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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

013122

TOXICOLOGY ENDPOINT SELECTION DOCUMENT as of 8-29-95

Chemical Name: AC 263,222 (CADRE)

PC Code: 128943

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.

Reviewer: Edwin Budd, M.A. Edwin R. Budd Date: 8/31/95
Section Head: Karen Hamernik, Ph.D. Karen Hamernik Date: 8/31/95
Acting Branch Chief: Marion Copley, D.V.M. Marion Copley Date: 10/23/95

Dermal Absorption Data: A dermal absorption study on AC 263,222 is not available. Oral and dermal NOELs from short-term studies in rabbits, however, are available.

Studies Selected - Guideline Nos.:

- (1) 83-3(b): developmental toxicity study in rabbits
(gavage study) MRID 427114-23
- (2) 82-2: 21-day dermal toxicity study in rabbits
MRID 427114-20

Summaries:

- (1) 83-3(b): See summary on page 3 (short term occupational or residential exposure).
- (2) 82-2: Doses of 0, 250, 500 or 1000 mg/kg/day of AC 263,222 were applied to the clipped backs of New Zealand albino rabbits for 6 hours/day, 5 days/week, for 3 weeks.

The highest dose tested was the limit dose (1000 mg/kg/day) specified in the guideline. The NOEL $\geq$ 1000 mg/kg/day for dermal irritation and systemic toxicity. A LOEL was not established.

% absorbed:

(1) 83-3(b): maternal NOEL = 350 mg/kg/day

(2) 82-2: NOEL $\geq$ 1000 mg/kg/day

Estimated Percent Dermal Absorption = $\frac{\text{oral NOEL}}{\text{dermal NOEL}}$ = $\frac{350 \text{ mg/kg/day}}{\geq 1000 \text{ mg/kg/day}}$ = $\leq 35\%$

Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.:

84-2: in vivo chromosome aberration in rat bone marrow cells MRID 427114-26

Summary:

84-2: Negative in the rat bone marrow in vivo cytogenetic assay in fasted male and female Sprague Dawley strain rats (4/sex/group) administered 5000 mg/kg of technical grade AC 263,222 by gavage using 6-, 18-, and 30-hour harvests. Male and female rats were also treated with 500 and with 1667 mg/kg, but cells from these animals were not analyzed. The diarrhea reported by the study author in "several" animals (group and sex not specified) was attributed to the corn oil solvent. No other signs of toxicity were reported.

Endpoint and dose for use in risk assessment:

None. No treatment-related effects were observed at a dose level of 5000 mg/kg.

Comments about studies and/or endpoint: An acute dietary risk assessment need not be performed since there were no treatment-related effects observed at the dose level of 5000 mg/kg in either male or female rats.

This risk assessment is not required.

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

Study Selected - Guideline No.:

83-3(b): developmental toxicity study in rabbits
(gavage study) MRID 427114-23

Summary:

In a developmental toxicity study, New Zealand White rabbits were administered AC 263,222 via gavage at daily doses of 0, 175, 350, 500 or 700 mg/kg/day on gestation days (GDs) 7-19, inclusive. High mortality among dams at 700 mg/kg/day precluded results from this dose level being considered in the determination of the NOELs and LOELs for maternal and developmental toxicity. [The time of death for the first treatment-related mortality at 700 mg/kg/day in this study was not reported in the DER.]

The maternal NOEL = 350 mg/kg/day and the maternal LOEL = 500 mg/kg/day, based on decreased body weight gain and decreased food consumption both beginning within 7 days after initiation of dosing on GD 7. At 700 mg/kg/day, increased mortality was also observed in the treated dams. The developmental NOEL = 500 mg/kg/day and the developmental LOEL was not determined (> 500 mg/kg/day).

Endpoint and dose for use in risk assessment:

Decreased body weight gain and decreased food consumption in dams beginning within 7 days after initiation of dosing at the LOEL of 500 mg/kg/day. Dose to be used for risk assessment is the NOEL of 350 mg/kg/day.

Comments about study and/or endpoint: Although maternal effects in developmental toxicity studies are ordinarily used as endpoints for intermediate term exposures (7 days to several months), rather than for short term exposures (1 to 7 days), in this particular study the effects were observed to begin to occur within 7 days after initiation of dosing (actually during GDs 7-14). These same effects continued through the remainder of the dosing period (GDs 14-19), but were observed to diminish thereafter in the post-dosing period. Treatment-related mortality for dams was not observed at the dosage level of 500 mg/kg/day.

When adjusted for percent dermal absorption ($\leq 35\%$), the maternal NOEL in this study is > 1000 mg/kg/day.

This risk assessment is not required.

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

Study Selected - Guideline No.:

83-1(b): 1-year chronic feeding study in dogs
(dietary study) MRID 427114-21

Summary:

83-1(b): AC 263,222 was administered to beagle dogs (6/sex/dose) via the diet for 1 year at dietary levels of 0, 5000, 20000 or 40000 ppm. The equivalent average daily test material intakes were 0, 137, 501 and 1141 mg/kg/day in males and 0, 180, 534 and 1092 mg/kg/day in females. At 5000 ppm, the following treatment-related effects were observed: minimal degeneration and/or necrosis with minimal lymphocyte and macrophage infiltration in the skeletal muscle of the thigh and/or abdomen of males and females [first observed at 1 year]; minimal infiltration in the diaphragm of 1 male and 1 female dog [first observed at 1 year]; and decreased serum creatinine in females [first observed at 6 months]. In addition, at 20000 ppm and above, both males and females showed increased salivation and effects on muscle, liver and blood. Additional effects on muscle included an increased incidence of lymphocyte and macrophage infiltration in the muscle fibers of the esophagus of both males and females and degeneration/necrosis of the muscle of the esophagus of 1 male. Decreased serum creatinine was also observed in males. Effects on the liver included increases in serum cholesterol, the liver/brain weight ratio in both males and females, and the absolute liver weight in males. Effects on the blood included decreases in hematocrit and hemoglobin and anisocytosis in both males and females, increases in reticulocytes count and hyperchromatic red cells and decreases in mean corpuscular volume and mean corpuscular hemoglobin in males; and decreases in red blood cell count in females. In addition, slightly increased erythropoiesis was observed in the bone marrow of 1 male and 1 female and in the spleen of 1 male. Females also showed decreases in food consumption, and males showed increases in serum phosphate. [Whereas histopathological and organ weight changes were first observed at 1 year, several of the changes in clinical chemistry enzymes and particularly the hematological parameters were first observed at 35 days, when these determinations were first made]. At 40000 ppm, both males and females also showed vomiting and decreased body weight gain, as well as additional effects on the muscle (further changes in skeletal muscle histopathology and related serum enzymes), liver (additional changes in serum enzymes), and the blood (additional changes in

hematology parameters and the hematopoietic system). The NOEL in this study < 5000 ppm (< 137 mg/kg/day in males). The LOEL = 5000 ppm, based on minimal effects on the skeletal muscle.

Endpoint and dose for use in risk assessment:

83-1(b): Changes in hematological parameters indicative of anemia and compensatory erythropoiesis first observed at 35 days and changes in clinical chemistry enzymes indicative of liver damage also first observed at 35 days. The effects were observed at the dose levels of 20000 ppm and above. The NOEL for these effects was 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females).

Comments about study and/or endpoint:

83-1(b): The most sensitive endpoint in this 1-year chronic feeding study was degeneration/necrosis in the skeletal muscle (with infiltration of lymphocytes/macrophages) accompanied by decreases in serum creatinine in females. These effects, however, were not observed until after 6 months. The changes in hematological parameters and changes in clinical chemistry enzymes, although observed at higher dose levels, were considered to be the appropriate endpoints for the intermediate term risk assessment (1 week to several months) because these effects were first observed at 35 days.

This risk assessment is required.

Chronic Occupational Exposure (Longer than Several Months)

Study Selected - Guideline No.:

83-1(b): 1-year chronic feeding study in dogs
(dietary study) MRID 427114-21

Summary:

83-1(b): See summary on pages 4 and 5 (intermediate term occupational or residential exposure).

Endpoint and dose for use in risk assessment:

83-1(b): Minimal degeneration/necrosis of skeletal muscle fibers (with minimal infiltration by lymphocytes/macrophages) in males and females (first observed at 1 year) and decreased serum creatinine in females (first observed at 6 months). The NOEL for this effect < 5000 ppm (< 137 mg/kg/day in males). The LOEL = 5000 ppm (137 mg/kg/day in males).

Comments about study and/or endpoint:

83-1(b): The most sensitive endpoint in this 1-year chronic feeding study was minimal degeneration/necrosis in the skeletal muscle (with minimal infiltration of lymphocytes/macrophages) accompanied by decreases in serum creatinine in females. These effects were observed at 5000 ppm (137 mg/kg/day in males and 180 mg/kg/day in females), the lowest dose level tested in both males and females. Since minimal treatment-related effects were observed at the lowest dose level tested, the LTL Peer Review Committee concluded that for the purposes of chronic risk assessment an acceptable MOE would be ≥ 300 .

This risk assessment is required.

Cancer Classification and Basis: The HED RfD/Peer Review Committee classified AC 263,222 as a **Group E carcinogen** (Evidence of Non-Carcinogenicity for Humans) on 8/24/95. This classification was based on the absence of treatment-related tumors in acceptable chronic feeding/carcinogenicity studies in both rats and mice. The HED RfD/Peer Review Committee also determined at the same meeting that it will not be necessary to convene a Cancer Peer Review Committee meeting to confirm their classification of AC 263,222.

RfD and Basis: RfD = 0.5 mg/kg/day, based on a LOEL of 5000 ppm (137 mg/kg/day in males) determined in a 1-year chronic feeding study in dogs (uncertainty factor = 300: 100 for interspecies extrapolation and intraspecies variability and an additional 3 to account for the lack of a NOEL in the critical study). Effects observed at the LOEL were minimal degeneration/necrosis in the skeletal muscle (with infiltration of lymphocytes/macrophages) and decreases in serum creatinine in females.

NOEL for critical study: < 137 mg/kg/day (lowest dose level tested)

LOEL for critical study: 137 mg/kg/day

Study Type - Guideline No.:

83-1(b): 1-year chronic feeding study in dogs
MRID 427114-23

Acute Toxicity Endpoints

The table below summarizes the results of acute toxicity studies on AC 263,222 and the toxicity categories for the different routes of administration:

ACUTE TOXICITY DATA FOR AC 263,333

Test	Acute Toxicity	
	Result	Category
Acute Oral LD ₅₀ (rat) ^{1,a}	> 5,000 mg/kg	IV
Acute Dermal LD ₅₀ (rabbits) ^{2,a}	> 2,000 mg/kg	III
Acute Inhalation LC ₅₀ (rat) ^{3,a}	> 5.52 mg/L	IV
Eye Irritation (rabbit) ^{4,a}	Mild Irritant	III
Dermal Irritation (rabbit) ^{5,a}	No Irritation	IV
Skin Sensitization (guinea pig) ^{6,a}	Negative	N/A

¹⁻⁶ MRIDs 427114-07, 427114-08, 427114-09, 427114-10, 427114-11 and 427114-12

^a Test material was technical grade AC 263,222.

N/A = not applicable

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