4-16-96
444
111501.TE1

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: **Sulprofos**

PC Code: **111501**

Structure: not available

The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for sulprofos at a meeting held on April 9, 1996. 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.

TOXICOLOGIST: William Dykstra (NAME) Date: 4/16/96

SECTION HEAD: Roger Gardner (NAME) Date: 4/16/96

BRANCH CHIEF: Karl Baetcke (NAME) Date: 4/16/96

DERMAL ABSORPTION DATA (If available) **None Available, Assume 100%**

MRID:

% absorbed:

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ACUTE DIETARY ENDPOINT (ONE DAY): 3 mg/kg. This NOEL is determined by extrapolation to lower dose from the LEL of 29 mg/kg in the acute neurotoxicity study in rats and was based on plasma and RBC ChE inhibition. This NOEL is supported by the maternal toxicity NOEL of 3 mg/kg/day in the rabbit developmental study.

Study Selected - Guideline No.: 81-8

MRID No.: **427370-01**

Summary: A single gavage dose of 0, 29, 71, or 206 mg/kg technical sulprofos in polyethylene glycol 400 (5 ml/kg) was administered to randomized groups of 10/sex/dose Sprague-Dawley rats. FOB and motor activity tests were conducted at pretreatment, on the day of dosing (peak effect), and days 7 and 14. Neural tissue from 5 control and high dose animals/sex was examined histopathologically. At 29 mg/kg, increased incidence of urine staining (7/10), tremors (1/10) on days 0-2, and ataxia (day 0) were noted. Severe muscle fasciculations (1/10) and slightly decreased motor activity were seen on day 0 in males. Plasma and RBC ChE inhibition was 50-72% in both sexes at 24 hours. LEL is 29 mg/kg/day. No NOEL was established in the study.

Endpoint and dose for use in risk assessment: **neurotoxicity**

Comments about study and/or endpoint: **NOEL of 3 mg/kg was extrapolated from LEL of 29 mg/kg. Uncertainty factor of 100.**

This risk assessment is required.

SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - Guideline No.:**83-3: Rabbit Teratology Study.**

MRID No.: **00043791**

Summary: Randomized groups of 12 to 13 mated Himalayan rabbits were orally gavaged with Bolstar technical dissolved in 0.5% aqueous Cremophor at doses of 0, 3, 10, or 30 mg/kg/day during days 6 through 18 of gestation. The dosing volume was 5.0 ml/kg. Animals were examined daily for clinical signs and mortality. Body weight was determined daily, but food consumption was not measured. Animals were sacrificed on day 29 of gestation and grossly examined. Uterine contents were examined. Fetuses were examined externally, sexed and weighed. Each fetus was examined by routine methods for brain, visceral and skeletal anomalies. Statistical analysis of the data was performed.

The NOEL for developmental toxicity is 10.0 mg/kg/day (MDT). At 30 mg/kg/day (HDT), there was a decrease of implantations/dam of 2.1 in comparison to controls (about 25%). However, due to maternal deaths at this dose (5 out of 13 does died), only 36 fetuses were examined in 7 litters. It is of interest to note that there were no fetuses in the entire study at any level with a "slight bone alteration". Similarly, there were no fetuses in the study with any sort of grade for delayed ossification. It is uncertain whether "slight bone alteration" is the same as delayed ossification.

The NOEL for maternal toxicity is 3.0 mg/kg/day (LDT). Two does out of 12 in the 10 mg/kg/day group hardly ate or drank for a time from the middle of the treatment period and had diarrhea. Ten animals out of 13 of the 30 mg/kg/day group showed marked toxic signs during the second half of the treatment period. The most frequent signs were diarrhea and drowsiness, and the affected animals ate and drank very little. Salivation and proneness were occasionally seen. Five of the 13 does in the 30 mg/kg/day group died between Gestation Day 15 and 20. The stomach and intestines of these does were essentially empty, usually containing only a little very thin liquid or gas.

The statistically significant loss of weight in the survivors of the 30 mg/kg/day group is considered toxicologically significant and an effect of treatment. After termination of treatment, these animals were unable to fully make up this loss of weight so that their weight gain during the entire gestation period was less than

controls, but was not statistically significant (weight gain in controls was 118.6 g vs. 79.3 g in HDT)

Endpoint and dose for use in risk assessment: **Maternal Toxicity NOEL of 3.0 mg/kg/day. Uncertainty factor, 100.**

Comments about study and/or endpoint: **Oral developmental study in which clinical signs occurred during Days 11-15 of gestation.**

This risk assessment is required.

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INHALATION EXPOSURE: None required, due to low acute inhalation toxicity (Toxicity Category III) of technical sulprofos. Use oral study for inhalation endpoint

Study Selected - Guideline No.:

MRID No.:

Summary (Enter Standard Executive Summary or equivalent):

Endpoint and dose for use in risk assessment:

Comments about study and/or endpoint:

This risk assessment is / is not required. (If not, why not?)

INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: **82-1 (90 day dog feeding study)**

MRID No.: **00043793**

Summary: Groups of 4/sex/dose beagle dogs were fed dietary levels of 0, 10, 20, or 200 ppm (**0.25, 0.50, or 5.0 mg/kg/day)** for 3 months. The NOEL for plasma ChE inhibition is 10 ppm (**0.25 mg/kg/day)**. At the LEL of 20 ppm (**0.50 mg/kg/day)**, plasma ChE was depressed significantly by 21% in males and 26% in females beginning at day 14. Although RBC and brain ChE were depressed by 10% at 20 ppm, this dose level was considered the NOEL for these parameters. The NOEL for systemic effects is 20 ppm (**0.50 mg/kg/day)**. At the LEL of 200 ppm, there was weight loss and decreased food consumption in males and decreased food consumption (but no weight loss) in females. High dose male dogs had vomiting and diarrhea, while high dose females had some rear leg involvement in the last 2 weeks of the study. There were no significant effects in organ weights or histopathology.

Endpoint and dose for use in risk assessment. **plasma ChE inhibition. NOEL = 0.25 mg/kg/day. Uncertainty factor to be used, 100.**

Comments about study and/or endpoint: **RBC and brain CHE at 0.50 mg/kg/day were inhibited by 10%, although statistics were not performed. This 10 ppm (0.25 mg/kg/day) NOEL for plasma ChE inhibition is supported by 90 day neurotoxicity study in rats which showed no NOEL at 10 ppm (0.5 mg/kg/day) for plasma and RBC ChE inhibition.**

This risk assessment is required.

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INHALATION EXPOSURE: None required or use oral study for inhalation endpoint.

Study Selected - Guideline No.:

MRID No.:

Summary: (Enter Standard Executive Summary or equivalent):

Endpoint and dose for use in risk assessment:

Comments about study and/or endpoint:

This risk assessment is / is not required. (If not, why not?)

CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: **83-1: 2-year chronic dog study**

MRID No.: **00085485**

Summary: Randomized groups of 4/sex/dose purebred beagle dogs were fed continuously in the diet with 0, 10, 100, or 150 ppm **(0.25, 2.5, or 3.8 mg/kg/day)** of Bolstar technical (purity 89.75%) for 24 months. Food consumption was measured daily and body weight was measured weekly. Ophthalmological examinations were performed on all dogs at the end of the study. Blood samples were taken at 1, 3, 6, 12, 18, and 24 months for hematology, clinical chemistries, and plasma and RBC cholinesterase determinations. Urinalysis determinations were performed at the same monthly intervals. At necropsy, organ weights were taken, brain cholinesterase determined, and tissues examined in all animals. Results were analyzed statistically with $p \leq 0.05$ being significant.

The NOEL for plasma, RBC, and brain cholinesterase is 10 ppm (0.25 mg/kg/day) and the LEL is 100 ppm. At the LEL of 100 ppm, plasma, RBC and brain cholinesterase values were decreased by more than 20% in both sexes. The NOEL for systemic effects is 150 ppm (HDT).

There were no toxic signs observed in any dog, control or treated, during the 2-year period. Additionally, there were no deaths during the study.

There were no toxicologically significant compound-related effects on body weight, food consumption, ophthalmological findings, or hematological findings. The NOEL for plasma, RBC, and brain cholinesterase is 10 ppm and the LEL is 100 ppm. There were no compound-related effects in other blood chemistry findings, in urinalysis findings or in absolute and relative organ weight values in treated groups when compared to controls.

The only non-neoplastic lesion which appeared more frequently in high-dose male dogs in comparison to controls was chronic cholecystitis in the gall bladder (1/4, 1/4, 1/4 and 3/4 in control, low, mid and high-dose groups, respectively). Since there was no elevation of liver enzymes, such as GGT, ALT, and AST, or other liver histopathology, the increased incidence of the gall bladder lesion in high-dose males was not considered compound-related, but rather an age-related finding.

Endpoint and dose for use in risk assessment. **Plasma, RBC, and brain ChE inhibition. NOEL = 0.25 mg/kg/day. Uncertainty factor to be used, 100.**

Comments about study and/or endpoint: **NOEL same as 90 day dog**

This risk assessment is required.

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INHALATION EXPOSURE: Not required or use oral study for inhalation endpoint

Study Selected - Guideline No.:

MRID No.:

Summary: (Enter Standard Executive Summary or equivalent):

Endpoint and dose for use in risk assessment:

Comments about study and/or endpoint:

This risk assessment is / is not required. (If not, why not?)

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CANCER CLASSIFICATION AND BASIS: Group E

Q_1* = none

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R_fD and basis: 0.0025 mg/kg/day based on ChE inhibition

NOEL for critical study: NOEL of 0.25 mg/kg/day for plasma, RBC, and Brain ChE inhibition

Study Type - Guideline No.: 83-1(b); 2-year dog feeding study at 0, 0.25, 2.5, or 3.8 mg/kg/day (10, 100, or 150 ppm) in diet for 2 years. Systemic NOEL is 3.8 mg/kg/day (HDT).

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of technical sulprofos

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00043785	LD_{50} = 176 mg/kg	II
81-2	Acute Dermal	00099107	LD_{50} = 820 mg/kg	II
81-3	Acute Inhalation	00043785	LC_{50} > 0.661 mg/L (no deaths)	III
81-4	Primary Eye Irritation	00099107	conjunctival redness at 1 hr., clearing at 2 hr.	IV
81-5	Primary Skin Irritation	00099107	P.I. = 0.6/8.0	IV
81-6	Dermal Sensitization	00255845	negative results	Neg
81-8	Acute Neurotoxicity	42737001	LEL = 29 mg/kg, No NOEL	