Paraquat; CASRN 1910-42-5

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 Paraquat

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/31/1987
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 — Paraquat
CASRN — 1910-42-5
Last Revised — 03/31/1987

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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Chronic pneumonitis **1-Year Dog Feeding Study** **Chevron Chemical Company, 1983a**	NOEL: 0.45 mg/kg/day LEL: 0.93 mg/kg/day	100	1	4.5E-3 mg/kg/day

* Conversion Factors: none

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

Chevron Chemical Company. 1983a. MRID No. 00132474. Available from EPA. Write to FOI, EPA, Washington, DC 20460. Alderly Park beagle dogs, 6/sex/dose, were fed diets for 52 weeks containing paraquat dichloride resulting in exposures of 0, 0.45, 0.93, and 1.51 mg/kg/day bw. The major effect of the paraquat cation was chronic pneumonitis in the mid- and high-dose groups. There were significant increases in the group mean lung weights. Therefore the NOEL and LEL for systemic toxicity are 0.45 and 0.93 mg/kg/day.

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

UF — An uncertainty factor of 100 has been used to account for the inter- and intraspecies difference in the extrapolation from laboratory animals to humans.

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) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=25 ppm (1.25 mg/kg/day); Systemic LEL=75 ppm (3.75 mg/kg/day) (increased incidence of opacities, cataracts and non-neoplastic lung lesions); core grade guideline for chronic toxicity, supplementary for oncogenicity (Chevron Chemical Co., 1983b)

3) 90-Day Feeding - dog: NOEL=20 ppm (0.5 mg/kg/day); LEL=60 ppm (1.5 mg/kg/day) (increased lung weight, alveolitis, and alveolar collapse); core grade minimum (Chevron Chemical Co., 1981a)

4) 3-Generation Reproduction - rat: Systemic NOEL=25 ppm (1.25 mg/kg/day); Systemic LEL=75 ppm (3.75 mg/kg/day) (increased incidence of alveolar histiocytosis in the lungs); Reproductive NOEL=150 ppm (7.5 mg/kg/day) (HDT); Reproductive LEL=none; core grade guideline (Chevron Chemical Co., 1982)

5) Teratology - rat: Maternal NOEL=1 mg/kg/day; Maternal LEL=5 mg/kg/day (piloerection, hunched appearance, and weight loss); Fetotoxic NOEL=1 mg/kg/day; Fetotoxic LEL=5 mg/kg/day (slight retardation in ossification and weight loss); core grade guideline (Chevron Chemical Co., 1977a)

6) Teratology - mouse: Maternal NOEL=1 mg/kg/day; Maternal LEL=5 mg/kg/day (14.2% reduction in body weight); Fetotoxic NOEL=5 mg/kg/day; Fetotoxic LEL=10 mg/kg/day (HDT; partially ossified sternebrae in 26.3% of fetuses); core grade minimum; (Chevron Chemical Co., 1977b)

Other Data Reviewed:

1) 99-Week Oncogenic - mouse: Systemic NOEL=12.5 ppm (1.87 mg/kg/day); Systemic LEL=37.5 ppm (5.62 mg/kg/day) (renal tubular degeneration and weight loss in males and decreased food intake in females); core grade minimum (Chevron Chemical Co., 1981b)

Data Gap(s): None

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The principal study is of good quality and, therefore, is given a high rating. The database is complete and supporting studies are of medium to high quality. Therefore, a high confidence rating is given to the database. 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

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 paraquat conducted in August 2003 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 (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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

Substance Name — Paraquat
CASRN — 1910-42-5

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Paraquat
CASRN — 1910-42-5
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 — Paraquat produced squamous cell carcinoma, an uncommon tumor, in the head region in both sexes of Fischer 344 rats.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Paraquat (cation form) was fed to Fischer 344 rats. Groups of 70/sex, housed 5/cage, were treated at concentrations of 0, 25, 75 and 150 ppm for 113-117 weeks (males) and 122-124 weeks (females). Control groups consisted of 140 animals housed 5/cage (Life Sciences Research, 1983). Squamous cell carcinoma of the skin (an uncommon tumor), found predominantly in the head region, occurred in 51.6% of all rats (both sexes) having tumors. The incidence of this type of tumor in the high-dose males was significantly increased over concurrent controls. The development of this tumor type in this study may have been confounded by group-housing of animals (which may lead to scratching and fighting especially in males) and the corrositivity of paraquat. Several other tumor types were also observed (e.g., lung adenomas and carcinomas, pituitary adenomas and carcinomas, thyroid adenomas, adrenal

pheochromocytomas, pancreatic islet cell adenomas, mammary fibroepithelial and testis interstitial cell tumors, malignant lymphomas and skin lysomas). Although several incidences were significantly elevated, none of these were attributable to compound administration (Life Sciences Research, 1983). A maximum tolerated dose (MTD) appeared to be achieved at the highest dose.

SPF Swiss-derived mice (60/sex/dose group) were fed paraquat in the diet at 0, 12.5, 37.5, or 100 ppm for 35 weeks followed by 125 ppm for remainder of life (Imperial Chemical Industries, 1981). No treatment-related tumors were present at the high dose, which probably approached the MTD for both sexes as suggested by the increased mortality in females at the high dose and evidence of renal tubular degeneration in males at the mid dose (U.S. EPA, 1986).

II.A.4. Supporting Data for Carcinogenicity

Paraquat is poorly absorbed through the gastrointestinal tract of mammals. In the rat, 69-96% of the dose following oral intubation was excreted mostly in the feces as unchanged paraquat, whereas 70-90% of the dose following subcutaneous injection was excreted mostly in the urine (U.S. EPA, 1986). Labeled paraquat dichloride applied to the forearms, legs and hands of adult male human volunteers was poorly absorbed (U.S. EPA, 1986).

Paraquat was negative in reverse mutation assays in Salmonella with or without metabolic activation using hepatic homogenates (Anderson et al., 1972; Benigni et al., 1979). It was also negative in dominant lethal tests using both CDI and Swiss-Webster mice (Pasi et al., 1974) and in rat bone marrow chromosomal aberration tests. Paraquat (analytical grade) was positive in the mouse lymphoma assay, either with or without S9 activation; when technical paraquat was tested, it was mutagenic only when S9-activated. The test material was positive for sister chromatid exchange in Chinese hamster lung fibroblast cells. Unscheduled DNA synthesis was not induced in Alderly Park male rat hepatocytes, but it was induced in human embryo epithelial cells. Paraquat was positive or weakly positive in DNA repair assays and in a forward mutation assay in Salmonella typhimurium and in Saccharomyces cerevisiae strains D4 and JDI (Benigni et al., 1979; Siebert and Lemperle, 1974; Parry, 1977).

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

An oral quantitative risk estimate was not prepared due to deficiencies of the Life Sciences Research (1983) study.

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, 1986

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

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

Agency Work Group Review — 10/07/1987

Verification Date — 10/07/1987

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 paraquat conducted in August 2003 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.

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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

VI. Bibliography

Substance Name — Paraquat
CASRN — 1910-42-5

VI.A. Oral RfD References

Chevron Chemical Company. 1977a. MRID No. 00113714. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1977b. MRID No. 00096338. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1981a. MRID No. 00072416. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1981b. MRID No. 00087924. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1982. MRID No. 00126783. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1983a. MRID No. 00132474. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Chevron Chemical Company. 1983b. MRID No. 00075505, 00124755, 00137292, 00138637, 00153223. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Andersen, K.J., E.G. Leighty and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agric. Food Chem. 20-3: 649-656.

Benigni, R., M. Bignami, A. Carere, et al. 1979. Mutational studies with diquat and paraquat in vitro. Mutat. Res. 68: 183-193.

Imperial Chemical Industries. 1981. Cited in U.S. EPA, 1986.

Life Sciences Research. 1983. Paraquat: Combined toxicity and carcinogenicity study in rats. Report No. 82/ILY217/328. Stock, England, October 27. (Cited in U.S. EPA, 1986)

Parry, J.M. 1977. The use of yeast cultures for the detection of environmental mutagens using a fluctuation test. Mutat. Res. 46: 165-176.

Pasi, A., J.W. Embree Jr., G.H. Eisenlord and C.H. Hine. 1974. Assessment of the mutagenic properties of diquat and paraquat in the murine dominant lethal test. Mutat. Res. 26: 171-175.

Siebert, D. and E. Lemperle. 1974. Genetic effects of herbicides: Induction of mitotic gene conversion in Saccaromyces cerevisiae. Mutat. Res. 22: 111-120.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances memorandum on paraquat. July 9.

VII. Revision History

Substance Name — Paraquat
CASRN — 1910-42-5

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
10/28/2003	I.A.6, II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Paraquat
CASRN — 1910-42-5
Last Revised — 03/31/1987

- 1910-42-5
- AH 501
- BIPYRIDINIUM, 1,1'-DIMETHYL-4,4'-, DICHLORIDE
- 4,4'-BIPYRIDINIUM, 1,1'-DIMETHYL-, DICHLORIDE
- CEKUQUAT
- CRISQUAT
- DEXTRONE
- DEXTRONE-X
- DEXURON
- 1,1'-DIMETHYL-4,4'-BIPYRIDYNIUM DICHLORIDE
- 1,1'-DIMETHYL-4,4'-DIPYRIDINIUM-DICHLORID
- 4,4'-DIMETHYLDIPYRIDYL DICHLORIDE
- 1,1'-DIMETHYL-4,4'-DIPYRIDYLIUM CHLORIDE
- DIMETHYL VIOLOGEN CHLORIDE
- ESGRAM
- GRAMIXEL
- GRAMONOL
- GRAMOXON
- GRAMOXONE
- GRAMOXONE D

- GRAMOXONE DICHLORIDE
- GRAMOXONE S
- GRAMOXONE W
- GRAMURON
- HERBAXON
- HERBOXONE
- METHYLVIOLOGEN
- METHYL VIOLOGEN DICHLORIDE
- N,N'-DIMETHYL-4,4'-BIPYRIDINIUM DICHLORIDE
- N,N'-DIMETHYL-4,4'-BIPYRIDYLIUM DICHLORIDE
- N,N'-DIMETHYL-4,4'-DIPYRIDYLIUM DICHLORIDE
- OK 622
- PARA-COL
- Paraquat
- PARAQUAT CHLORIDE
- PARAQUAT CL
- PARAQUAT, DICHLORIDE
- PATHCLEAR
- PILLARQUAT
- PILLARXONE
- PP148
- SWEEP
- TERRAKLENE
- TOTACOL
- TOXER TOTAL
- VIOLOGEN, METHYL-
- WEEDOL