3-15-94

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

TO: James Kariya, DRES
Larry Dorsey, OREB
Esther Saito, CCB
Caswell File
Debra Edwards, CBTS
Edward Zager, CBRS
William Burnam, SAB
George Ghali, RfD Secretary

Chemical Name: **Phosmet**

PC Code: **059201**

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 3/28/94 Date: 3/15/94

Branch Chief: Karl Baetcke Date: 3/15/94

****

Dermal Absorption Data

MRID: 40122201

% absorbed: The dermal absorption should be considered to be 5 %.

In a dermal absorption study, rats were dermally exposed to doses of 2.67, 0.52 or 0.058 mg/cm^2. Excretion was primarily urinary with less in the feces. The absorption value is an average of reported values ranging from 1 to 12 % derived over a 24 hour period. The phosmet is stored in the skin and released over 24 hours, resulting in a wide range of results.

****

****

Acute Dietary Endpoint (One Day)

Studies Selected - Guideline No.:

1) Chronic/onco toxicity in the rat (83-5)

MRID: 41916401

Summary (Enter Standard Executive Summary or equivalent):

In a 2-year chronic toxicity/oncogenicity study phosmet was administered to Sprague-Dawley Crl:CD® SD BR rats in the diet at 0, 20, 40, 200 or 400 ppm (400 ppm terminated at 12 months) (doses of: males - 0, 1.1, 1.8, 9.4 and 23 mg/kg/day; females - 0, 1.1, 2.1, 10.9 and 27 mg/kg/day) for 2 years.

At 20 ppm there was marginal RBC cholinesterase (ChE) inhibition (16 %) noted at 6 months in males only. At 40 ppm RBC (about 15-20 %) and serum ChE (5-36 % - m; 15-25 % - f) was inhibited in both males and females. Brain ChE was inhibited (>34 %) in males and females at 200 ppm. **The LEL for cholinesterase inhibition was = 40 ppm based on RBC and serum ChE in males and serum ChE in females. The threshold NOEL for (ChE) inhibition was = 20 ppm (RfD meeting 3/3/94).**

Other systemic toxicity was limited to increased incidence of fatty change in the liver of males at all doses. In addition, at 200 ppm and above (males) there were increases in the incidences of depressed hepatic foci, hyperkeratosis of the stomach; (females) fatty change in the liver, mineralization of the thyroid. At 400 ppm (males and females) body weight and body weight gain was decreased; (females) decreased kidney weight and increased BUN. **The systemic LEL is = 200 ppm based on decreased body weight gain, and liver, stomach and thyroid changes. The systemic NOEL = 40 ppm (RfD meeting 3/3/94).**

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. This study was determined to be tested at adequate but not excessive dose levels by the HED Cancer Peer Review Committee (meeting November 17, 1993) based on ChE inhibition.

This study is classified core-minimum data for carcinogenicity (83-2) and chronic (83-1) toxicity and satisfies the guideline requirements for a chronic/onco toxicity study in rats.

2) Reproduction study in the rat (83-4)

MRID: 41520001

Summary (Enter Standard Executive Summary or equivalent):

In a 2-generation reproduction study, 25 Sprague-Dawley (Crl:CD SD BR) rats per sex per dose were fed diets containing R-1504 technical at 0, 20, 80 or 300 ppm (mean test material consumption for both sexes combined - 0, 1.5, 6.1 and 23.4 mg/kg/day) continuously for 2 generations.

Signs of parental toxicity (males and females) included decreased RBC ChE at 20 ppm (8-16%). At 80 ppm there were decreases in RBC ChE (37 to 59 %) and serum ChE (14-24 %). At 300 ppm tremors were accompanied by decreases in RBC ChE (75 %) and serum ChE (65 %). **The LEL for parental toxicity is equal to or less than 20 ppm and the NOEL is less than 20 ppm.**

Signs of reproductive toxicity at 80 ppm included decreases in fertility, number of live pups/litter and pup weights. **The LEL for reproductive toxicity is 80 ppm based on decreased fertility, number of live pups/litter and pup weights. The NOEL for reproductive toxicity is 20 ppm.**

This study is classification core-minimum data for reproductive toxicity (83-4) and satisfies the guideline requirements for a reproductive toxicity study in rats.

Endpoint and dose for use in risk assessment:

The endpoint for acute dietary risk assessment is the threshold NOEL (1.1 mg/kg/day) from the rat chronic/onco study. The LEL (1.8 mg/kg/day) was based upon inhibition of both RBC and serum ChE.

Comments about study and/or endpoint:

Although the above were long term studies, it was considered appropriate to use this endpoint since inhibition of RBC ChE occurred as early as 6 months in the rat and appeared to be decreasing with time. This implies that inhibition of RBC ChE occurred at an unspecified earlier timepoint.

This risk assessment is required. The use of this endpoint will be reevaluated when the results of an acute neurotoxicity study and received and evaluated.

****

****

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

Studies Selected - Guideline No.:

1) Chronic/onco toxicity in the rat (83-5)

MRID: 41916401

Summary (Enter Standard Executive Summary or equivalent):

SEE ACUTE DIETARY EXPOSURE FOR DETAILS

2) Reproduction study in the rat (83-4)

MRID: 41520001

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 NOEL (1.1 mg/kg/day) from the chronic/onco rat study. It should be noted that a 5 % absorption factor should be taken into account. The LEL (1.8 mg/kg/day) from this study was based on inhibition of RBC and serum ChE.

Comments about study and/or endpoint:

Although the above were long term studies, it was considered appropriate to use this endpoint since inhibition of RBC ChE occurred as early as 6 months in the rat and appeared to be decreasing with time. This implies that inhibition of RBC ChE occurred at an unspecified earlier timepoint.

In addition, a developmental NOEL of 5 mg/kg/day (LEL = 15 mg/kg/day based on skelital variations) was considered as a potential endpoint, however, the RBC ChE inhibition NOEL was considered to ba a more appropriate endpoint.

This risk assessment is required. The use of this endpoint will be reevaluated when the results of an acute neurotoxicity study and received and evaluated.

****

****

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

Study Selected - Guideline No.:

1) Chronic/onco toxicity in the rat (83-5)

MRID: 41916401

Summary (Enter Standard Executive Summary or equivalent):

SEE ACUTE DIETARY EXPOSURE FOR DETAILS

2) Reproduction study in the rat (83-4)

MRID: 41520001

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 NOEL (1.1 mg/kg/day) from the chronic/onco rat study. It should be noted that a 5 % absorption factor should be taken into account. The LEL (1.8 mg/kg/day) from this study was based on inhibition of RBC and serum ChE.

Comments about study and/or endpoint:

Although the above were long term studies, it was considered appropriate to use this endpoint since inhibition of RBC ChE occurred as early as 6 months in the rat and appeared to be decreasing with time. This implies that inhibition of RBC ChE occurred at an unspecified earlier timepoint.

This risk assessment is required. The use of this endpoint will be reevaluated when the results of an acute neurotoxicity study and received and evaluated.

****

****

Cancer Classification and Basis:

Phosmet has been classified by the HED Cancer Peer Review Committee as a Group C carcinogen (no Q_1*) based on the following evidence:

NOTE: based on DRAFT Peer Review Document

1. There was an increased incidence of liver tumors in males $B_6C_3F_1$ mice at the high dose, that was statistically significant by pair-wise comparison, with a statistically significant trend and which also had an apparent early onset.
2. Female mice had a significant dose-related trend for liver tumors, and for mammary gland adenocarcinomas, as well.

****

RfD and Basis: 0.01 mg/kg/day based on a threshold NOEL of 1.1 mg/kg/day. The LEL was 1.8 mg/kg/day based on inhibition of RBC and serum ChE.

NOEL for critical study: 1.1 mg/kg/day

Study Type - Guideline No.: Chronic/onco feeding study in the rat (83-5)

MRID: 41916401

****