

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Alachlor
CASRN: 15972-60-8

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts.

RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 1 mg/kg-day [Study 1 NOAEL(adj)]
UF: 100 MF: 1 RfD: 1E-2 mg/kg-day Confidence: High

Crit Effect: (1) Hemosiderosis, hemolytic anemia

	NOAEL (Study 1)	LOAEL (Study 1)
Reported	1 mg/kg-day	3 mg/kg-day
ADJ	1 mg/kg-day	3 mg/kg-day
Study Type	1-Year Dog Feeding Study	1-Year Dog Feeding Study
Reference	Monsanto Co., 1984a	Monsanto Co., 1984a

1) Monsanto Co., 1984a
1-Year Dog Feeding Study

Critical Effect: Hemosiderosis, hemolytic anemia

Defined Dose Levels:

NOAEL= 1 mg/kg-day
NOAEL(ADJ)= 1 mg/kg-day
LOAEL= 3 mg/kg-day
LOAEL(ADJ)= 3 mg/kg-day

Conversion Factors: Actual dose tested

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

Monsanto Company. 1984a. MRID No. 00148923; HED Doc No. 004660. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Beagle dogs (6/sex/dose) were administered alachlor at levels of 0, 1, 3, and 10 mg/kg-day for 1 year. The test material was given neat (with no dilution)

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in gelatin capsules and administered daily at least 1 hour after feeding a ration of pelleted dog chow. Control dogs were given empty gelatin capsules. Animals were observed twice daily during the study for signs of toxicity and mortality. Body weight and food consumption were measured, and clinical chemistry, hematology, and urinalysis testing were performed. All surviving animals were sacrificed after 12 months and examined for gross pathological changes.

The LEL for systemic toxicity is 3 mg/kg-day based on hemosiderosis seen in the kidney (1/6) and spleen (1/6). No hemosiderosis was associated with the liver in the mid-dose group. In the high-dose group, the hemosiderosis was seen in the liver (3/6) and correlated with hematologic findings showing red cell destruction and consequent red cell replenishment. The hematologic findings noted in the high-dose males were also seen as a trend (except for the increased reticulocyte count) in the mid-dose dogs. In addition, liver weights (absolute and relative-to-body-weight) were significantly ($p < 0.05$) higher in high-dose males. High-dose females also showed dose-related increases, but they were not statistically significant. Therefore, the NOEL for systemic toxicity is 1 mg/kg-day.

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for intraspecies-variability.

MODIFYING FACTORS:

None

ADDITIONAL COMMENTS / STUDIES

- 1) 1-Year Feeding - dog: Principal study -- see previous description; core grade guideline (Monsanto Co., 1984a)
- 2) 2-Year Feeding/Oncogenicity - rat: Dietary levels tested: 0, 0.5, 2.5, and 15 mg/kg-day; Groups of Long-Evans rat (50/sex/dose) were administered alachlor in the diet for 2 years. The LEL for systemic toxicity is 15 mg/kg-day based on molting of retinal pigmentation and increased mortality rate in females and abnormal disseminated foci in the liver of males. The NOEL for systemic toxicity is therefore 2.5 mg/kg-day. Core grade minimum (Monsanto Co., 1984b)
- 3) 3-Generation Reproduction - rat: Dietary levels tested: 0, 3, 10, and 30 mg/kg-day; Groups of Charles River Sprague-Dawley CD rats were fed diets containing alachlor over three generations. No significant adverse effects on the reproduction of adult rats were observed at any dose tested. Therefore the NOEL for reproductive toxicity is equal to or greater than 30 mg/kg-day. Compound-related effects were not observed in litter size, survival and lactation indices, or the pup body weights. However, gross pathology examinations indicated compound-related effects on kidneys (in parents and progeny) in the high-dose males and females especially in the F2 parent generation and F3b pups. These effects were kidney discoloration and significant increases (5-18%, $p < 0.05$) in kidney weights and

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kidney-to-body-weight ratios. These adverse effects were further confirmed microscopically by the presence of chronic nephritis in the F2 high-dose males (8/10 compared with 1/10 animals in the control groups) and a healing infarct in 1/10 F3b male pups in addition to hydronephrosis in another F3b male pup (total of 2/10 animals as compared with none in the control group). Lower ovary weights were also noted in the high-dose females of each parental generation and in F3b pups. This decrease was maximal in the F0 generation in which a 17% decrease ($p < 0.05$) in ovary weights was noted. This decrease was also associated with 17% decrease ($p < 0.05$) in the ovaries-to-body-weight ratio in the F0 high-dose females. This effect on kidneys is more remarkable in male. Based on kidney effects in both F2 adults and F3b pups, the LEL for systemic toxicity is 30 mg/kg-day. The NOEL for systemic toxicity is 10 mg/kg-day. Core grade minimum (Monsanto Co., 1981a)

4) Developmental Toxicity - rat: Dose levels tested: 0, 50, 150, and 400 mg/kg-day; Groups of pregnant Charles River COBS CD rats (25/dose) were administered alachlor in a corn oil vehicle by gavage on days 6 through 19 of gestation. High-dose dams exhibited soft stools, red matter around the nose and mouth, hair loss, and anogenital staining. Four high-dose dams died during the last 5 days of gestation. The cause of death was not apparent at necropsy. Mean body weight gains were moderately reduced in the high-dose group throughout the treatment period. Uterine examinations indicated that for each group of 25 females, 0, 5, 2, and 2 in each of the control, low-, mid-, and high-dose groups, respectively, were non-gravid. The four high-dose dams which died were gravid. All were viable fetuses in the treated groups. There were no statistically significant differences in mean numbers of viable fetuses, resorptions, post-implantation losses, total implantations, corpora lutea, sex distribution of pups, or mean fetal body weights in any of the treated groups when compared to the control group. In the high-dose group, a slight increase in the mean numbers of early and late resorptions resulted in a slight increase in mean post-implantation loss and a slight decrease in the mean number of viable fetuses. Based on soft stools, hair loss, anogenital staining, and maternal death, the NOEL and LEL for maternal toxicity are 150 and 400 mg/kg-day, respectively. Based on a slight decrease in mean fetal body weight and a slight increase in mean post-implantation loss, the NOEL and LEL for developmental toxicity are 150 and 400 mg/kg-day, respectively. Core grade guideline (Monsanto Co., 1980)

5) Developmental Toxicity - rabbit: Dose levels tested: 0, 50, 100, and 150 mg/kg-day; Groups of pregnant New Zealand White rabbits (18/dose) were administered alachlor by gastric intubation from gestation days 7 through 19, inclusive. Due to the death of two females in the control group during the treatment period, two additional females were mated and added to this group. Maternal toxicity was noted at the high dose in the form of reduced body weight gain during the dosing period with a rebound increase in body weight gain in the period following dosing. No other maternal toxicity was noted. No biologically relevant fetal external, visceral, or skeletal anomalies were noted. The NOEL and LEL for maternal toxicity are 100 and 150 mg/kg-day, respectively. The NOEL for developmental toxicity is equal to or greater than 150 mg/kg-day. Core grade minimum (Monsanto Co., 1988)

Other Data Reviewed:

1) 2-Year Feeding/Oncogenicity - rat: Dietary levels tested: 0, 100, 300, and 1000 ppm (0, 14, 42, and 126 mg/kg-day); Groups of Long-Evans rats (50/sex/dose

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with a additional 10/sex/dose for clinical studies) were fed diets containing alachlor for 2 years. Degenerative ocular and hepatic changes as well as other pathological gross and microscopic findings in the thyroid, kidneys, brain, spleen, heart, prostate, and ovaries were noted at all dose levels tested. The LEL for systemic toxicity is therefore 100 ppm (14 mg/kg-day), the lowest dose tested. A NOEL for systemic toxicity could not be established. Core grade minimum (Monsanto Co., 1981b)

2) 6-Month Feeding - dog: Dietary levels tested: 0, 5, 25, 50, and 75/100 mg/kg-day; Groups of beagle dogs (6/sex/dose) were administered alachlor daily in capsules for 6 months. The high-dose level was 100 mg/kg-day for weeks 1 through 3 but due to the severe toxicity the dose was reduced to 75 mg/kg-day for the remainder of the study. Liver weight values (absolute, relative-to-body-weight, and relative-to-brain) increased in males at 5 mg/kg-day and in both sexes at 25 mg/kg-day and above. The increases were often statistically significant ($p < 0.05$). Discoloration of the liver, fatty degenerations and billiary hyperplasia were also noted in both sexes at 25 mg/kg-day and above. Significant increases in SAP and LDH activity were also indicative of liver pathology. Other organ weight changes were noted at 5 mg/kg-day. Dose-related emaciation and mortality were noted in both sexes at 25 mg/kg-day and above. Mortality in the mid- and high-dose groups was high; all but 1 high-dose female died during the first 2-3 months of the study, and 4/6 males and 3/6 females of the mid-dose group were sacrificed in extremis during the study. A slight reduction in body weight gain was also noted at 5 mg/kg-day as compared with the control group. Based on the effects noted at the all dose levels, the LEL for systemic toxicity is equal to 5 mg/kg-day. A NOEL for systemic toxicity was not established. Core grade minimum (Monsanto Co., 1981c)

Data Gap(s): None

CONFIDENCE IN THE RfD

Study: High

Data Base: High

RfD: High

The principal study is of good quality and is given a high confidence rating. In addition, there are generally good toxicologic studies available on alachlor which, overall provide high confidence in the data base. High confidence in the RfD follows.

EPA DOCUMENTATION AND REVIEW

Source Document: This assessment is not presented in any existing U.S. EPA document.

Other EPA Documention: None

Agency Work Group Review: 03/11/86, 03/27/91

Verification Date: 03/27/91

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REVISION HISTORY

12/88 RfD Add Com: Core graded added to studies 1, 3 and 4
09/93 RfD Data: Oral RfD revised; same study and number