

Oryzalin; CASRN 19044-88-3

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 Oryzalin

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/01/1989
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 — Oryzalin

CASRN — 19044-88-3

Last Revised — 07/01/1989

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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increases in serum cholesterol, alkaline phosphatase, and relative liver and kidney weights, and decreases in alanine transaminase and adrenal weights	NOEL: 5 mg/kg/day LEL: 50 mg/kg/day	100	1	5E-2 mg/kg/day
1-Year Dog Feeding Study				
Eli Lilly Co., 1986				

*Conversion Factors: Actual dose tested

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

Eli Lilly Company. 1986. MRID No. 46624800. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Beagle dogs, 4/sex/dose, were orally dosed with oryzalin at 0, 1.5, 5, 15/250/500*, and 50 mg/kg/day for one year (* This dose group was changed twice during the study because of a lack of overt evidence of toxicity. The dogs received daily doses of 15, 250, and 500 mg/kg/day for weeks 0-14, 15-32 and 33 to termination, respectively.) No effects were observed at the low- and mid-dose groups. At 50 mg/kg/day the following effects were observed: increased serum cholesterol, decreased adrenal weights, increased relative liver and kidney weights, and decreased alanine transaminase. At 15/250/500 mg/kg/day alkaline phosphatase was high but was not considered a dose-related effect. Therefore, based on the above effects the NOEL and LEL for systemic toxicity are 5 mg/kg/day and 50 mg/kg/day, respectively.

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

UF — An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF — None

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

Data Considered for Establishing the RfD

- 1) 1-Year Feeding - dog: Principal study - see previous description; core grade minimum
- 2) 3-Generation Reproduction - rat: Fetotoxic NOEL=250 ppm (12.5 mg/kg/day) (LDT); Fetotoxic LEL=750 ppm (37.5 mg/kg/day) (depressed growth); Reproductive NOEL=2250 ppm (112.50 mg/kg/day) (HDT); Reproductive LEL=none; core grade minimum (Elanco Products Co., 1980a)
- 3) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=300 ppm (15 mg/kg/day) (LDT); Systemic LEL=900 ppm (45 mg/kg/day) (decreased RBC, HCT, Hgb; increased mean leukocyte counts, BUN, and liver and kidney weights, inhibition of growth, decreased survival); core grade minimum (Elanco Products Co., 1980b)
- 4) Teratology - rat: Fetotoxic, Teratogenic, and Maternal NOEL=225 mg/kg/day (HDT); Fetotoxic, Teratogenic, and Maternal LEL=none; core grade minimum (Elanco Products Co., 1976a)
- 5) Teratology - rabbit: Maternal NOEL=25 mg/kg/day; Maternal LEL=55 mg/kg/day (decreased live litter size, increased resorptions); Fetotoxic NOEL=25 mg/kg/day; Fetotoxic LEL=55 mg/kg/day (decreased maternal food consumption and weight gain); Teratogenic NOEL=125 mg/kg/day (HDT); Teratogenic LEL=none; core grade guideline (Elanco Products Co., 1976b)

Other Data Reviewed:

- 1) 2-Year Feeding (oncogenic) - mouse: Systemic NOEL=500 ppm (75 mg/kg/day); Systemic LEL=1350 ppm (202.5 mg/kg/day) (decreased weight of uterus and ovary considered dose-related) (Elanco Products Co., 1981)
- 2) 1-Year Feeding - rat: NOEL=300 ppm (15 mg/kg/day); LEL=900 ppm (45 mg/kg/day) (HDT; decreased HCT, Hgb, and RBC); core grade minimum (Elanco Products Co., 1979)

3) 3-Month Feeding - dog: NOEL=750 ppm (18.75 mg/kg/day); LEL=2250 ppm (56.25 mg/kg/day) (reduced Hgb, HCT and RBC; increased BUN, alkaline phosphatase and sedimentation rate; increased blood sugar and SGPT; hyperplastic bone marrow; splenic hematopoiesis; anemia; hepatic changes); no core grade (Elanco Products Co., 1968)

4) Teratology - rat: Maternal, Teratogenic, and Fetotoxic NOEL=2250 ppm (112.5 mg/kg/day) (HDT); Maternal, Teratogenic, and Fetotoxic LEL=none; no core grade (Elanco Products Co., 1972)

5) Teratology - rabbit: Maternal, Teratogenic, and Fetotoxic NOEL=125 mg/kg/day (HDT); Maternal, Teratogenic, and Fetotoxic LEL=none; core grade minimum (Elanco Products Co., 1982)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — High

RfD — High

The critical study is of adequate quality and is given a medium confidence rating. Additional studies are supportive and of adequate 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

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

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 03/26/1986, 04/20/1989

Verification Date — 04/20/1989

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 Oryzalin conducted in November 2001 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.

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 — Oryzalin
CASRN — 19044-88-3

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Oryzalin
CASRN — 19044-88-3
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 — Oryzalin produced tumors (generally benign) at multiple sites in male and female rats. It is structurally related to 2,4-diaminoanisole sulfate which causes malignant tumors at similar sites.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Using Fischer 344 rats, two identically designed chronic studies were performed concurrently with oryzalin administered in the diet to 30 rats/sex/dose at 0, 300, 900, and 2700 ppm for 2 years (Eli Lilly Co., 1980). When the data from the two studies were combined and adjusted for animal loss, tumors were produced at a statistically significantly ($p=0.05$) increased incidence at the following sites: the thyroid gland (combined follicular cell adenomas and carcinomas in males and females); the skin (combined fibromas and fibrosarcomas in males; combined papillomas, keratoacanthomas and squamous cell carcinomas in males and females); and combined basal cell adenomas, preputial gland adenomas, sebaceous gland adenomas, Zymbal's gland carcinomas and trichoepitheliomas in males and females) and the mammary gland (combined adenomas, fibroadenomas and adenocarcinomas evaluated in females only). The statistically significant elevation of tumor incidence at these sites is primarily due to the benign tumor types. Although a statistically significant positive trend was seen for the combined hepatic and bile diet adenomas in male rats, the incidence at all doses was lower than in the historical controls. No liver tumors were reported in females. The highest dose tested appeared to exceed the maximum tolerated dose (MTD).

Two identically designed chronic studies were performed concurrently in B6C3F1 mice, 40 animals/sex/dose (60 animals in controls), at dietary levels of 0, 500, 1350, and 3650 ppm for 2 years (Eli Lilly Co., 1981). No oncogenic effect was reported for any dose, including the high dose, which represented an MTD in both sexes.

II.A.4. Supporting Data for Carcinogenicity

Oryzalin is structurally related to another para-substituted aniline, 2,4-diaminoaniline sulfate, which has been found to produce malignant tumors of the thyroid gland and the skin of rats in both sexes at 5000 ppm. In B6C3F1 mice, thyroid tumors were induced in both sexes at 2450 ppm (NCI, 1978). Studies are available for two structurally related sulfonamides (sulfamethoxazole and sulphisoxazole) (IARC, 1980). Orally administered sulfamethoxazole produces thyroid gland nodules and adenomas in rats whereas sulphisoxazole is not oncogenic in rats or mice. Data, however, were not available for review.

Oryzalin was negative in a test for gene mutation (Salmonella/mammalian microsomal test), germinal cell mutation, chromosomal aberrations (dominant lethal test) and unscheduled DNA synthesis (primary rat hepatocytes) (U.S. EPA, 1985). Depending on route of administration, both negative and positive responses were seen in in vivo assays for induction of sister chromatid exchange. In Chinese hamster bone marrow cells oryzalin induced sister chromatid exchange following i.p. administration, but there was no induction of sister chromatid exchange following oral administration (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 oryzalin.

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

Agency Work Group Review — 10/07/1987, 11/10/1987

Verification Date — 11/10/1987

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 Oryzalin conducted in November 2001 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 — Oryzalin
CASRN — 19044-88-3

VI.A. Oral RfD References

Elanco Products Company. 1968. MRID No. 00106670, 00026760. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1972. MRID No. 00026781. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1976a. MRID No. 00026783, 00038682. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1976b. MRID No. 00026785, 00073552. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1979. MRID No. 00026776, 00038680. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1980a. MRID No. 00026786, 00042908. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1980b. MRID No. 00044332. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1981. MRID No. 00068079. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Elanco Products Company. 1982. MRID No. 00098461. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Eli Lilly Company. 1986. MRID No. 46624800. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Eli Lilly Company. 1980. MRID No. 00044332. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Eli Lilly Company. 1981. MRID No. 00068079. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

IARC (International Agency for Research on Cancer). 1980. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some pharmaceutical drugs. Sulphisoxazole. Vol. 24, IARC, Lyon, France. p. 275-295.

NCI (National Cancer Institute). 1978. 2,4-Diaminoanisole Sulfate. Technical Report No. 84. 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 oryzalin. September 16.

VII. Revision History

Substance Name — Oryzalin
CASRN — 19044-88-3

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
05/01/1989	I.A.	Withdrawn; new RfD verified (in preparation)
07/01/1989	I.A.	Oral RfD summary replaced; RfD changed
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Oryzalin
CASRN — 19044-88-3
Last Revised — 01/31/1987

- 19044-88-3
- 3,5-DINITRO-N(sup 4),N(sup 4)-DIPROPYLSULFANILAMIDE
- 4-(DIPROPYLAMINO)-3,5-DINITROBENZENESULFONAMIDE
- DIRIMAL
- EL-119
- Oryzalin
- RYCELAN
- RYCELON
- RYZELAN
- SULFANILAMIDE, 3,5-DINITRO-N(sup 4),N(sup 4)-DIPROPYL-
- SURFLAN