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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: November 18, 1999

MEMORANDUM

SUBJECT: **CHLORFENAPYR**: - Report of the Hazard Identification Assessment Review Committee - dermal absorption revisit, inhalation endpoints and aggregate recommendation only.

FROM: Marion Copley, D.V.M., D.A.B.T., Toxicologist *Jan Rowland for MC*
Registration Action Branch 1
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THROUGH: Pauline Wagner, Co-Chair *Pauline Wagner 11/22/99*
and
Jess Rowland, Co-Chair *Jess Rowland 11/19/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Jennifer Rowell, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 129093

On October 19, 1999, the Health Effects Division (HED) Hazard Identification Review Committee (HIARC) evaluated the toxicity data base for chlorfenapyr (Pirate®) to determine which endpoints to use for risk assessment due to inhalation exposure. Also determined were the recommendations for aggregate exposure. This document only contains the results of this meeting.

There are documents available on the LAN that contain the conclusion of the TES (report dated 11/17/97), RfD (report dated 10/25/96) and Cancer Peer Review (report dated 9/25/96) meetings.

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Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Karen Hamernik, Pamela Hurley, Tina Levine, Nancy McCarroll, Nicole Paquette, Kathleen Raffaele, Jess Rowland, PV Shah, Pauline Wagner, and Brenda Tarplee (Executive Secretary).

Member(s) in absentia: Mike Ioannou and Susan Makris.

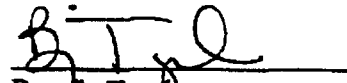
Data was presented by Marion Copley of the Registration Action Branch 1.

Data Presentation:
and
Report Presentation

 11/19/99

Marion Copley, D.V.M., D.A.B.T.
Toxicologist

Report Concurrence:



Brenda Tarplee
Executive Secretary

I. INTRODUCTION

On October 19, 1999, the Health Effects Division (HED) Hazard Identification Review Committee (HIARC) reevaluated the dermal absorption factor, and evaluated the toxicity data base to determine the endpoints to use for risk assessment due to inhalation exposure. Also determined were the recommendations for aggregate exposure. This document only contains the results of this meeting.

There are documents available on the LAN for TES (24-JUL-1996, 27-JAN-1997, 17-NOV-1997), RfD (25-OCT-1996, 21-NOV-1997) and cancer peer review (9-JAN-1997) meetings.

II. HAZARD IDENTIFICATION

A. Occupational/Residential Exposure

1. Dermal Absorption

Based on its physical form, molecular weight, partition coefficient value, and water solubility, Chlorfenapyr is unlikely to be readily absorbed through the human skin:

Physical State:	Solid
Molecular Weight:	407
Water Solubility:	0.14 mg/ml
Log K_{ow} :	4.85 at 25 degree C

Therefore the dermal absorption of chlorfenapyr is estimated to be 5%.

Dermal absorption 5%

2. Inhalation Exposure

Chlorfenapyr, based on the LC_{50} value of = 1.9 mg/L is placed in Toxicity Category III. Since only an acute inhalation toxicity study was available, the Committee recommended the use of oral NOAELs for the inhalation exposure risk assessments.

Study Selected: Subchronic Toxicity-Dog/1-year Neurotoxicity-Rat

MRID Nos 42770220 / 43492833

Executive Summaries:

Subchronic Oral Toxicity in Dogs

In a subchronic oral toxicity study in dogs (MRID 42770220), chlorfenapyr technical was administered to dogs for 13 weeks at doses of 0, 60, 120 or 247 ppm (0, 2.16, 4.23 or 6.1 mg/kg/day, respectively). The 247 ppm was based on the time weighted average concentration

of chlorfenapyr in the diet of 300 ppm from Day 1 - 14, 240 ppm from Day 15 - 25 and 200 ppm from Day 25 - 93 (5.2, 5.9 and 7.2 mg/kg/day, respectively). At the high dose of 247 ppm there was a significant reduction in body weight gain, feed efficiency, and increased emaciation. The LOAEL is 6.1 mg/kg/day (247 ppm), based on reduced body weight gain and feed efficiency and emaciation. The NOAEL is 4.23 mg/kg/day (120 ppm).

NOTE: these effects were first observed during the first several weeks of the study.

One-Year Dietary Neurotoxicity Study in Rats

In a one-year dietary neurotoxicity study (MRID 43492833), chlorfenapyr technical 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 rats 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 a 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 weeks 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 compared to the controls. At 52 weeks, a more generalized myelinopathic process consisting of vacuolar myelinopathy, vacuolation, and/or mild myelin sheath swelling, 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 were 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 three males 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 LOAEL is 13.6 mg/kg/day (300 ppm) based on the presence of myelinopathic alterations in the 300 ppm group male rats, decreased average body weights, body weight gains, feed efficiency, absolute feed consumption (females) and water consumption (males). The NOAEL is 2.6 mg/kg/day (60 ppm).**

Dose and Endpoint for Risk Assessment:

Short- and Intermediate-Term: Systemic NOAEL = 4.23 mg/kg/day based on reduced body weight gain and feed efficiency and emaciation at the LOAEL of 6.1 mg/kg/day.

Long-Term: Systemic NOAEL = 2.6 mg/kg/day based on myelinopathic alterations in the male rats, decreased average body weights, body weight gains, feed efficiency, absolute feed consumption (females) and water consumption (males) at 13.6 mg/kg/day.

Comments About Study and/or Endpoint: The Committee selected the oral NOAELs for these risk assessments because of the: 1) lack of short- and long-term inhalation studies and 2) potential for exposure via this route. For short term exposure signs of toxicity were observed as early as the first weeks of the study. For chronic exposure, similar central nervous system lesions and skin lesions were observed in the mouse carcinogenicity study (NOEL 2.8 mg/kg/day)(MRID 43492838).

Inhalation Risk Assessment The doses identified for inhalation risk assessments are from oral studies (i.e., use of oral NOAEL). Therefore the risk assessments should be conducted as follows:

For short- and intermediate-term inhalation exposure risk assessment, the inhalation exposure component (i.e. $\mu\text{g a.i./L/day}$) using 100% absorption rate (default value), application rate, and number of acres treated should be converted to an equivalent oral dose (mg/kg/day). This dose then should be compared to the oral subchronic dog NOAEL of 4.23 mg/kg/day to calculate the MOE. Dermal exposure can NOT be combined with inhalation, since the dermal assessment was based on a different endpoint (liver changes in a dermal study).

For chronic inhalation exposures, the dermal and inhalation exposures can be combined since the dose selected is an oral equivalent dose. Risk assessments should follow the route-to-route extrapolation as below:

- (i) The inhalation exposure component (i.e. $\mu\text{g a.i./L/day}$) using 100% absorption rate (default value) and application rate should be converted to an equivalent oral dose (mg/kg/day)
- (ii) The dermal exposure component (i.e. $\mu\text{g a.i./L/day}$) using a 5% absorption factor and the application rate should be converted to an equivalent oral dose (mg/kg/day)
- (iii) The equivalent oral doses (Step i and ii) should be combined and then compared to the oral NOAEL for the appropriate exposure period to calculate the MOEs. The NOAEL is as follows for chronic exposure: 2.6 mg/kg/day based on a 1 year rat neurotoxicity study.

These risk assessments are required.

III. Recommendation for Aggregate Exposure Risk Assessments

For short- and intermediate-term aggregate exposure risk assessment, oral and dermal exposures can not be combined due to differences in the toxicological endpoints via the oral (reduced body weight gain, feed efficiency and emaciation) and dermal (liver changes) routes.

For chronic-term aggregate exposure risk assessment, oral, dermal and inhalation exposures can be combined since dermal and inhalation exposure are corrected to oral equivalent doses and are all based on the same endpoint as the RfD.

TABLE 1. Summary of Toxicological Endpoints for Chlorfenapyr

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary	HIARC did not address the Acute RfD for Chlorfenapyr at this time.		
Chronic Dietary (non-cancer)	HIARC did not address the Chronic RfD for Chlorfenapyr at this time.		
Short-Term (dermal)	NOAEL=100 mg/kg/day (dermal study)	LOAEL=400 mg/kg/day (increased cholesterol, relative liver weights and cytoplasmic vacuolation of the liver in male and females)	28-day dermal toxicity study - rabbits
Intermediate-Term (dermal)	NOAEL: 100 mg/kg/day (dermal study)	LOAEL=400 mg/kg/day (increased cholesterol, relative liver weights and cytoplasmic vacuolation of the liver in male and females)	28-day dermal toxicity study - rabbits
Long-Term (dermal)	NOAEL=2.6 mg/kg/day ¹ (oral study)	LOAEL = 13.6 mg/kg/day (decreased body weight gains brain lesions (vacuolation) and/or scabbing of the skin in a 1 year neurotoxicity study in rats and a chronic/carcinogenicity study in mice) Acceptable MOE = 100	1 yr neurotox. study - rats (oral), chr/ onco - mice
Short-Term (inhalation)	NOAEL=4.2 mg/kg/day ² (oral study)	LOAEL = 6.1 mg/kg/day (reduced body weight gain and feed efficiency and emaciation)	Subchronic oral study-dog
Intermediate-Term (inhalation)	NOAEL=4.2 mg/kg/day ² (oral study)	LOAEL = 6.1 mg/kg/day (reduced body weight gain and feed efficiency and emaciation)	Subchronic oral study-dog
Long-Term (inhalation)	NOAEL=2.6 mg/kg/day ² (oral study)	LOAEL = 13.6 mg/kg/day (decreased body weight gains, brain lesions (vacuolation) and/or scabbing of the skin in a 1 year neurotoxicity study in rats and a chronic/ carcinogenicity study in mice)	1 yr neurotox. study - rats (oral), chr/ onco - mice
Cancer		Classified as "cannot be determined, suggestive". Use the RfD for chronic exposures.	Dietary/ Dermal/ Inhalation

¹ Use the appropriate dermal absorption factor (5 %) since the NOAEL is from an oral study.

² Use the appropriate inhalation absorption factor (100 %) since the NOAEL is from an oral study.

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