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MICROFICHE
013485

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

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Chemical Name: Paclobutrazol

PC Code: 125601

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 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: Pamela McHenley Date: 4/11/94

Branch Chief: Karl D. Baetcke Date: 4/11/94

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Dermal Absorption Data (if available)

MRID: 410482-02

% absorbed:

Male rats were dosed dermally on an area of 10 cm^2/rat. The highest % dose absorbed and remaining on washed application site for exposures of 10 and 24 hours are as follows: Dose of 0.011 mg/rat: total absorbed after 10 hrs.: 15.1%. After 24 hrs.: 24.5%.

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Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.: 83-3(a) and (b)

Accession Nos: 251747, 251747, 254864;
MRID No: 407343-02

Summary (Enter Standard Executive Summary or equivalent):

In a developmental toxicity study in New Zealand white rabbits, Paclobutazol was tested at the following dose levels: 0, 25, 75 or 125 mg/kg/day. The maternal NOEL was 75 mg/kg/day and the maternal LOEL was 125 mg/kg/day based on decreased bodyweight gain during dosing period. The fertility was low and only the low and mid-dose groups had greater than the minimum number of litters at sacrifice. The developmental NOEL was greater than 125 mg/kg/day. No effects were observed. The study was graded as Core Supplementary.

In a second developmental toxicity study in rabbits, Paclobutrazol was tested at the following dose levels: 0, 25, 75 or 125 mg/kg/day. The maternal NOEL was 75 mg/kg/day and the maternal LOEL was 125 mg/kg/day (HDT) based on decrease in body weights and food consumption during dosing. The developmental NOEL is 75 mg/kg/day and the developmental LOEL is 125 mg/kg/day based on and increased incidence of pups with extra ribs. The study was graded Core Guideline.

In a developmental toxicity study in rats, Paclobutrazol was tested at the following dose levels: 0, 40, 100, 250 mg/kg/day. The maternal NOEL was 40 mg/kg/day and the maternal LOEL was 100 mg/kg/day based on decreased bodyweight gain and food utilization efficiency during dosing. Mortality (5/24) and grossly observable liver pallor and enlargement were observed at 250 mg/kg/day (HDT). The deaths occurred between 2 and 5 doses. The developmental NOEL was 40 mg/kg/day and the developmental LOEL was close to 40 but set at 100 mg/kg/day. The following effects were observed: delayed ossification and partial ossification of the odontal bone at 100 and 250 mg/kg/day (delayed ossification was statistically significant for fetuses at 40 mg/kg/day but not for litters). There was partial ossification of the occipital bone at 250 mg/kg/day. Cleft palate in 3 fetuses from 2 litters was observed at 250 mg/kg/day.

In a second developmental toxicity study in rats Paclobutrazol was tested at the following dose levels: 0, 2.5, 10, 40, 100 mg/kg/day. The maternal NOEL was greater than 100 mg/kg/day. The developmental NOEL was 10 mg/kg/day and the developmental LOEL was 40 mg/kg/day. The effects observed consisted of renal

dilatation, hydroureter and minor skeletal defects or variations. The study was graded Core Minimum.

Endpoint and dose for use in risk assessment: No endpoint could be found for acute dietary risk assessment.

Comments about study and/or endpoint: None.

This risk assessment is not required because no endpoint could be found. The results of four developmental toxicity studies in rats and rabbits indicated no acute endpoint.

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

Study Selected - Guideline No.: 83-3(a) and (b) and 82-2

Accession Nos.: 251747, 251747, 254864 251746;
MRID No: 407343-02

Summary (Enter Standard Executive Summary or equivalent):

In a developmental toxicity study in New Zealand white rabbits, Paclobutazol was tested at the following dose levels: 0, 25, 75 or 125 mg/kg/day. The maternal NOEL was 75 mg/kg/day and the maternal LOEL was 125 mg/kg/day based on decreased bodyweight gain during dosing period. The fertility was low and only the low and mid-dose groups had greater than the minimum number of litters at sacrifice. The developmental NOEL was greater than 125 mg/kg/day. No effects were observed. The study was graded as Core Supplementary.

In a second developmental toxicity study in rabbits, Paclobutrazol was tested at the following dose levels: 0, 25, 75 or 125 mg/kg/day. The maternal NOEL was 75 mg/kg/day and the maternal LOEL was 125 mg/kg/day (HDT) based on decrease in body weights and food consumption during dosing. The developmental NOEL is 75 mg/kg/day and the developmental LOEL is 125 mg/kg/day based on and increased incidence of pups with extra ribs. The study was graded Core Guideline.

In a developmental toxicity study in rats, Paclobutrazol was tested at the following dose levels: 0, 40, 100, 250 mg/kg/day. The maternal NOEL was 40 mg/kg/day and the maternal LOEL was 100 mg/kg/day based on decreased bodyweight gain and food utilization efficiency during dosing. Mortality (5/24) and grossly observable liver pallor and enlargement were observed at 250 mg/kg/day (HDT). The deaths occurred between 2 and 5 doses. The developmental NOEL was 40 mg/kg/day and the developmental LOEL was close to 40 but set at 100 mg/kg/day. The following effects were observed: delayed ossification and partial ossification of the odontal bone at 100 and 250 mg/kg/day (delayed ossification was statistically significant for fetuses at 40 mg/kg/day but not for litters). There was partial ossification of the occipital bone at 250 mg/kg/day. Cleft palate in 3 fetuses from 2 litters was observed at 250 mg/kg/day. However, these were not statistically significant when compared to controls.

In a second developmental toxicity study in rats Paclobutrazol was tested at the following dose levels: 0, 2.5, 10, 40, 100 mg/kg/day. The maternal NOEL was greater than 100 mg/kg/day.

The developmental NOEL was 10 mg/kg/day and the developmental LOEL was 40 mg/kg/day. The effects observed consisted of renal dilatation, hydroureter and minor skeletal defects or variations. The study was graded Core Minimum.

In a 21-day dermal study in rabbits, Paclobutrazol was tested at the following dose levels: 0, 10, 100, 1000 mg/kg/day. The NOEL was 10 mg/kg/day (intact skin) and the LOEL was 100 mg/kg/day. There was irritation at all dose levels with abraded skin and at 100 and 1000 mg/kg/day with intact skin. Irritation began to appear during 2nd week of applications. The degree increased with increasing dose. Hyperkeratosis, acanthosis and inflammatory changes of superficial dermis were observed. The study was graded Core Minimum.

Endpoint and dose for use in risk assessment: None

Comments about study and/or endpoint: None

This risk assessment is not required.

Although one developmental toxicity study in rats reported renal dilatation at 40 mg/kg/day, the effect was not reproduced in three other developmental toxicity studies (2 in rabbits). The NOEL for systemic effects from a 21-day dermal toxicity study was 1000 mg/kg/day on intact skin.

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

Study Selected - Guideline No.: 82-2

Accession No.: 251746

Summary (Enter Standard Executive Summary or equivalent):

In a 21-day dermal study in rabbits, Paclobutrazol was tested at the following dose levels: 0, 10, 100, 1000 mg/kg/day. The NOEL was 10 mg/kg/day (intact skin) and the LOEL was 100 mg/kg/day. There was irritation at all dose levels with abraded skin and at 100 and 1000 mg/kg/day with intact skin. Irritation began to appear during 2nd week of applications. The degree increased with increasing dose. Hyperkeratosis, acanthosis and inflammatory changes of superficial dermis were observed. The study was graded Core Minimum.

In a second developmental toxicity study in rats Paclobutrazol was tested at the following dose levels: 0, 2.5, 10, 40, 100 mg/kg/day. The maternal NOEL was greater than 100 mg/kg/day. The developmental NOEL was 10 mg/kg/day and the developmental LOEL was 40 mg/kg/day. The effects observed consisted of renal dilatation, hydroureter and minor skeletal defects or variations. The study was graded Core Minimum.

Paclobutrazol was tested in a two-generation reproduction study in Wistar rats at the following dose levels: 0, 50, 250 and 1250 ppm (0, 2.5, 12.5 or 62.5 mg/kg/day) in the diet. The reproductive/systemic LOEL is 250 ppm (12.5 mg/kg/day) based on increases in liver weights and on fatty change in the liver of parental females; and on an increased incidence of chromodacryorrhea and thickened eyelids, dental malocclusion, increased liver weights, mottling or accentuation of the lobular structure, liver enlargement, pallor and discoloration in male and female pups. The reproductive/systemic NOEL is 50 ppm (2.5 mg/kg/day). The study is classified as Core Guideline Data and satisfies the regulatory requirement for a multigeneration study in rats (MRID No. 407343-03).

Endpoint and dose for use in risk assessment: The endpoints used for the risk assessment are as follows: increases in liver weights, liver enlargement, mottling or accentuation of the lobular structure, pallor and discoloration and fatty change in the liver; increased incidence of chromodacryorrhea and thickened eyelids and dental malocclusion. The dose to be used in a risk assessment is a LOEL of 12.5 mg/kg/day and a NOEL of 2.5 mg/kg/day in the diet.

Comments about study and/or endpoint: None.

This risk assessment is required.

Paclobutrazol is 24.5% absorbed in a dermal absorption study after 24 hours. Therefore, the NOEL for the reproduction study (2.5 mg/kg/day) is multiplied by approximately 4 when calculating the risk due to dermal exposure. This gives a value of 10 mg/kg/day.

The reproduction study was also the basis for the RfD value.
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Cancer Classification and Basis: The Agency RfD Committee has reviewed this chemical, however, the draft is not yet final. The two oncogenicity studies are considered to be inadequate because the animals were not tested at high enough dose levels.

Q_1^* = N/A

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R_fD and basis: The recommended RfD is 0.025 mg/kg/day. This value was calculated by using the 2-generation reproduction study in the rat NOEL for reproductive/systemic effects of 2.5 mg/kg/day and a safety factor of 100. This RfD has been verified or approved by the Health Effects Division RfD Committee, but not the Agency RfD Committee.

NOEL for critical study: 2.5 mg/kg/day

Study Type - Guideline No.: 83-4

MRID: 407343-03

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