7-24-96 MICROFICH

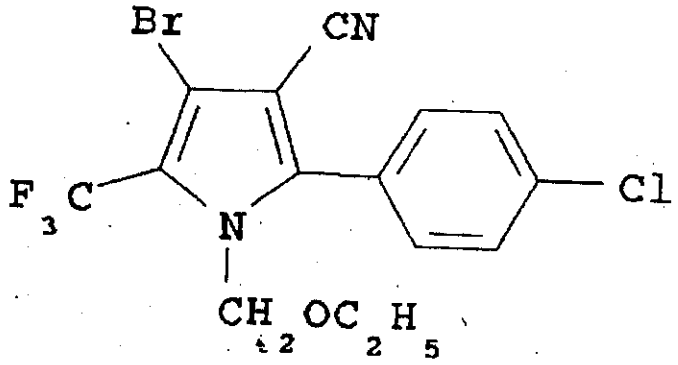
TOXICOLOGY ENDPOINT SELECTION DOCUMENT

013501

Chemical Name: Pirate®

PC Code: 129093

Structure



- The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Pirate at a meeting held on July 23, 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: Guruva B. Reddy Date: 7/24/96

SECTION HEAD: Marion P. Copley Date: 7/24/96

BRANCH CHIEF: Karl Baetcke Date: 7/24/96

DERMAL ABSORPTION DATA: A dermal absorption study was not available. Therefore, a dermal absorption value of 5% was calculated based on the route-to-route extrapolation using the maternal NOEL of 5 mg/kg/day from the developmental toxicity study in rabbits and the systemic NOEL of 100 mg/kg/day from the 28-day dermal toxicity study in rabbits. This dermal absorption value will be used ONLY for the chronic exposure risk assessment since an oral study was selected for this scenario. Dermal absorption factor is not needed for the short-and intermediate-term exposure risk assessments since a 21-day dermal toxicity was used for these scenarios.

MRID: 42770222 and 43492831

% absorbed: 5%

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Acute neurotoxicity study - rats §81-8

MRID No.:43492829

Summary: In an acute neurotoxicity study, AC 303,630, (94.5% ai, Lot No. AC 7504-59-A) was dissolved in 0.5% carboxymethylcellulose and administered once, via gastric intubation in a dosing volume of 10 ml/kg/dose, to 60 Sprague-Dawley CD rats (10/sex/group) at dose levels of 0, 45, 90, and 180 mg/kg. All rats were observed for 2 weeks following dosing. The rats were evaluated for reactions in functional observational and motor activity measurements pretest and on study days 1, 8, and 15. In addition, five rats per group were examined for neuropathologic lesions.

Two males and two females in the 180 mg/kg dose group died within 7 hours of dosing, possibly as a result of accidental injury during treatment. Surviving rats in this dose group exhibited changes in gait, locomotion, and arousal, and 20-30% of the males and females were lethargic on the day of treatment. In the 90 mg/kg dose group, 20% of the males were lethargic on the day of treatment. No dose-related effects on body weights, food consumption, neurobehavioral observations, or gross or histological post mortem examinations were noted. **The LOEL is 90 mg/kg, based on lethargy of the rats on the day of treatment. The NOEL is 45 mg/kg.**

This acute neurotoxicity study is **Supplemental**, but can be upgraded to acceptable if adequate historical control FOB data are provided.

Dose and Endpoint for use in risk assessment: NOEL = 45 mg/kg/day based on lethargy exhibited by rats at the 90 mg/kg/day (LOEL) on the day of treatment.

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)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 28-day dermal toxicity study - rabbit §82-2

MRID No.: 43492831

Summary: In a repeated dose dermal toxicity study, AC 303,630 (Pirate; 94.5% a.i., Lot No. AC 7504-59A) was applied to the shaved skin of six New Zealand White rabbits/sex/dose at dose levels of 0, 100, 400, or 1000 mg/kg, 6 hours/day, 5 days/week for 4 weeks.

Rabbits of both sexes in the 400 and 1000 mg/kg treatment groups exhibited statistically significant and concentration-related increases in serum cholesterol (60-95%) and relative liver weights (22-43%), and suffered from cytoplasmic vacuolation of the liver. The vacuolation of the liver was minimal to slight for male and female rabbits in the 400 mg/kg treatment groups (4 of 12 animals), and minimal to moderately severe for the 1000 mg/kg treatment groups (8 of 11 animals). In addition, female rabbits in the 1000 mg/kg treatment group exhibited a 97% increase in serum alanine aminotransferase ($p < 0.05$) concentrations. No differences were observed between rabbits in the 100 ppm treatment groups and the control groups. **The LOEL is 400 mg/kg for both sexes, based on changes in liver chemistry and morphology. The NOEL is 100 mg/kg.**

This subchronic toxicity study is classified **acceptable** and does satisfy the guideline requirement for a repeated dose dermal toxicity study (§82-2) in rabbits.

Dose and Endpoint for use in risk assessment: NOEL = 100 mg/kg/day based on increases in cholesterol and relative liver weights and histological lesions in the liver of both sexes of rabbits at 400 mg/kg/day (LOEL).

Comments about study and/or endpoint: None

This risk assessment is required.

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

DERMAL EXPOSURE:

Study Selected - Guideline No.: 28-day dermal toxicity study - rabbit §82-2

MRID No.: 43492831

Summary: **See Short Time Exposure.**

Dose and Endpoint for use in risk assessment: NOEL = 100 mg/kg/day based on increases in cholesterol and relative liver weights and histopathological lesions in the liver of both sexes of rabbits at 400 mg/kg/day (LOEL).

Comments about study and/or endpoint:

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: Combined chronic toxicity/oncogenicity study - mice §83-5

MRID No.: 43492838

Summary: In a chronic toxicity/oncogenicity study, Pirate (94.5% a.i., Lot No. AC-7504-59A) was administered to 65 male and 65 female Swiss Crl:CD-1(ICR)BR mice/sex/dose in the diet at dose levels of 0, 20, 120, or 240 ppm (0, 2.8, 16.6, or 34.5 mg/kg/day, respectively, in males; 0, 3.7, 21.9, or 44.5 mg/kg/day, respectively, in females) for 80 weeks.

Chronic toxicity observed in males and females at 120 and 240 ppm included non-neoplastic brain vacuolation primarily in the white matter of the corpus callosum, tapetum, hippocampus, and cerebellum. The incidence of brain vacuolation in males was 4/65 control, 14/64 mid-, and 49/65 high-dose, and in females it was 10/65 control, 28/65 mid-, and 58/65 high-dose. Males and females at 240 ppm also exhibited vacuolation of the spinal cord and optic nerve. Treatment-related gross pathological changes, including skin ulceration and scabbing, occurred in males and females at the 240 ppm level, and scabbing occurred in males at 120 ppm. **The LOEL for systemic toxicity is 120 ppm (16.6 and 21.9 mg/kg/day in males and females, respectively) based on brain toxicity and scabbing of the skin (males), and the NOEL is 20 ppm (3 and 4 mg/kg/day for males and females, respectively).**

At the doses tested, there was no treatment-related increase in tumor incidence when compared to controls. The animals may have tolerated a higher dose; however, males and females receiving 240 ppm and females administered 120 ppm exhibited decreased body weight gains of 30% in males and 14% in both female groups. Survival in females was depressed by 40% in the 240 ppm treatment group. Dosing was considered adequate based on decreased body weight gain in males and females.

This chronic/oncogenicity study in mice is acceptable for oncogenicity and satisfies the guideline requirement for a carcinogenicity study (83-2) in mice. The study is supplementary for chronic toxicity (83-1) because it is missing clinical chemistry and urinalysis data, and absolute organ weights were measured on only 10 mice/sex/dose at terminal sacrifice.

Dose and Endpoint for use in risk assessment: NOEL = 3 mg/kg/day based on the non-neoplastic brain lesions observed in both sexes of mice as well as the scabbing of skin in male mice at 16.6 mg/kg/day (LOEL).

Comments about study and/or endpoint: This study was used to establish the RfD. Since this oral study was selected for dermal exposure scenario, the dermal absorption factor of 5% must be used in risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the combined LC_{50} of 1.9 mg/L, Pirate is placed in Tox. Cat. III. Therefore, risk via the inhalation route is not a concern at this time.

Study Selected - Guideline No.: Acute inhalation toxicity study - rat §81-3

MRID No.:42770209

This risk assessment NOT required.

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CANCER CLASSIFICATION AND BASIS: Pirate® is being reviewed for the HED Cancer Peer Review Committee because of possible carcinogenicity trends.

Q_1^* = not established

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RfD AND BASIS: The HED RfD Peer Review Committee (July 18, 1996) has established an RfD of 0.03 mg/kg/day, based on mouse central nervous system lesions applying an Uncertainty Factor (UF) of 100 to account for interspecies and intraspecies variability.

NOEL for critical study: 2.8 mg/kg in male mice

Study Type - Guideline No.: Combined chronic toxicity/oncogenicity study - mice §83-5

MRID: 43492838

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Pirate

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	42770207/ 42884201	LD_{50} (95% C.I.) = 441 (195 - 832) mg/kg, males LD_{50} (95% C.I.) = 1152 mg/kg, females LD_{50} (95% C.I.) = 626 (274 - 1086) mg/kg, combined	II
81-2	Acute Dermal	42770208	LD_{50} > 2000 mg/kg (Limit Dose)	III
81-3	Acute Inhalation	42770209	LC_{50} (95% C.I.) = 0.83 (0.48 - 1.4) mg/l, (males) LC_{50} (95% C.I.) = > 2.7 mg/l, females) LC_{50} (95% C.I.) = 1.9 (1.1 - 3.3) mg/l, combined	III
81-4	Primary Eye Irritation	42770210	Corneal opacity (4/6), iritis (2/6) and conjunctivitis (6/6) present at 48 hours. At 72 hours iritis was resolved. All rabbits were normal by Day-7.	III
81-5	Primary Skin Irritation	42770211	Non-irritating	IV
81-6	Dermal Sensitization	42770212	Not a skin sensitizer	N/A
81-8	Acute Neurotoxicity	43492829	The LOEL is 90 mg/kg, based on lethargy of the rats on the day of treatment. The NOEL is 45 mg/kg.	Supplementary