements for all products containing cypermethrin should advise that this may occur and washing the skin should result in reversal of the reaction.

Cypermethrin has been demonstrated to be positive in 2 of 3 guinea pig dermal sensitization studies. The label precautionary statements for all products should advise that some individuals may develop sensitization reactions if the product is handled frequently.

2. **Carcinogenicity**

The HED Peer Review Panel (refer to "Peer Review of Cypermethrin" dated Feb. 17, 1988 from J.A. Quest, Ph.D.) has reviewed the carcinogenicity and related data base for cypermethrin and determined that the carcinogenicity classification is C based on increased incidence of lung tumors in mice. Based on the recommendations of the Peer Review, current Agency policy is that quantitative risk assessments based on carcinogenicity are not required for registrations and tolerances with cypermethrin.

3. **RfD**

The RfD is 0.01 mg/kg/day based on the dog chronic feeding study and with a NOEL of 1 mg/kg/day and a 100 fold safety factor. The LEL for this study was 5 mg/kg/day and gastrointestinal disturbances resulted at this dose level.

The RfD was verified by the Agency RfD committee on January 18, 1989.

4. Non-carcinogenic special review and non-dietary risk assessment.

No special review triggers are recognized as of July 1992.

5. **Mutagenicity/genetic toxicity comments**

The mutagenicity/genetic toxicity data base needs to be rereviewed. As of October 1991, there are four studies available. None have been classified for acceptability but none show mutagenic activity. There is a data gap for the third category (other mechanism of genetic toxicity) study.

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.

In order to comply with the current guidelines, the registrant may reformat the existing studies and resubmit them for rereview and provide an additional study to satisfy the requirement for a study under the category of other mechanism of genetic toxicity. On receipt of these studies HED will determine if they are acceptable or otherwise.

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 absorption.**

No data.

7. **Neurotoxicity testing.**

Cypermethrin is a pyrethroid insecticide which acts as a nerve poison. The series 81-8, 82-7 and 85- special neurotoxicity screen and nerve function/operant studies have not been submitted but the registrant has committed to conduct these studies.