Glyphosate; CASRN 1071-83-6

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 Glyphosate

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	10/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Glyphosate
CASRN — 1071-83-6
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

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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
Increased incidence of renal tubular dilation in F3b offspring. **3-Generation Rat Reproduction Study** **Monsanto Co., 1981a**	NOEL: 10 mg/kg/day LEL: 30 mg/kg/day	100	1	1E-1 mg/kg/day

*Conversion Factors: Actual dose tested

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

Monsanto Company. 1981a. MRID No. 0081674, 00105995. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Rats (CD Sprague-Dawley) were administered glyphosate continuously for three successive generations. Dietary concentrations of glyphosate were adjusted weekly during growth, and between mating rest periods to achieve dose levels of 0, 3, 10, and 30 mg/kg/day. Each generation (F0, F1, F2) consisted of 12 male and 24 female rats. Each parent generation was mated to produce to litters. Offspring from the second litters of the F0 and F1 parents (F1b and F2b litters, respectively) were selected to be parents for subsequent generations. Offspring not included in the selection procedure and offspring from the first litter intervals of each generation (F1a, F2a, F3a) were given a gross postmortem examination and discarded. Randomly selected offspring from the second litters of the F2 generation (F3b litters) were given a gross postmortem examination and selected tissues taken and saved. Subsequently tissues from control and high-dose F3b offspring were evaluated microscopically (10/sex/group). Tissues from control and high-dose parent generations parent generations (F0, F1, and F2) were also evaluated.

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No treatment-related effects on fertility were noted, nor were any systemic effects in adult rats apparent. Male pups from the F3b mating of the high dose group (30 mg/kg/day) showed an increase in the incidence of unilateral renal tubular dilation. Based on this finding, the NOEL and LEL for this study are 10 and 30 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) Reproduction - rat: Principal study - see previous description; core grade minimum

2) 2-Year Feeding (oncogenicity) - rat: Dietary levels tested: 0, 30, 100, and 300 ppm (Male: 0, 3.05, 10.3, and 31.39 mg/kg/day; Female: 0, 3.37, 11.22, and 34.02 mg/kg/day; Groups of Sprague-Dawley rats (50/sex/dose) were fed glyphosate in the diet for 2 years. No effect on clinical signs, body weights, or mortality was noted. No effects on clinical pathology or organ pathology was apparent. Therefore, the NOEL for systemic toxicity is 300 ppm (Male: 31.39 mg/kg/day; Female: 34.02 mg/kg/day), the highest dose tested; core grade minimum for chronic feeding (Monsanto Co., 1981b)

3) 1-Year Feeding - dog: Dietary levels tested: 0, 20, 100, and 500 mg/kg/day; Groups of beagle dogs (6/sex/dose) were administered glyphosate by gelatin capsules for 1 year. A decrease in absolute and relative pituitary weights were observed in mid- and high-dose male dogs. Based on these findings, the NOEL and LEL for systemic toxicity are 20 and 100 mg/kg/day; core grade guideline (Monsanto Co., 1985)

4) Developmental Toxicity - rat: Dose levels tested: 0, 300, 1000 and 3500 mg/kg/day; Groups of pregnant Charles River COBS CD rats (25/dose) were administered glyphosate orally by gavage as a single daily dose on days 6 through 19 of gestation. A definite reduced mean maternal body weight gain was noted in the 3500 mg/kg/day dose group over the treatment period due to mean maternal body weight loss during the first 3 days of treatment. At 3500 mg/kg/day a statistically significant increase in the mean number of early resorptions resulted in a slight increase in mean postimplantation loss. A statistically significant decrease in the mean number of total implantations, viable fetuses, and mean fetal body weight and a slight decrease

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in the mean number of corpora lutea was noted in this group. Based on these findings, the NOEL and LEL for maternal toxicity are 1000 and 3500 mg/kg/day, respectively. An increase in the number of litters and fetuses with unossified sternebrae was noted in the 3500 mg/kg/day dose group. Based on this finding, the NOEL and LEL for developmental toxicity are 1000 and 3500 mg/kg/day, respectively; core grade minimum (Monsanto Co., 1980a)

5) Developmental Toxicity - rabbit: Dose levels tested: 0, 75, 175, and 350 mg/kg/day; Groups of pregnant Dutch Belted rabbits (16/dose) were administered glyphosate orally by gavage as a single daily dose on days 6 through 27 of gestation. A slight increase in the incidence of soft stools and diarrhea was noted in the 175 mg/kg/day group and a definite increase in these signs and nasal discharge were noted in the 350 mg/kg/day group. Based on these findings, the NOEL and LEL for maternal toxicity are 175 and 350 mg/kg/day, respectively. No developmental toxicity effects were noted at any dose tested. Therefore, the NOEL for developmental toxicity is equal to or greater than 350 mg/kg/day; core grade minimum (Monsanto Co., 1980b)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The quality of the chosen study is good; therefore, it receives a high confidence rating. The quantity and quality of the available supporting studies warrant high confidence in the data base. High confidence in the RfD follows.

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

Office of Pesticide Programs Files

Agency Work Group Review — 03/11/1986

Verification Date — 03/11/1986

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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 — Glyphosate
CASRN — 1071-83-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Glyphosate
CASRN — 1071-83-6
Last Revised — 10/01/1989

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

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Basis — Inadequate evidence for oncogenicity in animals. Glyphosate was originally classified as C, possible human carcinogen, on the basis of increased incidence of renal tumors in mice. Following independent review of the slides the classification was changed to D on the basis of a lack of statistical significance and uncertainty as to a treatment-related effect.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Charles River CD-1 mice (50/sex/dose level) were fed diets containing glyphosate at dose levels of 0, 1000, 5000, or 30,000 ppm for 24 months. The incidence of renal tubule adenomas observed in the male mice exceeded that of the controls (0/49 controls; 0/49 low-dose; 1/50 mid-dose; 3/50 high-dose). A re-evaluation of the renal tumor slides prepared from the male mice indicated the presence of an additional adenoma in the control group and malignant tumors in the two higher dose groups. Therefore, the incidences of the reevaluated data are 1/49 control adenoma; 0/49 low; 1/50 mid, carcinoma; 3/50 high, 1 adenoma, 2 carcinomas. It was the judgment of two reviewing pathologists that the renal tumors were not treatment-related. In addition, the inclusion of a tumor in the control group eliminated statistical significance for the high-dose group.

In a 26-month study Sprague-Dawley (CD) rats, 50/sex/dose were fed 0, 30, 100, or 300 ppm glyphosate in the diet. The study is being repeated to include the MTD. There were some thyroid tumors, which were considered of normal incidence. Power to detect an effect was reduced since a MTD was not demonstrated, and the highest dose tested was less than 1/100 of the high dose in the mice (Monsanto, 1981). OPP has requested that the study be repeated on the basis of the degree of species difference in the highest dose tested and the possibility that higher doses (MTD) might produce additional tumors.

II.A.4. Supporting Data for Carcinogenicity

Glyphosate was not mutagenic for Salmonella, E. coli or Chinese hamster ovary cells. It was also negative in DNA repair assays in Bacillus subtilis and hepatocyte cultures.

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

Not available.

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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 reviewed data on glyphosate.

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

Agency Work Group Review — 03/16/1988, 08/15/1988

Verification Date — 08/15/1988

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 — Glyphosate
CASRN — 1071-83-6

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VI.A. Oral RfD References

Monsanto Company. 1981a. MRID No. 0081674, 00105995. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Monsanto Company. 1981b. MRID No. 00093879. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Monsanto Company. 1985. MRID No. 00153374. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Monsanto Company. 1980a. MRID No. 00046362. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Monsanto Company. 1980b. MRID No. 00046363. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Monsanto and Company. 1981. MRID No. 00093879. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

U.S. EPA. 1985. Toxicology Branch Peer Review Committee memorandum on glyphosate, March 4, 1985.

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VII. Revision History

Substance Name — Glyphosate
CASRN — 1071-83-6

Date	Section	Description
10/01/1989	II.	Carcinogen summary on-line

VIII. Synonyms

Substance Name — Glyphosate
CASRN — 1071-83-6
Last Revised — 01/31/1987

- 1071-83-6
- GLYCINE, N-(PHOSPHONOMETHYL)-
- Glyphosate
- MON 0573
- N-(PHOSPHONOMETHYL)GLYCINE

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