(11-17-97)

Image

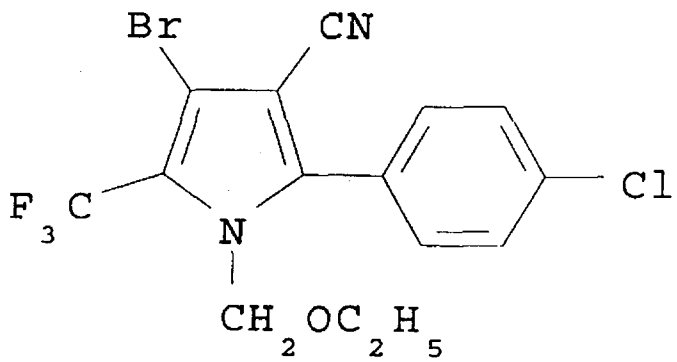
TOXICOLOGY ENDPOINT SELECTION DOCUMENT
SECOND REVISION 11/17/97

013499

Chemical Name: Pirate®

PC Code: 129093

Structure



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Chlorfenapyr (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. *This is a second revision of the original TES document on Pirate® (report date 7/24/96):there is no change in the endpoints selected for use in risk assessment including the RfD and the uncertainty factors used, however there is a modification in which studies are used to support the chronic dermal and chronic dietary exposure scenarios. This document also includes the call made by the Cancer Peer Review Committee. This document supersedes the previous Toxicology Endpoint Selection Document (7/24/96)and the first revision (1/27/97).*

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: Marion Copley 11/17/97 Date: 11/17/97

Branch Senior Scientist (RAB1): Melba Morrow 11/20/97 Date: 11/17/97

Chair, Hazard ID Committee: Clark Swentzel 11/21/97 Date: 11/21/97

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. An Uncertainty Factor (UF) of 100 and 10-fold modifying factor (MF) is appropriate.

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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. An Uncertainty Factor (UF) of 100 and 10-foid modifying factor (MF) is appropriate.

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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. An Uncertainty Factor (UF) of 100 and 10-fold modifying factor (MF) is appropriate.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Two Studies Selected -

1) Guideline No.: One Year Neurotoxicity study - rats §82-7
MRID No.: 43492833

Summary: In a one-year dietary neurotoxicity study[1] (MRID 43492833), AC 303,630 (Pirate; 94.5% ai, Lot No. AC 7504-59-A) was administered in the diet at 0, 60, 300, or 600 ppm (52-week average 0, 2.6, 13.6, or 28.2 mg/kg/day, respectively, for males; 0, 3.4, 18.0, or 37.4 mg/kg/day, respectively, for females) to Sprague-Dawley CD BR VAF/Plus rats (25/sex/group) for 52 weeks, followed by a 16-week recovery period during which the remaining rats were fed the control diet. The rats were evaluated for reactions in functional observational battery followed by motor activity measurements 1 week before the test diets were provided; 4, 8, 13, 26, 39, and 52 weeks after the first day of exposure; and 13 weeks after the cessation of treatment. A portion of the rats in each treatment group were sacrificed for neuropathological examination following 13 or 52 of exposure, or 16 weeks of recovery.

In the 600 ppm dose group, both sexes exhibited statistically significant decreases in average body weights, body weight gains, absolute and relative feed consumption, feed efficiency, and water consumption (males only). Neurohistological examination of males sacrificed after 13 weeks of exposure revealed myelin sheath swelling in the spinal nerve roots (5/5), compared to 2/5 in the controls. At 52 weeks, a more generalized myelinopathic process consisting of vacuolar myelinopathy (6/10), vacuolation (6/10), and/or mild myelin sheath swelling (9/10), was found. This process was not associated with myelin or axon degeneration and was not evident in rats sacrificed after 16 weeks of recovery. In the 300 ppm dose group, both sexes exhibited decreases in average body weights, body weight gains, feed efficiency, absolute feed consumption (females only) and water consumption (males only) at various times during the exposure period and body weight gains were reduced (non-significantly) for males during recovery. The myelinopathic observations described in the 600 ppm group males was also found in the 300 ppm group of rats after 13 and 52 weeks exposure but were less severe and at a lower incidence. In the 60 ppm dose group rats, minimum myelin sheath swelling was seen in the Gasserian ganglia of one male at 52 weeks and spinal nerve roots of 3/5 males (compared to 2/5 controls) after 13 weeks of exposure. The toxicologic importance of these findings is equivocal since swelling in the spinal nerve roots was absent in the 60 ppm group after 52 weeks. Neuropathological changes were confined to males; females were not affected. **The LOEL is 300 ppm (13.6 mg/kg/day) based on the presence of myelinopathic alterations in the 300 ppm group male rats, decreased average body weights, body weight gains, feed**

[1] Although, the sponsor put 83-1a on the cover of the study, the study only satisfies the 82-7SS requirement and was not meant to be a chronic rat study.

efficiency, absolute feed consumption (females) and water consumption (males). The NOEL is 60 ppm (2.6 mg/kg/day).

This one-year dietary neurotoxicity study is classified **Acceptable** and satisfies the guideline requirement for a neurotoxicity study (82-7SS) in rats.

2) 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 (2.8 and 3.7 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 (rounded from 2.6 and 2.8 mg/kg/day from studies 1 and 2 above, respectively) based on the non-neoplastic brain lesions observed in male rats and both sexes of mice as well as the scabbing of skin in male mice at 16.6 mg/kg/day (LOEL).

efficiency, absolute feed consumption (females) and water consumption (males). The NOEL is 60 ppm (2.6 mg/kg/day).

This one-year dietary neurotoxicity study is classified **Acceptable** and satisfies the guideline requirement for a neurotoxicity study (82-7SS) in rats.

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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 (2.8 and 3.7 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 (rounded from 2.6 and 2.8 mg/kg/day from studies 1 and 2 above, respectively) based on the non-neoplastic brain lesions observed in male rats and 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: The neurotoxicity study was used to establish the RfD /also supporting this endpoint were similar central nervous system lesions observed in

the mouse carcinogenicity study (NOEL 2.8 mg/kg/day)]. Since these oral studies were selected for a dermal exposure scenario, the dermal absorption factor of 5% must be used in risk assessment.

This risk assessment is required. An Uncertainty Factor (UF) of 100 and 10-fold modifying factor (MF) is appropriate.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the combined LC_{50} of 1.9 mg/L, chlorfenapyr (Pirate) is placed in Tox. Cat. III, indicating low toxicity by this route (MRID No.:42770209). *However, if there is a concern for high exposure via this route, a risk assessment may be required.*

With the exception of the acute inhalation toxicity study, there are no inhalation toxicity studies available for selection of a dose and endpoint for inhalation exposure risk assessment. There an oral NOEL should be used for risk assessment if needed.

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CANCER CLASSIFICATION AND BASIS: *Pirate® was reviewed by the HED Cancer Peer Review Committee because of possible carcinogenicity trends (meeting date 9/25/96). In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), chlorfenapyr was characterized as "cannot be determined, suggestive".*

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 rat 1-year neurotoxicity study (NOEL 2.6 mg/kg/day) *[also supporting this endpoint are similar central nervous system lesions observed in the mouse carcinogenicity study (NOEL 2.8 mg/kg/day)]* and applying an Uncertainty Factor (UF) of 100 to account for interspecies and intraspecies variability and additional 10-fold modifying factor (MF) for lack of understanding of the cause, and possible further unknown toxicity with regard to the developing young is considered appropriate for this chemical.

NOEL for critical study: 2.6 mg/kg in male rats

Study Type - Guideline No.: One year neurotoxicity - rat §82-7

MRID: 43492833

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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 - 1085) 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