



Integrated Risk Information System

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Cyanide, free (CASRN 57-12-5)

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Reference Dose for Chronic Oral Exposure (RfD)

0031

Cyanide, free; CASRN 57-12-5

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Cyanide, free

File First On-Line 01/31/1987

| Category (section) | Status | Last Revised |
|----------------------------------|---------|--------------|
| Oral RfD Assessment (I.A.) | on-line | 02/01/1993 |
| Inhalation RfC Assessment (I.B.) | no data | |
| Carcinogenicity Assessment (II.) | on-line | 03/01/1991 |

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 02/01/1993

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

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| Critical Effect | Experimental Doses* | UF | MF | RfD |
|--|-------------------------------|-----|----|----------------|
| Rat Chronic Oral Study | NOAEL: 10.8 mg/kg/day cyanide | 100 | 5 | 2E-2 mg/kg/day |
| Howard and Hanzal, 1955 | | | | |
| Weight loss, thyroid effects and myelin degeneration | LOAEL: 30 mg/kg/day cyanide | | | |
| Rat Subchronic to Chronic Oral Bioassay | | | | |
| Philbrick et al., 1979 | | | | |

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*Conversion Factors: none

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

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity to rats of food treated with hydrogen cyanide. *J. Agric. Food Chem.* 3: 325-329.

Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander and R.G. Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. *J. Toxicol. Environ. Health.* 5: 579-592.

Hydrogen cyanide (HCN) is soluble in water and dilute acid (which includes the gastric environment) and is readily hydrolyzed to 1 molar equivalent of cyanide (CN) and 1 molar equivalent of hydrogen (Hartung, 1982).

In this 2-year dietary study, rats (10/sex/group) were administered food fumigated with HCN. The average daily concentrations were 73 and 183 mg CN/kg diet. From the data reported on food consumption and body weight, daily estimated doses were 4.3 mg and 10.8 mg CN/kg bw. The average food CN concentrations were estimated based on the authors' data for concentration at the beginning and end of each food preparation period and by assuming a first-order rate of loss for the intervening period. There were no treatment related effects on growth rate, no gross signs of toxicity, and no histopathologic lesions.

Studies by Philbrick et al. (1979) showed decreased weight gain and thyroxin levels and myelin degeneration in rats at 30 mg/kg/day CN. Other chronic studies either gave higher effect levels or used the subcutaneous route (Crampton et al., 1979; Lessell, 1971; Hertting et al., 1960). Human data do not provide adequate information from which to derive an RfD because effective dose levels of chronically ingested CN are not documented. Therefore, the study of Howard and Hanzel (1955) provides the highest NOAEL, 10.8 mg/kg/day for CN, and is chosen for the derivation of an RfD for CN of 1.5 mg/day or 0.02 mg/kg/day.

Cyanide is metabolized extensively in the liver, indicating that the only relevant route of administration for quantitative risk assessment in the derivation of an oral RfD is the oral route of administration.

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

UF -- According to the U.S. EPA (1985), an uncertainty factor of 100 is used to derive the RfD (10 for species extrapolation, 10 for sensitive population).

MF -- A modifying factor of 5 is used to account for the apparent tolerance to cyanide when it is ingested with food rather than when it is administered by gavage or by drinking water.

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

Decreased protein efficiency ratio was produced by dietary cyanide treatment of rats during gestation, lactation and postweaning growth phase in the Tewe and Maner (1981a) experiment: the dose level of cyanide (10.6 mg/kg/day) producing that effect is slightly lower than the currently accepted NOAEL of 10.8 mg/kg/day (U.S. EPA, 1985). Furthermore, Tewe and Maner (1981b) tested sows. Possible effects observed at about 9.45 mg/kg/day were proliferation of glomerular cells of the kidneys and reduced activity of the thyroid glands in the gilts. However, the number of animals in this experiment was very small. A Japanese study (Amo, 1973) indicated that 0.05 mg/kg/day of cyanide obtained from drinking water decreased the fertility rate and survival rate in the F1 generation and produced 100% mortality in the F2 generation in mice. However, these data are not consistent with the body of available literature.

I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Medium
RfD -- Medium

The confidence in the study is medium because adequate records of food consumption and body weight were maintained and animals of both sexes were tested at two doses for 2 years. The data base is rated medium because a small but sufficient number of studies support the chosen study. Medium confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanides. Office of Drinking Water, Washington, DC.

The ODW criteria document and OERR health effects assessment have both had extensive Agency-wide and limited external review.

Agency Work Group Review -- 08/05/1985

Verification Date -- 08/05/1985

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).

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

Substance Name -- Cyanide, free
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Not available at this time.

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__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 03/01/1991

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 a human carcinogen.

Basis -- Pertinent data regarding carcinogenicity have not been located in the available literature.

__II.A.2. Human Carcinogenicity Data

None.

__II.A.3. Animal Carcinogenicity Data

None.

__II.A.4. Supporting Data for Carcinogenicity

In vitro studies of genotoxicity have been negative except for a marginally mutagenic response for HCN in Salmonella typhimurium strain TA100 (Kushi et al., 1983). This response was decreased in the presence of rat hepatic homogenates.

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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.

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II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1987

The 1987 Drinking Water Criteria Document on Cyanide has received OHEA review.

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

Agency Work Group Review -- 03/23/1988

Verification Date -- 03/23/1988

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).

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III. [reserved]

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V. [reserved]

VI. Bibliography

Substance Name -- Cyanide, free

CASRN -- 57-12-5

Last Revised -- 01/01/1990

VI.A. Oral RfD References

Amo, H. 1973. Effects of oral administration of cyanide and heavy metals in long term on breeding and chromosomes analyses of mice. Nagoya shiritsu Diagaku Igakkai Zasshi. 24(1): 48-66.

Crampton, R.F., I.F. Gaunt, R. Harris et al. 1979. Effects of low cobalamin diet and chronic cyanide toxicity. Toxicology. 12: 221-234.

Hartung, R. 1982. Cyanides and nitriles. In: Patty's Industrial Hygiene and Toxicology, 3rd revised ed., Vol. 2c, G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 4845-4900.

Hertting, G., O. Kraupp, E. Schnetz and S. Weeketich. 1960. Untersuchungen uber die

Folgen einer chronischen Verabreichung akut toxischer Dosen von Natriumcyanid an Hunden. *Acta Pharmacol. Toxicol.* 17: 27-43.

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. *Agric. Food Chem.* 3: 325-329.

Lessell, S. 1971. Experimental cyanide optic neuropathy. *Arch. Ophthalmol.* 86(2): 194-204.

Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander and R.G. Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. *J. Toxicol. Environ. Health.* 5: 579-592.

Tewe, O.O. and J.H. Maner. 1981a. Long-term and carry-over effect of dietary inorganic cyanide (KNC) in the life cycle performance and metabolism of rats. *Toxicol. Appl. Pharmacol.* 58: 1-7.

Tewe, O.O. and J.H. Maner. 1981b. Performance and pathophysiological changes in pregnant pigs fed cassava diets containing different levels of cyanide. *Res. Veter. Sci.* 30: 147-151.

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

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_VI.B. Inhalation RfC References

None

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_VI.C. Carcinogenicity Assessment References

Kushi, A., T. Matsumoto and D. Yoshida. 1983. Mutagen from the gaseous phase of protein pyrolyzate. *Agric. Biol. Chem.* 47(9): 1979-1982.

U.S. EPA. 1987. Drinking Water Criteria Document for Cyanide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

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_VII. Revision History

Substance Name -- Cyanide, free
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| Date | Section | Description |
|------------|---------------|--|
| 03/31/1987 | IV.B. | RQ - new rationale text |
| 03/01/1988 | I.A.5. | Confidence levels revised |
| 03/01/1988 | III.A. | Health Advisory added |
| 09/07/1988 | II. | Carcinogen summary on-line |
| 01/01/1990 | VI. | Bibliography on-line |
| 08/01/1990 | III.A.10 | Primary contact changed |
| 08/01/1990 | IV.F.1. | EPA contact changed |
| 03/01/1991 | II.D.3. | EPA contacts changed |
| 01/01/1992 | I.A.7. | Primary contact changed |
| 01/01/1992 | IV. | Regulatory actions updated |
| 02/01/1993 | I.A.7. | Minor text change |
| 04/01/1997 | III., IV., V. | Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information. |

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VIII. Synonyms

Substance Name -- Cyanide, free
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 Last Revised -- 01/31/1987

57-12-5
 CARBON NITRIDE ION
 CYANIDE
 CYANIDE ANION
 Cyanide, free
 CYANIDE ION
 CYANURE
 FREE CYANIDE
 ISOCYANIDE
 RCRA WASTE NUMBER P030

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