

Metribuzin; CASRN 21087-64-9

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 Metribuzin

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	12/01/1993

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Substance Name — Metribuzin
CASRN — 21087-64-9
Last Revised — 01/31/1987

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 metribuzin 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
Liver and kidney effects, decreased body weight, mortality	NOEL: 100 ppm (2.5 mg/kg/day)	100	1	2.5E-2 mg/kg/day
2-Year Feeding Study in Dogs	LEL: 1500 ppm (37.5 mg/kg/day)			
Mobay Chemical, 1974a				

*Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

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

Mobay Chemical Corporation. 1974a. MRID No. 00061260, 00139397. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Sixteen male and 16 female Beagle dogs were fed 0 (control), 25, 100, and 1500 ppm of metribuzin in the diet for 2 years. Animals were examined daily for physical appearance and weighed weekly during the first year and biweekly thereafter. Clinical-chemical tests were performed at the beginning of the study and at 2, 4, 6, 12, and 24 months (an additional hematologic test was conducted at 23 months). High mortality, decreased body weight, increased relative liver weight along with related clinical tests, and histopathologic findings of liver and kidney damage were noted in the 1500 ppm test group. The two lower dose groups did not exhibit any treatment-related effects.

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

UF — Based on a chronic exposure study, an uncertainty factor of 100 was used to account for the inter- and intra-species differences.

MF — None

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

Data Considered for Establishing the RfD

- 1) 2-Year Feeding - dog: Principal study - see discussion above; core grade minimum
- 2) 2-Year Feeding (oncogenic) - rat: NOEL=100 ppm (5.0 mg/kg/day), LOEL=300 ppm (15.0 mg/kg/day) (decreased body weight gain and pathologic changes in the liver, kidneys, uterus and mammary glands); core grade minimum (Mobay Chemical, 1974b)
- 3) Teratology - rabbit: Developmental Toxicity NOEL=15 mg/kg/day, Developmental Toxicity LEL = 45 mg/kg/day (no malformations noted); Maternal NOEL=15 mg/kg/day, Maternal LEL=45 mg/kg/day; Teratogenic NOEL=135 mg/kg/day (HDT); A/D ratio = 1; core grade guideline (Mobay Chemical, 1981a)
- 4) Teratology - rat: Maternal Toxicity NOEL=100 mg/kg (HDT); Teratogenic NOEL=100 mg/kg (HDT); core grade supplementary (Mobay Chemical, 1972)
- 5) 3-Generation Reproduction - rat: Reproductive NOEL=300 ppm (15 mg/kg/day) (HDT); Maternal Toxicity NOEL=300 ppm (HDT); core grade supplementary (Mobay Chemical, 1974c)

Other Data Reviewed

- 1) 2-Year Oncogenic - mouse: Systemic NOEL=800 ppm (120 mg/kg/day), Systemic LEL=3200 ppm (480 mg/kg/day) (based on hematocrit, hemoglobin, and liver weight data); core grade guideline (Mobay Chemical, 1981b)

Data Gap(s): Rat Teratology Study; Rat Reproduction Study

I.A.5. Confidence in the Oral RfD

Study — High

Database — Medium

RfD — Medium

The principal study is of good quality; although there was a minor question of dosage selection, it is given a high rating. Additional studies are also of good quality, but reproductive data are missing; therefore, confidence in the database can be considered medium to high. Confidence in the RfD can also be considered medium to high.

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

Pesticide Registration Standard June, 1985

Agency Work Group Review — 05/30/1986, 02/16/1994, 12/08/1994

Verification Date — 05/30/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Metribuzin conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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 — Metribuzin

CASRN — 21087-64-9

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Metribuzin

CASRN — 21087-64-9

Last Revised — 12/01/1993

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 — D; not classifiable as to human carcinogenicity

Basis — No human data and inadequate evidence from animal bioassays. Metribuzin did not increase the incidence of tumors in a lifetime dietary study using CD-1 mice when compared with both concurrent and historic controls. In a 2-year feeding study in Wistar rats, no significant differences in neoplastic findings between the test and control groups were found. Short-term studies in bacteria and mammalian systems suggest that metribuzin is not mutagenic.

II.A.2. Human Carcinogenicity Data

None. There are no studies investigating an association between human cancer and exposure to metribuzin.

II.A.3. Animal Carcinogenicity Data

Inadequate. No evidence of carcinogenicity was seen in CD-1 mice or Wistar rats exposed to metribuzin in the diet for 2 years. The study in rats was determined to be an adequate cancer bioassay; the study in mice was adequate in females only, as it appears that the MTD may not have been achieved in male mice.

Mobay Chemical Corp. (1981) examined the carcinogenic properties of metribuzin in a 2-year feeding study in outbred CD-1 mice. In this study, metribuzin technical (92.9% pure) dissolved in corn oil was added to a commercial diet fed to the mice (50/sex/group) at levels of 0, 200, 800 or 3200 ppm for 104 weeks. Based on food consumption and analytical chemistry results, the investigators estimated that these dietary levels of metribuzin provided doses of 0, 25, 111 or 438 mg metribuzin/kg/day for males and 0, 35, 139 or 567 mg metribuzin/kg/day for females. The body weights of the treated males did not differ significantly from those of the control group. A statistically significant increase in body weight (approximately 7%) was noted in the 800-ppm female dose group twice during the first year of the bioassay; with this exception body weights of female dose groups did not differ significantly from controls. Treatment with the pesticide did not affect survival rates. All major organs were examined upon necropsy and the tissues were prepared for histology. Organ-specific tumor incidences were not reported; with the exception of the total number of tumor-bearing animals, data were reported only as percentages. Malignant lymphomas were found in 20- 26% of the female mice in each group, and in 6% (high dose) to 26% (control group) in males. Hepatocellular neoplasms (adenomas and adenocarcinomas) were reported almost exclusively in male mice (7% high-dose group, 25% control group). The incidence of pulmonary neoplasms ranged from 20% in control males to 6% in the high-dose males, and from 2% in high-dose females to 22% in the low- and middle-dose female groups. The total number of tumor-bearing males was inversely related to the dose (28/50, 26/50, 22/50 and 18/50 for controls, low-, middle- and high-dose groups, respectively). The total number of tumor-bearing females was increased in the low- and middle-dose groups (28/50 and 29/50, respectively), but the incidence in the high-dose groups (20/50) was comparable with that in control females (19/50). Early mortality did not depress tumor occurrences. The percentage of total tumors that was determined to be malignant was either lower than or comparable to that of controls: 91%, 81%, 85% and 83% for control, low-, middle- and high-dose males, respectively; and 92%, 94%, 81% and 91% for control, low-, middle- and high-dose females, respectively.

The U.S. EPA Office of Pesticide Programs performed statistical analysis of these data using the Chi square test. A decrease in malignant and total tumor-bearing male mice in the high-dose group was statistically significant ($p=0.037$ and $p=0.045$, respectively). The number of tumor-bearing female mice appeared to be increased in the low-dose group (not statistically significant, $p=0.071$) and was statistically significantly increased in the middle-dose group ($p=0.45$ for malignant tumors and $p=0.0499$ for benign tumors). The tumor incidence in high-dose females was comparable to that in control female mice. The overall conclusion drawn was that under the test conditions in the Mobay Chemical Corp. (1981) study, metribuzin did not increase the incidences of tumors in mice. This study fulfills the criteria for an adequate cancer bioassay in female mice. Sufficient numbers of animals were used, the study was of sufficient duration, and survival was not affected. The MTD was achieved in the high-dose group females, as evidenced by a significant decrease in hemoglobin and hematocrit levels, and a statistically significant increase in liver weight (absolute and relative), kidney weight (absolute and relative), and spleen

weight (relative only). In male mice, liver weight (absolute and relative) was increased in the middle-dose group only, suggesting that the MTD may not have been reached.

In a 2-year feeding study, 40 Wistar rats/sex/group received 25, 35, 100 and 300 ppm metribuzin (99.5% pure) in their diets; 80 rats/sex served as controls (Mobay Chemical Corp., 1974a). These doses corresponded to 0, 1.3, 1.9, 5.3 and 14.4 mg metribuzin/kg/day, respectively, in the males and 0, 1.7, 2.3, 6.5 and 20.4 mg metribuzin/kg/day, respectively, in females (Mobay Chemical Corp., 1974a). No significant differences in food consumption were reported between the treated animals and the respective control groups. The body weights of animals in the 25-, 35- and 100-ppm dose groups (both sexes) did not differ significantly from those of respective controls. Body weights in the male high-dose group were significantly decreased during weeks 70-80 and 90-100; high-dose female body weights were significantly decreased from weeks 20-100. At the end of study (104 weeks) there were no significant differences between the body weights of high-dose males and females and their respective controls.

All of the animals in the control and high-dose groups were subjected to a complete histopathologic evaluation; 10 rats/sex in the 25-, 35- and 100-ppm groups were subjected to a partial evaluation. The initial evaluation by Mobay Chemical Corp. (1974a) reported statistically significant increases in the incidence of liver bile duct adenomas and pituitary gland adenomas in the female high-dose groups by pair-wise comparison. The incidence of bile duct adenoma in the females was 13/71, 4/10, 5/10, 1/10 and 19/35 in the control, 25-, 35-, 100- and 300-ppm groups, respectively; the incidence in males was 19/66, 10/10, 8/10, 5/10 and 9/29, respectively. The incidence of pituitary gland adenomas in the female control and high-dose groups was 27/71 and 21/35, respectively; in males the incidences were 10/62 and 6/29, respectively. Pituitary glands were not subjected to histopathologic evaluation in other treated groups.

The U.S. EPA Office of Pesticide Programs apparently reevaluated the original histopathology in the Mobay Chemical Corp. (1974) study; in this reevaluation all of the female liver bile duct adenomas were reclassified as bile duct proliferation. The pituitary glands from all animals were also histopathologically reevaluated; the incidences of pituitary adenoma in the female groups were 16/71 (23%), 6/34 (18%), 9/31 (29%), 11/33 (33%) and 14/35 (40%) in the control, 25-, 35-, 100- and 300-ppm groups, respectively. The increase in the high-dose group was statistically significantly increased by pair-wise comparison with the control. This increase was discounted because of high incidences reported in nine historical control studies; the average incidence reported in these studies was 22%. In four of these studies (two in each sex) the control incidences were 40%. The no-observed-effect level (NOEL) for systemic effects in this study was 100 ppm; the lowest-observed-effect level (LOEL) was 300 ppm, based on decreased weight gain and pathologic changes in the liver, kidneys, uterus and mammary glands. Based on these findings, this study was deemed adequate to determine that metribuzin was not oncogenic to SPF rats at dietary concentrations up to 300 ppm.

Pertinent data regarding the carcinogenic effects of metribuzin following inhalation exposure in animals were not located in the available literature.

II.A.4. Supporting Data for Carcinogenicity

Metribuzin was not mutagenic when tested in unspecified strains of *Salmonella typhimurium* or *Escherichia coli* (Mobay Chemical Corp., 1977; 1978). Metribuzin tested negative in the SOS Chromotest (DNA damage) conducted in *Escherichia coli* with or without metabolic activation (Xu and Schurr, 1990). Metribuzin did not induce reverse mutation in the D7 strain of *Saccharomyces cerevisiae* either in the presence or absence of metabolic activation (Mobay Chemical Corp., 1987).

Metribuzin was negative when tested for dominant lethal effects in male and female mice (unspecified strain) treated with doses of 300 mg metribuzin/kg (Mobay Chemical Corp., 1974b, 1975, 1976). Doses of 100 mg metribuzin/kg did not induce chromosomal aberrations in Chinese hamster spermatogonia (Mobay Chemical Corp., 1974c). Metribuzin also did not cause a significant increase in the unscheduled DNA synthesis when added to test cultures of rat primary hepatocytes (Mobay Chemical Corp., 1986a) and was found to be negative in the CHO/HGPRT mutation assay (Mobay Chemical Corp., 1986b). However, S-9 activated (but not nonactivated) metribuzin was found to be clastogenic in CHO cells (Mobay Chemical Corp., 1990).

Based on urinary excretion data, 36-51.9% of an orally administered dose of metribuzin was absorbed by Sprague-Dawley rats (Mobay Chemical Corp., 1972a). The half-life for elimination of radiolabeled metribuzin was 19.1- 30.4 hours for male rats and 22.4-33.6 hours for female rats (Mobay Chemical Corp., 1972a). In dogs, 52-60% of an administered oral dose was absorbed (Mobay Chemical Corp., 1972b). Within a 72- to 120-hour period, over 90% of the oral dose was excreted; about 52-60% was excreted in the urine as metabolites or conjugates and about 30% in the feces predominantly as unchanged metribuzin. In rats, about 90% of administered metribuzin was found to be excreted within 16 days by one investigator (Mobay Chemical Corp., 1972a) or within 5 days by another (Bleeke et al., 1985). Roughly equal amounts were excreted in the urine and feces. The major urinary metabolite was deamino metribuzin mercapturate (Bleeke et al., 1985). Mobay Chemical Corp. (1972a) also reported urinary metabolites of diketo metribuzin and deaminated diketo metribuzin. Conjugates of metribuzin were thought to account for the large water-soluble fraction of metabolites.

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, 1992

The Drinking Water Quantification of Toxicologic Effects Document for Metribuzin has received Agency Review.

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

Agency Work Group Review — 02/03/1993

Verification Date — 02/03/1993

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Metribuzin conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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 — Metribuzin
CASRN — 21087-64-9

VI.A. Oral RfD References

Mobay Chemical Corporation. 1972. MRID No. 00061257. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1974a. MRID No. 00061260, 00139397. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1974b. MRID No. 00061261, 00065136. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1974c. MRID No. 00061262, 00065135. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1981a. MRID No. 00087796. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1981b. MRID No. 00087795. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Bleeke, M.S., M.T. Smith and J.E. Casida. 1985. Metabolism and toxicity of metribuzin in mouse liver. *Pestic. Biochem. Physiol.* 23(1): 123-130.

Mobay Chemical Corporation. 1972a. MRID No. 00045265. HED Doc. No. 001146. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1972b. MRID No. 0004564. HED Doc. No. 001146. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

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Mobay Chemical Corporation. 1974b. MRID No. 00086766. HED Doc. No. 001762. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

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Mobay Chemical Corporation. 1986a. MRID No. 00157526. HED Doc. No. 005709. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1986b. MRID No. 00157527. HED Doc. No. 005709. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1987. MRID No. 40347701. HED Doc. No. 007369. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Mobay Chemical Corporation. 1990. MRID No. 41555102. HED Doc. No. 009520. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Xu, H.H. and K.M. Schurr. 1990. Genotoxicity of 22 pesticides in microtitration SOS chromotest. *Tox. Assess.* 5: 1-14.

U.S. EPA. 1992. Revised and Updated Drinking Water Quantification of Toxicologic Effects for Metribuzin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Final Report)

VII. Revision History

Substance Name — Metribuzin
CASRN — 21087-64-9

Date	Section	Description
12/01/1993	II.	Carcinogenicity assessment on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Metribuzin

CASRN — 21087-64-9

Last Revised — 01/31/1987

- 21087-64-9
- 4-AMINO-6-(1,1-DIMETHYLETHYL)-3-(METHYLTHIO)-1,2,4-TRIAZIN-5(4H)-ONE
- 4-AMINO-6-tert-BUTYL-3-(METHYLTHIO)-1,2,4-TRIAZIN-5-ON
- 4-AMINO-6-tert-BUTYL-3-METHYLTHIO-as-TRIAZIN-5-ONE
- BAY 61597
- BAY DIC 1468
- BAYER 6159H
- BAYER 6443H
- BAYER 94337
- DIC 1468
- LEXONE
- Metribuzin
- SENCOR
- SENCORAL
- SENCORER
- SENCOREX
- 1,2,4-TRIAZIN-5(4H)-ONE, 4-AMINO-6-(1,1-DIMETHYLETHYL)-3-(METHYLTHIO)-
- 1,2,4-TRIAZIN-5-ONE, 4-AMINO-6-tert-BUTYL-3-(METHYLTHIO)-
- as-TRIAZIN-5(4H)-ONE, 4-AMINO-6-tert-BUTYL-3-(METHYLTHIO)-