Metolachlor; CASRN 51218-45-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Metolachlor

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1990
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 10/01/1990

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. 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 Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that 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 Section II of this file.

NOTE: The Oral RfD for metolachlor may change in the near future pending the outcome of a further review now being conducted by the RfD/RfC Work Group.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weight gain **2-Year Rat Feeding Study** **Ciba-Geigy, 1983**	NOEL: 300 ppm (15 mg/kg/day) LEL: 3000 ppm (150 mg/kg/day)	100	1	1.5E-1 mg/kg/day
Reduced pup weights and parental food consumption **2-Generation Rat Reproduction Study** **Ciba-Geigy, 1981**	NOEL: 300 ppm (15 mg/kg/day) LEL: 1000 ppm (50 mg/kg/day)			

* Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

Ciba-Geigy Corporation. 1983. MRID No. 00129377. Ciba-Geigy Corporation. 1981. MRID No. 00080897. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Albino CD rats were divided into four groups and fed diets containing 0 (70 animals/sex), 30 (60 animals/sex), 300 (60 animals/sex), and 3000 (70 animals/sex) ppm (0, 1.5, 15, and 150 mg/kg/day) of technical metolachlor for 2 years (Ciba-Geigy, 1983). The apparent increase in the incidence of "testicular atrophy" in male rats that died on test in this study is of doubtful toxicological significance. This finding was not present at final sacrifice, and historical control data demonstrate that this finding is relatively common in rats. Therefore, the NOEL for this study is 300 ppm, based on decreased body weight gain in rats fed 3000 ppm, the highest dose tested.

Metolachlor technical was fed in the diet at dose levels of 0, 30, 300, or 1000 ppm (0, 1.5, 15, and 50 mg/kg/day) to Charles River CD strain albino rats (15 males and 30 females/group) beginning at 32 days (Ciba-Geigy, 1981). Animals were mated after either 14 weeks (F0) or 17 weeks (F1) on test. Mating occurred once per generation. The F1 parental animals were randomly selected from the F1a litter after weaning of F1a. F0 males were sacrificed after 135 days on test and F0 females were sacrificed after 164 days on test. Gross examination was conducted on all F0 males and females that displayed "untoward developmental anomalies". After 157 to 167 days on test, F1 males were sacrificed and after 197 to 208 days, F1 females were sacrificed. Gross and histological examinations were performed on all F1 parents. Five randomly selected male and 5 female F1a progeny in each dose group were also examined histologically.

No compound related effect on parental body weight was observed. Food consumption was not effected by treatment in the F0 generation, but was significantly reduced for the F1 30 ppm females at week 16, 300 ppm females at weeks 6, 7, and 10 and the 1000 females at weeks 1, 6, 7, 8, 10, 13, 13, and 15, as compared to controls. Clinical observations of parental rats indicated no treatment-related effects. Pup survival was likewise not effected by treatment. Pup body weights of the 1000 ppm dose group were significantly reduced for F1a litters on days 14 and 21 and on days 4, 7, 14, and 21 for the F2a litters. Pup body weights of the 30 and 300 ppm dose groups did not appear to be effected in a compound-related manner. Liver-to-body weight ratios were significantly increased for both F1 parental males and females at 1000 ppm. The thyroid-to-body weight ratio and thyroid-to-brain weight ratio of 1000 ppm F1 males were significantly increased. Body weights of the weanling 1000 ppm F1a females and F2a males were reduced, though not significantly, and body weights of F2a weanling females were significantly reduced. The NOEL and LEL for reproductive toxicity are 300 and 1000 ppm (15 and 50 mg/kg/day), respectively, based on reduced pup weights and reduced parental food consumption.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 100 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A) and uncertainty in the threshold for sensitive humans (10H).

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

1) 2-Year Feeding (oncogenic) - rat: Principal study - see previous description; core grade minimum (Ciba-Geigy Corp., 1983)

2) 2-Generation Reproduction - rat: Co-Principal study - see previous description; core grade guideline (Ciba-Geigy Corp., 1981)

3) Teratology - rat: Maternal, Fetotoxic, and Teratogenic NOEL=360 mg/kg/day (HDT); Maternal, Fetotoxic, and Teratogenic LEL=none; core grade minimum (Ciba-Geigy Corp., 1976)

4) Teratology - rabbit: Maternal NOEL=120 mg/kg/day; Maternal LEL=none; Fetotoxic and Teratogenic NOEL=360 mg/kg/day; Fetotoxic and Teratogenic LEL=none; core grade minimum (Ciba-Geigy Corp., 1980)

Other Data Reviewed:

1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=1000 ppm (150 mg/kg/day); Systemic LEL=3000 ppm (450 mg/kg/day); core grade minimum (Ciba-Geigy Corp., 1982)

Data Gap(s): 6-Month Dog Study is under review

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — High

Both co-critical studies are of good quality and are jointly given a medium confidence rating. Additional studies are supportive and of good quality; therefore, the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Pesticide Registration Standard, September 1980

Pesticide Registration Files

Agency Work Group Review — 04/22/1986, 05/25/1988, 06/22/1988, 12/14/1993

Verification Date — 06/22/1988

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name —Metolachlor
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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document.

IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen.

Basis — Classification is based on the appearance of proliferative liver lesions (combined neoplastic nodules and carcinomas) at highest dose tested (3000 ppm) in female rats.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Two chronic rat studies were conducted wherein metolachlor was incorporated in the diet for 2 years. Industrial Biotest Laboratories (IBT, 1979) fed 0, 30, 300, 1000, and 3000 ppm of metolachlor in the diet to 60 Charles River strain albino rats/sex/group. Proliferative hepatic lesions were significantly increased only in high-dose females when hyperplastic or neoplastic nodules were combined with angiosarcomas, cystic cholangiomas, cholangiomas and carcinomas. Inadequacies of this study, such as incomplete hematology, urinalysis, clinical chemistry, and dietary preparation records, prompted a repeat of the study.

Hazelton-Raltech, Inc. (1983) administered 0, 30, 300, or 3000 ppm metolachlor to 60-70 Charles River CD rats/sex/group for 104 weeks. There was a statistically significant increase in liver neoplastic nodules and carcinomas in the high-dose females when compared to controls. The increase was largely due to the occurrence of neoplastic nodules. No statistically significant increase in liver tumors was observed in male rats in either study.

Two chronic (2-year) mouse studies (IBT, 1977; Hazelton-Raltech, 1982) were conducted in which metolachlor was incorporated into the diet. IBT (1977) administered metolachlor at 0, 30, or 300 ppm; Halzelton-Raltech (1982) administered the compound at 300, 1000, or 3000 ppm. There were no oncogenic effects ($p>0.05$) noted in either study. The high dose produced weight reduction, thereby indicating that an MTD had been reached.

II.A.4. Supporting Data for Carcinogenicity

Metolachlor was not mutagenic in reverse mutation assays in Salmonella (U.S. EPA, 1985). Its structure is similar to alachlor, which has been classified B2, but alachlor produces oncogenic response at different tumor sites (alachlor produces nasal turbinate, stomach and thyroid tumors). Available metabolic data indicate that both metolachlor and alachlor are metabolized to aniline derivatives (U.S. EPA, 1985).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985

The Toxicology Branch Peer Review Committee Office of Pesticide Programs, Office of Pesticides and Toxic Substances reviewed data on metolachlor.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 11/10/1987

Verification Date — 11/10/1987

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name —Metolachlor
CASRN — 51218-45-2

VI.A. Oral RfD References

Ciba-Geigy Corporation. 1976. MRID No. 00015396. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1980. MRID No. 00041283. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1981. MRID No. 00080897. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1982. MRID No. 00039194, 00117597. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1983. MRID No. 00063398, 00084005, 00129377, 00144364, 00158924. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Hazelton-Raltech, Inc. 1982. Carcinogenicity Study with Metolachlor in Albino Mice. Cited in U.S. EPA, 1985.

Hazelton-Raltech, Inc. 1983. Chronic Rat Study of Metolachlor. Cited in U.S. EPA, 1985.

IBT (Industrial Biotest Laboratories). 1977. Oncogenic Mice. Cited in U.S. EPA, 1985.

IBT (Industrial Biotest Laboratories). 1979. Two-year Chronic Oncogenicity Oral Toxicity Study with Metolachlor in Albino Rats. Cited in U.S. EPA, 1985.

U.S. EPA. 1985. Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances memorandum on metolachlor. May 30.

VII. Revision History

Substance Name —Metolachlor
CASRN — 51218-45-2

Date	Section	Description
06/30/1988	I.A.	Withdrawn pending further review
08/22/1988	II.	Carcinogen summary on-line
09/07/1988	I.A.	Revised oral RfD summary added
10/01/1990	I.A.1.	Oral RfD corrected

VIII. Synonyms

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 01/31/1987

- 51218-45-2
- ACETAMIDE, 2-CHLORO-N-(6-ETHYL-o-TOLYL)-N-(2-METHOXY-1-METHYLETHYL)-
- o-ACETOTOLUIDIDE, 2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-
- 2-AETHYL-6-METHYL-N-(1-METHYL-2-METHOXYAETHYL)-CHLORACETANILID
- BICEP
- CGA-24705
- alpha-CHLOR-6'-AETHYL-n-(2-METHOXY-1-METHYLAETHYL)-ACET-o-TOLUIDIN
- alpha-CHLORO-2'-ETHYL-6'-METHYL-N-(1-METHYL-2-METHOXYETHYL)-ACETANILIDE
- 2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)ACET-o-TOLUIDIDE
- 2-CHLORO-N-(2-ETHYL-6-METHYLPHENYL)-N-(2-METHOXY-1-METHYLETHYL)ACETAMIDE
- CODAL
- COTORAN MULTI
- DUAL
- 2-ETHYL-6-METHYL-1-N-(2-METHOXY-1-METHYLETHYL)CHLOROACETANILIDE
- METELILACHLOR
- Metolachlor
- MILOCEP
- ONTRACK 8E
- PRIMAGRAM
- PRIMEXTRA