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TOXICOLOGY ENDPOINT SELECTION DOCUMENT as of 4/26/94

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013494

Chemical Name: **Permethrin**

PC Code: **109701**

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Marion Copley/John Doherty Date: 4/26/94

Branch Chief: Karl Baetcke Date: 4/26/94

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Dermal Absorption Data

MRID: 00431690

% absorbed: The dermal absorption tentatively should be considered to be 50 % pending review of the new rat dermal absorption study listed above.

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Acute Dietary Endpoint (One Day)

Studies Selected - Guideline No.:

Acute neurotoxicity study in the rat rabbit (81-8ss)

MRID: not available (attached to HED DOC. # 10888)
CITATION: Special acute toxicity study in rats; McDaniel and Moser, Neurotoxicology and Teratology, 15:71-83 (1993)

Summary (Enter Standard Executive Summary or equivalent):

A total of eight groups of 8/sex Long-Evans rats were dosed with permethrin (95% a.i., control, 25, 75 or 150 mg/kg) in corn oil at 1 ml/kg. Separate groups were treated for the FOB and motor activity assessments. Permethrin had reported equal ratios of cis and trans isomers. Following dosing, FOB (2 and 4 hours for permethrin) and motor assessments (4 hours for permethrin) were made. FOB and motor activity assessments were also made at pretest, and after 24 and 48 hours.

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 males and females) decreased forelimb (males 29%, $p < 0.05$) and hindlimb (males 30%, females 15%, both $p < 0.05$) grip strength and motor activity was decreased (estimated 40% for males) and body temperature was increased about 1 °C. At 150 mg/kg: arousal score (males), righting reflex (males) and approach response score (females) were all 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 LEL is 75 mg/kg based on several neurotoxicity parameters being affected. THE NOEL is 25 mg/kg.**

This study when taken together with another acute neurotoxicity study satisfies the guideline requirements for 81-8ss, acute neurotoxicity in the rat.

Endpoint and dose for use in risk assessment:

The endpoint for acute dietary risk assessment is the acute neurotoxicity NOEL (25 mg/kg/day) from the rat study. The LEL (75 mg/kg/day) is based upon clinical signs (ie. aggression, abnormal and/or decreased movement), and increased body temperature.

Comments about study and/or endpoint:

none

This risk assessment is required.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Studies Selected - Guideline No.:

Acute neurotoxicity study in the rat rabbit (81-8ss)

MRID: not available (attached to HED DOC. # 10888)
CITATION: Special acute toxicity study in rats; McDaniel and Moser, Neurotoxicology and Teratology, 15:71-83 (1993)

Summary (Enter Standard Executive Summary or equivalent):

SEE ACUTE DIETARY EXPOSURE FOR DETAILS

Endpoint and dose for use in risk assessment:

The endpoint for short term occupational or residential risk assessment is the acute neurotoxicity NOEL (25 mg/kg/day) from the rat study. The LEL (75 mg/kg/day) is based upon clinical signs (ie. aggression, abnormal and/or decreased movement), and increased body temperature.

Comments about study and/or endpoint:

none

This risk assessment is required. Dermal absorption should be taken into account.

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Intermediate Term Occupational or Residential (1 Week to Several Months)

Study Selected - Guideline No.:

Subchronic neurotoxicity screen in the rat (82-7ss)
MRID: 429337-01

Summary (Enter Standard Executive Summary or equivalent):

In this study designed to assess the subchronic neuro-toxicity of permethrin, four groups of 10/sex Sprague-Dawley strain rats were dosed with 0, 250, 1500 or 2500 ppm in their diets for 13 weeks. These doses corresponded to 15.49, 91.51 or 150.35 mg/kg/day in males and 18.66, 111.37 or 189.63 mg/kg/day in females. Assessments for clinical signs were made daily and FOB and motor activity assessments were made at weeks pretest and 4, 8 and 13 of the study. Following sacrifice, the control and high dose group rats were perfused and subjected to histopathological assessments.

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. The tremors started at day 1 and persisted throughout the study. 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 LEL for neurotoxicity is 1500 ppm (91.51 mg/kg/day in males) based primarily tremors and staggered gait. The NOEL is 250 ppm (15.49 mg/kg/day).**

This study satisfies the guideline requirements for 82-7ss, subchronic neurotoxicity in the rat.

Endpoint and dose for use in risk assessment:

The dose for intermediate term occupational or residential risk assessment is the subchronic systemic/neurotoxicity NOEL (15.45 mg/kg/day) from the rat subchronic neurotoxicity study. The LEL (91.51 mg/kg/day) is based upon clinical signs (ie. including tremors, staggered and/or impaired gait, splayed hindlimbs) and decreased body weight.

Comments about study and/or endpoint:

Although the NOEL in the 90 day oral rat study is lower (20 ppm, about 2 mg/kg/day), it was determined that it is inappropriate to use this value since the value used for chronic risk assessment (RfD) is higher (5 mg/kg/day). In addition the endpoint in the 90 day study consists of minimal liver changes.

This risk assessment is required. Dermal absorption should be taken into account.

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Cancer Classification and Basis:

Permethrin is classified as a group C carcinogen (September 18, 1989) with a Q1* of 1.84 X 10^{-2} $(mg/kg/day)^{-1}$. This is based on the FMC mouse study using dose related increases in combined lung adenomas and/or carcinomas observed in females.

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RfD and Basis: 0.05 mg/kg/day based on a NOEL of 5 mg/kg/day. The LEL was 25 mg/kg/day based on increase in liver weight. The uncertainty factor (UF) was 100 to account for inter-species extrapolation (10) and intra-species variability (10).

NOEL for critical study: 5 mg/kg/day (a slight increase in liver weight at this dose level was not considered a toxicological effect).

Study Type - Guideline No.: Combination of several chronic rat and mouse feeding studies (83-1,2,5)

MRID: For the 5 studies considered in setting the Rfd (FMC Bio/Dynamics rat study: Accession No.: 0097421, 097419, 097418, 096693 and 099964; Life Science Research rat study: 243977, 243979 and 070305 and ICI rat study. MRID No.: not available; Welcome Foundation mouse study 243975 and 243976 and ICI mouse study MRID Nos. not available).

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