Prochloraz; CASRN 67747-09-5

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 Prochloraz

File First On-Line 01/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/01/1989
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 — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542
Last Revised — 01/01/1989

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
Increase in SAP and liver weights, liver histopathology **2-Year Dog Feeding Study** **FBC Limited, 1981**	NOEL: 30 ppm (0.90 mg/kg/day) LEL: 135 ppm (4.07 mg/kg/day)	100	1	9E-3 mg/kg/day

*Conversion Factors: Actual dose tested

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

FBC Limited. 1981. MRID No. 40267708; HED Doc. No. 004456. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Pure bred Beagle dogs (5 dogs/sex/dose) were fed diets containing 0, 30, 135, or 600 ppm (male: 0, 0.94, 4.47, 18.1, 28.9 mg/kg/day; females: 0, 0.90, 4.07, 18.0, 27.5 mg/kg/day) prochloraz for 104 weeks. An additional 2 males and 2 females fed diets containing 600 ppm were sacrificed after 13 weeks on the study. After 56 weeks on the study, the highest dosage level was increased to 1000 ppm (male: 28.9 mg/kg/day; female: 27.5). At 135 ppm an increase in serum alkaline phosphatase (SAP) and liver weights was observed. At the HDT, 600/1000 ppm, increases in SAP, liver weight, and prostatic atrophy were observed. The overall NOEL for dogs fed prochloraz was 30 ppm and the LEL was 135 ppm, based on liver weight data, increased SAP levels and liver histopathology.

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) 2-Year Feeding - dog: Principal study - see previous description; core grade minimum

2) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=37.5 ppm (1.875 mg/kg/day); Systemic LEL=150 ppm (7.5 mg/kg/day) (enlarged swollen livers, decreased body weight); At the HDT, 625 ppm (31.25 mg/kg/day), nodular hyperplasia in liver was observed; core grade minimum (Nor-Am Chemical Co., 1982)

3) 2-Generation Reproduction - rat: Fetal/Maternal NOEL=150 ppm (7.5 mg/kg/day); Fetal/Maternal LEL=625 ppm (31.25 mg/kg/day) (HDT; increase in stillbirths, decreased litter size); core grade minimum (Nor-Am Chemical Co., 1981)

4) Teratology - rat: Maternal NOEL=5.15 mg/kg/day; Maternal LEL=21.75 mg/kg/day (depressed body weight); Fetal NOEL=5.15 mg/kg/day; Fetal LEL=21.75 mg/kg/day (depressed body weight); Teratogenic NOEL=84.5 mg/kg/day (HDT); core grade minimum (Nor-Am Chemical Co., 1980)

5) Teratology - rabbit: Maternal, Fetotoxic, Teratogenic NOEL=48 mg/kg/day (HDT); core grade supplementary (Boots Company Ltd., 1980)

Other Data Reviewed:

1) Lifetime Feeding (oncogenic) - mice: Systemic NOEL=1300 ppm (195 mg/kg/day) (HDT); At the LDT, 78 ppm (11.7 mg/kg/day), liver tumors were observed; core grade guideline (Nor-Am Chemical Co., 1983)

Data Gap(s): Rabbit Teratology Study

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. The supporting studies are also of adequate quality and together are 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 — 07/20/1988

Verification Date — 07/20/1988

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 Prochloraz 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 — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542
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 — C; possible human carcinogen

Basis — Statistically significantly increased incidence and dose-related trend in liver adenomas and carcinomas (combined) in both sexes of one strain of mouse.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. In a 2-year chronic study, prochloraz was fed in the diet to CD- 1 mice, 52/sex/group (controls 104/sex), at 0, 78, 325, or 1300 ppm (Nor-Am Chemical Co., 1983). In males, prochloraz in the diet was associated with a statistically significant increase in incidence of

hepatocellular carcinoma (24/49), adenoma (20/49) and combined carcinoma/adenoma (44/49) at the high dose. At the mid dose there was a statistically significant increase in incidence of hepatocellular carcinoma (17/42) and combined carcinoma/adenoma (28/44). There were also statistically significant dose-related trends in incidence of carcinoma, adenoma and combined carcinoma/adenoma. The first appearance of a tumor was 52 and 62 weeks for adenoma and carcinoma, respectively.

In females, there was a statistically significant increase in incidence of hepatocellular carcinoma (9/44) at the high dose and in adenoma (30/44 high dose, 10/42 mid dose) and combined carcinoma/adenoma (39/44 high dose, 11/42 mid dose) at the mid and high dose; there was also a statistically significant dose-related trend for these tumors, both individually and combined. The first tumors were observed at 89 weeks.

The dose selection was considered adequate for oncogenicity testing because significantly lowered body weight gain was observed in the males for the entire study and in the females through week 52.

There were no differences in survival on a trend basis in both sexes; however, in male mice there was a pairwise increase in mortality in the mid- dose.

In a 2-year chronic study, prochloraz was fed in the diet to Sprague- Dawley CD rats, 60/sex/group (controls 120/sex), at dosages of 0, 37.5, 150, or 625 ppm (Nor-Am Chemical Co., 1982). The original reading of the liver slides from the high dose indicated an increase in the incidence of nodular hyperplasia. These liver slides were reevaluated and a statistically significant trend for liver carcinoma was concluded for the males, but there were no statistically significant increases in any individual treated group as compared to concurrent controls. Furthermore, the incidence of malignant or benign liver tumor types in the three dose groups was within the same range as those among seven historical control groups from the same laboratory. Although the time of performance of these control groups is not provided, these appear to be concurrent controls from other studies at the same laboratory and, therefore, are not considered too old to provide a valid comparison. OPP did not consider the significant positive trend in incidence of liver carcinoma in the male sufficient evidence to warrant a B2 classification since the liver carcinoma was not a rare type, the pairwise comparison was not significant, and the comparison to historical controls was within the same range.

Dose selection was adequate based on decreased body weight gain in the high-dose groups. There was no indication of an adverse effect on survival.

II.A.4. Supporting Data for Carcinogenicity

Prochloraz was negative in the following genotoxicity assays: unscheduled DNA synthesis (human fibroblasts), with and without activation (Unscheduled DNA synthesis, Iversesk Research, 1983); mutagenicity for Salmonella (TA 1535, 1537, 98 and 100) with and without activation (Ames reverse mutation study on Salmonella, Boots Company, 1977); and the mouse micronucleus test (Mutagenic Micronucleus Assay, Nor-Am Chemical Co., 1986).

Prochloraz is structurally related to 2,4,6-trichlorophenol, 2,4,5- trichlorophenoxyacetic acid (2,4,5-T), and 2(2,4,5-trichlorophenoxy)phenoxy- acetic acid (Silvex). 2,4,6-Trichlorophenol is associated with leukemia and pituitary and mammary gland adenomas in male Fischer rats and liver tumors in both sexes of B6C3F1 mice. 2,4,5-T in drinking water appears to be associated with increased tumor incidence in several sites in C3HF mice. Data for Silvex were not available.

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.5E-1 per (mg/kg)/day

Drinking Water Unit Risk — 4.3E-6 per (ug/L)

Extrapolation Method — Male mice: time-to-tumor linearized multistage procedure in dose, Weibull in time. Female mice: linearized multistage procedure.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+1 ug/L
E-5 (1 in 100,000)	2 ug/L
E-6 (1 in 1,000,000)	2E-1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — liver adenoma/carcinoma combined
Test Animals — mouse/CD-1, male and female
Route — diet
Reference — Nor-Am Chemical Co., 1983

Administered Dose		Human Equivalent	Tumor Incidence	
(ppm)	**(mg/kg)/day**	**Dose (mg/kg)/day**	**male**	**female**
0	0	0	37/92	5/73
78	3.90	0.88	21/48	6/39
325	16.25	3.66	28/44	11/42
1300	65.00	14.63	44/49	39/44

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The unit risk for mice was converted to human equivalents by use of the interspecies surface area adjustment according to the EPA Cancer Guidelines and assuming adult body weights of mice and humans to be 0.025 and 60 kg, respectively. Mortality was increased in the male mid-dose only. Accordingly, a time-to-tumor model was used for the risk estimate for the male mice. Survival adjustments were made as needed in the calculation.

The final risk estimate is a geometric mean of the estimates based on male and female mouse data [1.95E-1 and 1.14E-1 per (mg/kg)/day, respectively]. Estimates were combined in order that relevant data not be excluded; the individual estimates were so similar as to preclude choice of one or the other.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals, lifetime exposure, and adequate dose selection were all factors establishing confidence in the risk estimate. Survival was not affected in the female mice nor in the males on a trend basis. Survival adjustments were made as needed in the calculations.

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, 1987; 1988a,b,c; 1989

The risk assessment for prochloraz was reviewed by the OPP Peer Review Group and by the FIFRA Science Advisory Panel.

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

Agency Work Group Review — 04/05/1989

Verification Date — 04/05/1989

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 Prochloraz 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 — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542

VI.A. Oral RfD References

Boots Company Limited. 1980. MRID No. 00150410. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

FBC Limited. 1981. MRID No. 40267708. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Nor-Am Chemical Company. 1980. MRID No. 00144953. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Nor-Am Chemical Company. 1981. MRID No. 00150425. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Nor-Am Chemical Company. 1982. MRID No. 40267708. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Nor-Am Chemical Company. 1983. MRID No. 00150409. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Boots Company Limited. 1977. MRID No. 00150420. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Inveresk Research. 1983. MRID No. 00150424. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

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Nor-Am Chemical Company. 1983. MRID No. 00150409. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Nor-Am Chemical Company. 1986. MRID No. 00163652. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

U.S. EPA. 1987. Memorandum from B. Fisher to L. Taylor. Prochloraz, Mouse Study-Qualitative Risk Assessment.

U.S. EPA. 1988a. Memorandum from R. Engler, U.S. EPA to Addressees, Toxicology Branch Peer Review Committee Draft Document on Prochloraz.

U.S. EPA. 1988b. Memorandum from R. Engler, U.S. EPA to Addressees, Peer Review Committee Draft Document on Prochloraz.

U.S. EPA. 1988c. Memorandum from B. Fisher to L. Taylor. Prochloraz - Rat Study, Qualitative Risk Assessment.

U.S. EPA. 1989. One-liner: 03/16/1989. Toxchem No. 704E-Prochoraz.

VII. Revision History

Substance Name — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542

Date	Section	Description
01/01/1989	I.A.	Oral RfD summary on-line
10/01/1989	II.	Carcinogen summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Prochloraz
CASRN — 67747-09-5
Primary Synonym — BTS 40542
Last Revised — 01/01/1989

- 67747-09-5
- BTS 40542
- Prochloraz