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Environmental Protection
Agency

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EPA

Research and Development

VERIFIED REFERENCE DOSES (RfDs) OF THE U.S. EPA

Prepared for

THE RISK ASSESSMENT FORUM AND
THE RISK ADVISORY GROUP

Prepared by

THE ADI WORK GROUP OF THE RISK
ASSESSMENT FORUM

DISCLAIMER

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AVAILABILITY NOTICE

For information contact Dr. Peter Preuss, Acting Director, Office of Health and Environmental Assessment, Office of Research and Development, Washington, DC (202/382-7317).

As of May 1, 1985, the Agency established a group of scientists familiar with the development of reference doses (RfDs) under the direction of Dr. Peter Preuss, Acting Director of the Office of Health and Environmental Assessment of the Office of Research and Development. The purpose of this group is to verify existing Agency RfDs and to resolve conflicting values within the Agency.

The current procedure to accomplish these tasks is a biweekly meeting of scientists from within the Agency. A file is created for each chemical that includes the critical reference, the supporting studies, the U.S. EPA document that describes the calculation of the RfD, and a two page cover form that summarizes the RfD, the chosen critical toxic effect, the chosen uncertainty factors, and statements concerning the confidence in the data base, the critical study, and the RfD.

The group has discussed 144 RfDs. This package reflects the first 65 of these values that were verified. Complete files are available on all RfDs that have been discussed. The files consist of:

1. A cover form (one to several pages) that summarizes information pertinent to the development of an RfD, such as the chosen effect levels and uncertainty factors, and statements of confidence in the RfD, the chosen study and the associated data base

2. The U.S. EPA documentation that supports the RfD

3. The critical study from which the chosen effect level is taken and

4. Supporting literature.

OUTLINE

I. CAS NO. LISTING OF CHEMICALS FOR WHICH RfDs HAVE BEEN VERIFIED

II. ALPHABETICAL LISTING OF CHEMICALS FOR WHICH RfDs HAVE BEEN VERIFIED

III. COVER FORMS FOR CHEMICALS

LIST OF ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable daily intake
AEL	Adverse-effect level
bw	Body weight
CAS	Chemical Abstract Services
CAG	Carcinogen Assessment Group
cu. m	Cubic meter
FEL	Frank-effect level
g	Gram
i.p.	Intraperitoneal
kg	Kilogram
L	Liter
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MF	Modifying factor
mg	Milligram
MTD	Maximum tolerated dose
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NTP	National Toxicology Program
RfD	Reference dose
s.c.	subcutaneous
TLV	Threshold limit value
UF	Uncertainty factor
ug	Microgram

CAS No. Listing of Chemicals for Which RfDs Have Been Verified

Chemical CAS No.	Chemical CAS No.
Carbon Tetrachloride CAS: 56-23-5	1,1,2-Trichloro-1,2,2-trifluoroethane CAS: 76-13-1
Cyanides CAS: 57-12-5	Tetraethyl Lead CAS: 78-00-2
Strychnine CAS: 57-24-9	Methyl Ethyl Ketone CAS: 78-93-3
2,3,4,6-Tetrachlorophenol CAS: 58-90-6	Acrylic Acid CAS: 79-10-9
Dimethoate CAS: 60-51-5	Pentachloronitrobenzene (PCNB) CAS: 82-68-8
Phenyl Mercuric Acetate CAS: 62-38-4	Pentachlorophenol CAS: 87-86-5
Carbaryl CAS: 63-25-2	Dinoseb CAS: 88-85-7
Formic Acid CAS: 64-18-6	MCPA CAS: 94-74-6
Hydrogen Cyanide CAS: 74-90-8	2,4-DB CAS: 94-82-6
Methylene Chloride CAS: 75-09-2	1,2-Dichlorobenzene CAS: 95-50-1
Carbon Disulfide CAS: 75-15-0	2,4,5-Trichlorophenol CAS: 95-95-4
Cacodylic Acid CAS: 75-60-5	Nitrobenzene CAS: 98-95-3
Trichlorofluoromethane CAS: 75-69-4	Ethylbenzene CAS: 100-41-4
Dichlorodifluoromethane CAS: 75-71-8	Toluene CAS: 108-88-3

Chemical CAS No.	Chemical CAS No.
Chlorobenzene CAS: 108-90-7	Copper Cyanide CAS: 544-92-3
Phenol CAS: 108-95-2	Nickel Cyanide CAS: 557-19-7
Pyridine CAS: 110-86-1	Zinc Cyanide CAS: 557-21-1
Malathion CAS: 121-75-7	Thallium Acetate CAS: 563-68-8
Tetrachloroethylene CAS: 127-18-4	Mercury Fulminate CAS: 628-86-4
Sodium Cyanide CAS: 143-33-9	Selenourea CAS: 630-10-4
Potassium Cyanide CAS: 151-50-8	Thallic Oxide CAS: 1314-32-5
Linuron CAS: 330-55-2	Cresols CAS: 1319-77-3
Cyanogen Cyanide CAS: 460-19-5	Methyl Ethyl Ketone Peroxide CAS: 1338-23-4
Calcium Cyanide CAS: 502-01-8	Thallium Carbonate CAS: 6533-73-9
Potassium Silver Cyanide CAS: 506-61-6	Mercury (inorganic) CAS: 7439-97-6
Silver Cyanide CAS: 506-64-9	Barium CAS: 7440-39-2
Chlorine Cyanide CAS: 506-77-4	Thallium Sulfate CAS: 7446-18-16
Barium Cyanide CAS: 542-62-1	Fluoride (fluorine) CAS: 7782-41-4

Chemical CAS No.	Chemical CAS No.

Selenious Acid
CAS: 7783-00-8

Hydrogen Sulfide
CAS: 7783-06-4

Thallium Chloride
CAS: 7791-12-0

Phosphine
CAS: 7803-51-2

Nitrogen Oxide
CAS: 10102-43-9

Nitrogen Dioxide
CAS: 10102-44-0

Thallium Nitrate
CAS: 10102-45-1

Thallium Selenite
CAS: 12039-52-0

Aluminum Phosphide
CAS: 20859-73-8

Alphabetical Listing of Chemicals for Which RfDs Have Been Verified

Chemical	Chemical
Acrylic Acid	Fluoride (Fluorine)
Aluminum Phosphide	Formic Acid
Barium Cyanide	Hydrogen Cyanide
Barium	Hydrogen Sulfide
Cacodylic Acid	Linuron
Calcium Cyanide	Malathion
Carbaryl	MCPA
Carbon Disulfide	Mercury Fulminate
Carbon Tetrachloride	Mercury (inorganic)
Chlorine Cyanide	Methylene Chloride
Chlorobenzene	Methyl Ethyl Ketone
Copper Cyanide	Methyl Ethyl Ketone Peroxide
Cresols	Nickel Cyanide
Cyanide (free)	Nitric Oxide
Cyanogen	Nitrobenzene
2,4-DB	Nitrogen Dioxide
1,2-Dichlorobenzene	Pentachloronitrobenzene (PCNB)
Dichlorodifluoromethane	Pentachlorophenol
Dimethoate	Phenol
Dinoseb	Phenyl Mercuric Acetate
Ethylbenzene	Phosphine

Chemical CAS No.	Chemical
Potassium Cyanide	1,1,2-Trichloro-1,2,2-trifluoroethane
Potassium Silver Cyanide	Zinc Cyanide
Pyridine	
Selenious Acid	
Selenourea	
Silver Cyanide	
Sodium Cyanide	
Strychnine	
Tetrachloroethylene	
2,3,4,6-Tetrachlorophenol	
Tetraethyl Lead	
Thallic Oxide	
Thallium Acetate	
Thallium Carbonate	
Thallium Chloride	
Thallium Nitrate	
Thallium Selenate	
Thallium Sulfate	
Toluene	
Trichlorofluoromethane	
2,4,5-Trichlorophenol	

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Acrylic Acid CAS #: 79-10-7

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
DePass et al. (1983) Rat oral subchronic study (drinking water)	83 mg/kg/day NOAEL	1000	-	0.08 mg/kg/day or 6 mg/day for a 70 kg man
Reduced body weights altered organ weights	250 mg/kg/day (LOAEL)			

Endpoint and Experimental Doses:

DePass, L.R., M.D. Woodside, R.H. Garman and C.S. Weil. 1983. Subchronic and reproductive toxicology studies on acrylic acid in drinking water of the rat. Drug Chem. Toxicol. 6(1): 1-20.

In this subchronic study acrylic acid was incorporated into the drinking water of rats (15/group/sex) for 3 months at doses of 750, 250, 83 and 0 mg/kg/day. At the high (750 mg/kg) and middle (250 mg/kg) dose levels reduction in body weight and changes in organ weights were observed. These effects coincided with a dose-related reduction in food and water consumption. At the 83 mg/kg dose the only effect was a reduction in water consumption. No significant treatment-related histological effects were seen at any dose level. A NOAEL of 83 mg/kg was established in this study.

In a short-term inhalation study (Gage, 1970) no adverse effects were observed in eight rats exposed to 80 ppm (about 240 mg/cu. m) acrylic acid, 6 hours/day, 5 days/week for 4 weeks. This exposure is approximately equivalent to an oral exposure of 14 mg/kg/day (i.e., 240 mg/cu. m x 0.223 cu. m/day x 6 hours/24 hours x 5 days/7 days x 0.5/1.0 / 0.35 = 14 mg/kg/day). Eight rats exposed at 300 ppm (about 51 mg/kg/day) experienced nose irritation, lethargy and reduced weight gain. Histological and hematological examinations were normal. Higher doses for shorter periods of time resulted in liver, kidney and lung damage.

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

The subchronic oral study of DePass et al. (1983) appears to be the most appropriate for deriving an ADI, in view of the limited data available.

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Uncertainty Factors (UFs):

Using the NOAEL of 83 mg/kg/day and aplying an uncertainty factor of 1000, (10 to account for subchronic to chronic conversion, 10 for intraspecies extrapolation and 10 to protect sensitive individuals) an ADI of 0.08 mg/kg/day or 6 mg/day was derived.

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Modifying Factors (MFs):

None.

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Additional Comments:

No oral chronic data are available.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Medium

The confidence in the study is medium because of the number of animals/dose used, several parameters were studied, and a good dose-severity was obtained. The confidence in the data base is low because of the general lack of supporting studies. The overall confidence in the RfD is rated medium to low.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Acrylic Acid: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/19/85
Second Review:
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Aluminum Phosphide CAS #: 20859-73-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Hackenburg (1972) Rat chronic oral study Body weight and clinical parameters	0.51 mg/kg of food or 0.025 mg/kg/day (phosphine) converted to 0.043 mg/kg/day aluminum phosphide (NOAEL) Conversion Factors: Food consumption: 5% bw; molecular weight: AlP/PH3: x 57.95/34.0 thus, 0.51 mg/kg of food x 0.05 kg food/kg bw/day x 57.95/34.0 = 0.043 mg/kg/day	100	-	0.0004 mg/kg/day or 0.03 mg/day for a 70 kg person

Endpoint and Experimental Doses:

Hackenburg, U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. Toxicol. Appl. Pharmacol. 23(1): 147-158.

Aluminum phosphide pellets and tablets (Phastoxin) are used as fumigants for wheat and other grains (Dieterich et al., 1967). Upon exposure to moisture in the air, they immediately decompose to phosphine gas, with little trace residue of phosphide remaining, which could be lost in handling of the grain.

A chronic feeding study of aluminum phosphide-fumigated chow fed to 30 rats/sex was conducted by Hackenburg (1972). The average concentration was 0.51 mg phosphine/kg food for a 2-year period. At the end of the treatment period, there were no differences between treated and control rats in blood or urine chemistry, histological parameters.

The phosphine gas measured in the Hackenburg (1972) study was liberated by decomposition of aluminum phosphide pellets. Acute toxicity data generated (Sax, 1984) suggest that the phosphide moiety contributes the most to the

Preparation Date: 01/06/86

Endpoint and Experimental Doses (cont.):

acute toxicity of this compound as opposed to any deleterious effect due to aluminum cation. The steep slope of the dose-response curve of phosphine gas (Klimmer, 1969) implies that phosphine is extremely hazardous at doses slightly above a NOEL. Therefore, it is appropriate to derive an ADI for aluminum phosphide based upon the ADI for phosphine.

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Uncertainty Factors (UFs):

After correcting for the molecular weight of aluminum phosphide relative to that of phosphine (57.95/34.00), and by application of an uncertainty factor of 100 (10 for interspecies conversion and 10 for sensitive population), an ADI for aluminum phosphide of 0.00043 (0.00025 mg/kg/day phosphine x 1.70) can be derived.

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Modifying Factors (MFs):

None.

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Additional Comments:

The ACGIH (1984) has recommended a TLV of 0.3 ppm (0.42 mg/cu. m) for phosphine, based principally upon an epidemiological study by Jones (1964) where workers were exposed intermittently to about 10 ppm phosphine gas. Based on this TLV an ADI of 0.0021 mg/kg/day (i.e., 0.42 mg/cu. m x 10 cu. m/day x 5 day/7 day x 0.5/70 kg/10 = 0.0021 mg/kg/day) can be derived. However, an ADI for phosphine of 0.00025 mg/kg/day based on the 2-year rat study by Hackenburg (1972) (described above) has been derived for providing adequate protection against adverse human health effects.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

The confidence in the study was rated high because of the moderate number of animals/dose, the extensive methodology employed to assure proper administration of the test compound, and the extensive number of parameters measured. The data base was rated high because the effectiveness and safety of this chemical has been long reported through supporting studies. The overall rating for the RfD is, thus, high.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Aluminum Phosphide: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

Agency RfD Review:

First Review:	08/19/85
Second Review:	-
Verification Date:	08/19/85

U.S. EPA Contact:

Primary:	C.T. DeRosa FTS/684-7534 or 513/569-7534
Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Barium Cyanide CAS #: 542-62-1

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Perry et al. (1983) Rat oral chronic study	10 ppm barium in drinking water (NOAEL)	100	-	0.07 mg/kg/day or 5 mg/day for a 70 kg man
Hypertension	100 ppm (LOAEL) estimated as 5.1 mg/kg/day (U.S. EPA, 1985) converted to 7 mg Ba (CN)2			

Conversion Factor: Exposure dose was based on U.S. EPA (1985) estimate; molecular weight ratio of Ba(CN)2/Ba is 189/137; thus, 5.1 mg/kg/day x (189/137) = 7 mg/kg/day

Endpoint and Experimental Doses:

Perry, H.M., E.F. Perry, M.N. Erlanger and S.J. Kopp. 1983. Cardiovascular effects of chronic barium ingestion. In: Proc. 17th Ann. Conf. Trace Substances in Environmental Health, Vol. 17. University of Missouri Press, Columbia, MO. p. 155-164.

Perry et al. (1983) exposed 10 female rats/group to 0, 1, 10 or 100 ppm barium in drinking water for up to 16 months. Barium exposure produced no change in growth rate, and no evidence of toxicity was recognized. Limited and preliminary physiologic and biochemical parameters, such as, myocardial pathophysiology and disturbances in myocardial metabolism were significantly depressed in rats exposed to 100 ppm barium (Perry et al., 1983; Kopp et al., 1985). In addition, rats from this exposure group showed increased average systolic blood pressure (16 mm Hg average elevation).

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

A moderate increase (6 mm Hg) in systolic blood pressure was observed in rats exposed to 10 ppm barium; however, the U.S. EPA (1985) determined that the increase seen after 16 months is not large enough to constitute an adverse health effect.

Brenniman et al. (1979, 1981) reported a significant increase in death rate for cardiovascular diseases in communities whose water supply contained an average of 7 mg Ba/L, compared with communities whose water supply contained an average of 0.1 mg Ba/L. The exposure levels tested in these studies did not evaluate a continuous range of exposure to barium and so, although a NOEL may well have been identified, it is impossible to identify the highest NOAEL within the framework of their experimental designs.

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Uncertainty Factors (UFs):

The U.S. EPA (1985) justified the use of an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive population) to the estimated dose of 5.1 mg/kg/day barium on the grounds that the rats in Perry et al. (1985) study were exposed to very low levels of all essential metals (specifically calcium).

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Modifying Factors (MFs):

None.

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Additional Comments:

If an ADI for barium cyanide is based on cyanide (0.02 mg/kg/day CN/0.28, % CN) an ADI of 0.08 mg/kg/day for barium cyanide would result in a daily intake of 0.06 mg/kg/day of barium. An ADI of 0.07 mg/kg/day (0.051 mg/kg/day Ba/0.72, % Ba) for barium cyanide is somewhat lower than would be derived by analogy to cyanide (0.08 mg/kg/day) and is, therefore, recommended to provide adequate protection against adverse health effects.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

The confidence in the study is rated medium because three doses were used and a sensitive indicator (i.e., blood pressure changes) of the critical effect of barium (i.e., cardiac toxicity) was measured. The confidence in the study is not rated any higher because of the use of only one sex, and the low

Confidence in the RfD (cont.):

level of essential element exposure that may have predisposed the animals to barium toxicity. The data base is rated low because it is limited to a few studies. The overall confidence in the RfD is rated low.

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Documentation of RfD and Review:

Limited peer review and ECAO-Cincinnati internal review, August, 1985.

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

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Barium CAS #: 7440-39-2

Carcinogenicity:

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)

Information to be provided by the Office of Drinking Water

Endpoint and Experimental Doses:

Preparation Date:

Uncertainty Factors (UFs):

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Modifying Factors (MFs):

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Additional Comments:

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Confidence in the RfD:

Study: Data Base: RfD:

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Documentation of RfD and Review:

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary:
FTS/684-75 or 513/569-75

Secondary:
FTS/684-75 or 513/569-75

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Cacodylic Acid CAS #: 75-60-5

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Nees (1968) Rat subchronic feeding study (30-90 days)	100 ppm in diet as NOEL converted to 10 mg/kg/day Conversion Factor: Young rat food consumption = 10% bw/day	1000	-	0.01 mg/kg/day or 0.7 mg for a 70 kg man

Endpoint and Experimental Doses:

Nees, P.O. 1968. Report on cacodylic acid toxicity to animals. Wisconsin Alumni Res. Found. EPA Pesticide Petition No. 0F0911.

In this study weanling rats were fed cacodylic acid as 3, 15, 30 or 100 ppm in the diet for 90 days (estimated 0.3, 1.5, 3 or 10 mg/kg/day). No effects were seen on body weight, food consumption, hematology, organ weight or histology which were attributed to treatment. Therefore, 10 mg/kg represents a free-standing NOEL from this study.

Nees et al. (1960) cited in the same pesticide petition (Report on Cacodylic Acid Toxicity to Animals Wisconsin Alumni Res. Found.) reported that feeding 280 mg/kg cacodylic acid to weanling rats for 20 days resulted in testicular histopathological changes, while feeding 140 mg/kg represented a NOEL. While these results provide additional support that the Nees et al. (1968), feeding levels were indeed below effect levels and also suggest that the highest NOEL from Nees (1968) may be considerably below the threshold region this study was of inadequate duration for use in ADI calculation. In addition, doses of 130 mg/kg/day administered to pregnant rats by gastric intubation resulted in irregular palatine rugae in the offspring. Higher doses resulted in increased prenatal death delayed sternal and cerndal ossification, and depressed fetal weight. These data provide additional supports for not employing the doses from the 20-day study as a basis for ADI estimation.

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

The low confidence ratings for this study and data base reflect the limited secondary descriptions available at the time of this writing. Low confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cin Internal Review, 1985.

U.S. EPA. 1985. Cacodylic Acid: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH

Agency RfD Review:

First Review: 08/05/85
Second Review:
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Calcium Cyanide CAS #: 502-01-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat chronic oral study	10.8 mg/kg/day CN (NOAEL) converted to 19.1 mg/kg/day of calcium cyanide	100	5	0.04 mg/kg/day or 3 mg/day for a 70 kg man
Philbrick et al. (1979) Rat subchronic to chronic oral bioassay Weight loss, thyroid effects and myelin degeneration	30.0 mg/kg/day CN (LOAEL)			
	Conversion Factor: Molecular weight ratio of Ca(CN)2/2 CN is 92/52; thus 10.8 mg/kg/day x 92/52 = 19.1 mg/kg/day			

Endpoint and Experimental Doses:

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

Since calcium is present in a very high level physiologically, ADIs for CaCN2 can be calculated based on the maximum molar equivalents of cyanide generated in adequeous or dilute acid solution.

In this 2 yr. 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 author's data for concentration at the be-

Preparation Date: 01/06/86

Endpoint and Experimental Doses (cont.):

ginning 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 3 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

Chemical: Carbaryl CAS #: 63-25-2

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Carpenter et al. (1961)	200 ppm of diet (9.6 mg/kg/day (NOAEL)	100	-	0.1 mg/kg/day
Rat chronic feeding study	400 ppm of diet 15.6 mg/kg/day (LOAEL)			
Kidney and liver toxicity				

Endpoint and Experimental Doses:

Carpenter, C.P., C.W. Weil, P.E. Polin, et al. 1961. Mammalian toxicity of 1-naphthayl-N-methylcarbamate (Sevin insecticide). J. Agric. Food Chem. 9: 30-39.

Groups of 20 CF-N rats/sex were fed carbaryl at 0, 50, 100, 200 or 400 ppm of diet for 2 years. Food consumption and body weight records were maintained. Interim sacrifices (4-8 animals) from concurrent auxiliary groups were performed at 6, 9 and 12 months for organ weight comparisons and histopathological analysis. Hematological analyses were done at semi-regular intervals throughout the study. Surviving animals were sacrificed at 2 years with gross and histopathological examinations performed. The only noteworthy effects reported were slight histopathological changes in the kidneys and liver at the high-dose level. Diffuse cloudy swelling of renal tubules was observed at 1 and 2 years. A statistically significant increase in cloudy swelling of the hepatic cords was also observed after 2 years. Based on body weight and food consumption data, the LOAEL of 400 ppm was equivalent to a dose of 15.6 mg/kg bw/day. The NOAEL established was 9.6 mg/kg bw/day.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

UF = 10a x 10h. The UF of 100 includes uncertainties in interspecies and intrahuman variability.

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Modifying Factors (MFs):

None.

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Additional Comments:

Effect and no-effect levels (14 and 7 mg/kg/day, respectively) similar to those found in the critical study were observed for rat body weight reduction and cholinesterase inhibition in a 1 year study. In subchronic rat studies, higher dose levels (85-200 mg/kg/day) caused kidney toxicity and biochemical changes. Kidney lesions were observed in dogs fed carbaryl at 5 mg/kg/day for 1 year; however, the effect was not clearly associated with treatment since the lesions appeared in control animals but not in lower dose groups.

Carbaryl was teratogenic for several species with widely varying NOELs. The lowest effect levels of 5-6 mg/kg were observed for dogs, with NOELs of 2-3 mg/kg. Other LOELs were higher than the established chronic LOAEL of 15.6 mg/kg/day. Carbaryl was not teratogenic for monkeys at 20 mg/kg. The dog studies were judged inappropriate for human health risk assessment because of differences in the metabolism of carbaryl between dogs and humans.

Carbaryl has induced numerical chromosome aberrations (aneuploidy and polyploidy) in experimental animals. Carbaryl has not been found to be carcinogenic, but the data are equivocal.

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium

The critical study was well designed and clearly reported with unequivocal effect levels established. The data base is moderately supportive of the nature of the critical effect, if somewhat sparse. The principal problem is the observation of teratogenicity in dogs at lower doses. Because the significance of these data cannot be discounted entirely, confidence in the RfD should be considered medium to low.

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Documentation of RfD and Review:

Limited Agency review of 1984 Health and Environmental Effects Profile with the help of two external scientists.

U.S. EPA. 1984. Health and Environmental Effects Profile for Carbaryl. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P039.

Agency RfD Review:		U.S. EPA Contact:	
First Review:	05/31/85	Primary:	M.L. Dourson FTS/684-7544 or 513/569-7544
Second Review:	-		
Verification Date:	05/31/85	Secondary:	C.T. DeRosa FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Carbon Disulfide CAS #: 75-15-0

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Hardin et al. (1981) Rabbit inhalation teratogenic Toxicity/fetal malformations	20 ppm (62.3 mg/cu. m) (NOEL) converted to 11.0 mg/kg/day	100	-	0.1 mg/kg/day or 8 mg/day for a 70 kg man
Price et al. (1984) Rabbit oral teratology study Fetal resorptions	25 mg/kg/day (LOAEL)			
	Conversion Factors: 6 hour/24 hour, 1.6 cu. m/day breathing rate; 1.13 kg bw and 0.5 absorption rate (i.e., 62.3 mg/cu. m x 6 hour/24 hours x 1.6 cu. m/day / 1.13 kg bw x 0.5 = 11.0 mg/kg/day)			

Endpoint and Experimental Doses:

Hardin, B.D., G.P. Bond, M.R. Sikor, F.D. Andrew, R.P. Belilles and R.W. Niemeir. 1981. Testing of selected work place chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl. 4): 66-75.

The data reported in this study were generated at Litton Bionetics, Maryland (under contract to NIOSH). Rats and rabbits were exposed to 20 ppm or 62.3 mg/cu. m (recommended occupational exposure limit) and 40 ppm or 124.6 mg/cu. m of CS2 during the entire length of the pregnancy period and also 3 weeks prior to breeding to simulate occupational exposure. This report containing data on maternal/fetal toxicity and fetal malformations failed to show any adverse effects of CS2 exposure, even at the high dose (124.6 mg/cu. m).

Preparation Date: 01/06/86

Endpoint and Experimental Doses (cont.):

A NCTR/NTP study (Price et al., 1984) observed 25 mg/kg in rabbits as an AEL (fetal resorption). Fetotoxicity and fetal malformations in this study were not observed in rats at the lowest level (100 mg/kg) of CS2 exposure.

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Uncertainty Factors (UFs):

The 100-fold uncertainty factor reflects 10-fold adjustments for both the expected intra- and interspecies variability to the toxicity of this compound in lieu of chemical-specific data. Note that the usual factor of 10S (subchronic to chronic extrapolation is not used here since the exposure duration covered the entire critical period for the elicitation of the critical effect.

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Modifying Factors (MFs):

None.

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Additional Comments:

A Bulgarian study (Tabatsova et al., 1983) reported significant fetal malformations in rats exposed to a low CS2 dose of 0.03 mg/cu. m over three generations. Based on these data, an ADI would be drastically lower than the ADIs that could be derived from existing guidelines, epidemiological data or other experimental data. Moreover, the Bulgarian study did not present information on mode of control exposure, animal diet, selection of F1/F2 breeding pairs and purity of CS2 (hydrogen sulfide, a potent teratogen, is often found as a contaminant). In a multigeneration study, toxic effects of a compound can be confounded by the above factors. The data of Price et al. (1984) also suggest that the rabbit fetus is more sensitive than the rat fetus to CS2-induced toxicity. Hardin et al. (1981) observed no effects on fetal development in rats or rabbits following inhalation exposure to 62.3 or 124.6 mg/cu. m which corresponds to estimated equivalent oral dosages of 5 and 10 mg/kg for rats, and 11 and 22 mg/kg in rabbits. The highest NOEL from this study, 22 mg/kg in the rabbit, should not be used for an ADI estimate because adverse effects were seen in rabbit fetuses following oral exposure of pregnant does to 25 mg/kg. Therefore, the highest NOEL which is below an effect level is the estimated low dose from the Harden et al. (1981) inhalation study using rabbits. This dose level, >11 mg/kg, is proposed as the basis for ADI derivation.

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Confidence in the RfD:

Study: High Data Base: Low RfD: Low

The confidence in the chosen study is high because the exposure encompassed the critical period, and several species and doses were tested. Confidence in the data base is low because of the unavailability of supporting oral chronic studies. Overall confidence in the RfD is low because of uncertainty in the inter-route conversion model. Until further oral chronic/reproductive studies using U.S. EPA multigeneration protocol are available, a low confidence in the RfD is recommended.

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Documentation of RfD and Review:

U.S. EPA. 1985. Carbon Disulfide: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH.

This RfD received an ECAO-Cincinnati Internal Review during May 1985.

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Agency RfD Review:

First Review: 07/08/85
Second Review:
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Carbon Tetrachloride CAS #: 56-23-5

Carcinogenicity:

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)

Information to be provided by the Office of Drinking Water

Endpoint and Experimental Doses:

Preparation Date:

Uncertainty Factors (UFs):

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Modifying Factors (MFs):

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Additional Comments:

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Confidence in the RfD:

Study: Data Base: RfD:

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Documentation of RfD and Review:

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary:
FTS/684-75 or 513/569-75

Secondary:
FTS/684-75 or 513/569-75

Chemical: Chlorine Cyanide (cyanogen chloride) CAS #: 506-77-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat chronic oral study	10.8 mg/kg/day CN (NOAEL), converted to 25.3 mg/kg/day of chlorine cyanide	100	5	0.05 mg/kg/day or 4 mg/day for a 70 kg man
Philbrick et al. (1979) Rat subchronic to chronic oral bio-assay Weight loss and thyroid effects; myelin degeneration	30 mg/kg/day (LOAEL)			
	Conversion Factor: Molecular weight ClCN/CN is 61/26; thus, 10.8 mg/kg/day x 61/26 = 25.3 mg/kg/day			

Endpoint and Experimental Doses:

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

Since chloride is present in very high levels physiologically an ADI of 3.5 mg/day is recommended based on the maximum number of molar equivalents (1) of cyanide released in aqueous solutions or dilute acids.

In this 2 yr. 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

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

concentrations were estimated based on the author's 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 3.5 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

ECAO-Cincinnati Internal Review, July 1985.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Chlorobenzene CAS #: 108-90-7

Carcinogenicity:

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)

Last minute information prevented the release of these values.

Endpoint and Experimental Doses:

Preparation Date:

Uncertainty Factors (UFs):

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Modifying Factors (MFs):

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Additional Comments:

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Confidence in the RfD:

Study: Data Base: RfD:

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Documentation of RfD and Review:

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary:
FTS/684-75 or 513/569-75

Secondary:
FTS/684-75 or 513/569-75

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Copper Cyanide CAS #: 544-92-3

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat chronic oral study	10.8 mg CN/kg/day (NOAEL) converted to 37.2 mg Cu(CN)2/kg/day	100	5	0.07 mg/kg/day or 5 mg/day for a 70 kg man
Philbrick et al. (1979) Rat subchronic to chronic oral bioassay Weight loss, thyroid effects and myelin degeneration	30 mg/kg/day CN (LOAEL)			
	Conversion Factors: Molecular weight: Cu(CN)2/CN is 89.5/26; thus, 10.8 mg CN kg x (89.5/26) = 37.2 mg/kg/day)			

Endpoint and Experimental Doses:

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

Copper cyanide has not been tested for toxicity. Copper cyanide can exist as cupric cyanide or cuprous cyanide. Cupric cyanide is extremely unstable and dissociates to form cyanide and a cuprous cyanide complex. An ADI can be derived for cupric cyanide based on the molar equivalents of free cyanide only since cuprous cyanide (CuCN) is not soluble in water or dilute acid. An ADI calculated based on molar equivalents (1) of free CN would be 5.20 mg/day.

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

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 author's 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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.

Additional Comments (cont.):

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. Thus, until additional chronic studies are available, an ADI of 5.2 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

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 low because this chemical has not been tested. The confidence in the RfD is low because it is based on analogy. Chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

ECAO-Cincinnati Internal Review, July 1985.

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Agency RfD Review:

First Review: 08/05/85
Second Review:
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Cresols CAS #: 1319-77-3

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
NIOSH (1978) Occupational exposure criterion TLV = 10 mg/cu. m	10 mg/cu. m TLV converted to 0.51 mg/kg/day	10	-	0.05 mg/kg or 4 mg/day for a 70 kg man

Conversion Factors:

10 mg/cu. m x 10 cu. m/day x 0.5 absorption factor x 5 days/7 days / 70 kg = 0.51 mg/kg/day

Endpoint and Experimental Doses:

NIOSH (National Institute of Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Cresol. U.S. DHEW, PHS, CDC, Cincinnati, OH. DHEW (NIOSH) Publ. No. 78-133.

NIOSH's recommendation is based on a review and assessment of the available literature primarily the subchronic inhalation studies of Uzhdavine et al. (1972). Uzhdavine et al. (1972) exposed rats and guinea pigs to O-cresol at a concentration of 9.0 (plus or minus 0.9) mg/cu. m. No effect was seen in guinea pigs. In rats, the authors reported various hematopoietic effects, respiratory tract irritation and sclerosis of lungs. Uzhdavine et al. (1972) also reported humans exposed to 6 mg/cu. m (duration unspecified) cresol experienced nasopharynegeal irritation. No adequate chronic or subchronic data exist to base an ADI. Environ lists an ADI of 0.113 mg/kg/day based on ACGIH (1980) TLV of 22 mg/cu. m. The NIOSH (1978) criterion based on a far more complete, detailed and critical review of the available literature than is the ACGIH TLV. Other studies support the findings (effects) reported in the Uzhdavine et al. (1972) study cited by NIOSH. Consequently, the NIOSH (1978) criterion is a more prudent basis for an ADI of 0.051 mg/kg/day to protect against adverse health effects.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The 10-fold uncertainty factor represents the expected intrahuman variability to the toxicity of this chemical in lieu of chemical-specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

No chronic toxicity studies were conducted and the subchronic data was poorly characterized and documented. Until further oral chronic, subchronic or reproductive data is available, a low confidence in the RfD is recommended. An additional factor of 10 was not deemed necessary due to the fact the various hematopoietic effects observed in rats were considered slight and reversible. No effects wre seen in guinea pigs and no histopathological effects were reported in either species.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

The confidence in both the procedure to estimate an oral RfD by a TLV and the resulting RfD is low since this method is only used when sufficient oral and inhalation toxicity data do not exist.

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Documentation of RfD and Review:

U.S. EPA. 1985. Cresol: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. Health and Environmental Effects Profile for Cresols. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P138.

The Health and Environmental Effects Profile has received an Agency-wide review with the help of two external scientists.

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Agency RfD Review:

First Review: 07/08/85
Second Review: -
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Cyanide (free) CAS #: 57-12-15

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat oral chronic study	10.8 mg/kg/day CN (NOAEL)	100	5	0.02 mg/kg/day or 2 mg/day for a 70 kg man
Philbrick et al. (1979) Rat oral subchronic to chronic study Primary myelin degeneration and decreased thyroxin levels	30 mg/kg/day CN (LOAEL)			

Endpoint and Experimental Doses:

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

Hydrogen cyanide is soluble in water and dilute acid (which includes the gastric environment) and is readily hydrolysed to 1 molar equivalent of 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 author's data for concentration at the beginning and end of each food preparation period and by assuming a first

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

order rate of loss for the intervening period. There were no treatment related effects on growth rate, no gross signs of toxicity, and no histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

.....

Additional Comments:

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. Thus, until additional chronic studies are available, an ADI of 1.5 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H011.

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 an extensive Agency-wide and limited external review.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Cyanogen CAS #: 460-19-5

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat chronic oral study	10.8 mg/kg day CN (NOAEL) converted to 21.6 mg/kg/day of cyanogen	100	5	0.04 mg/kg/day or 3 mg/day for a 70 kg man
Philbrick et al. (1979) Rat subchronic to chronic oral bioassay Weight loss and thyroid effects; myelin degeneration	30 mg/kg/day CN (LOAEL)			

Conversion Factors: Molecular weight of C2N2/CN is 52/26; thus 10.8 mg/kg/day x 52/26 = 21.6 mg/kg/day.

Endpoint and Experimental Doses:

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

Cyanogen does not completely dissociate into free CN in water or dilute acetic solution. However, without an evaluation of the toxicity of the parent compound, an ADI based on molecular equivalents (1) CN would be 3 mg/day.

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 esti-

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

mated doses were 4.3 mg and 10.8 mg CN/kg bw. The average food CN concentrations were estimated based on the author's 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

An additional 5 is used for apparent tolerance of cyanide when it is ingested with food than when administered by gavage or drinking water.

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 3.0 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

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 low because this chemical has not been tested. The confidence in the RfD is low because it is based on analogy. Chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: 2,4-DB CAS #: 94-82-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
CBI	8 mg/kg/day (NOAEL)	1000	-	0.008 mg/kg/day
Dog subchronic oral bioassay	25 mg/kg/day (LOAEL)			
Internal hemorrhage, mortality				

Endpoint and Experimental Doses:

CBI (Confidential Business Information)

Four beagle dogs/sex/group were fed 2,4-DB at dose levels of 0, 2.5, 8.0, 25 or 80 mg/kg bw/day for 90 days. The two higher doses produced frank effects including death, hemorrhage throughout the body and aspermatogenesis within 3-9 weeks of treatment. Slightly increased liver-to-body weight ratios were observed at both lower dose levels, but no gross or microscopic pathology was evident.

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

Preparation Date: 01/09/86

Modifying Factors (MFs):

None.

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Additional Comments:

A subchronic rat study (CBI) showed somewhat higher effect and no-effect levels than were observed in the dog study. Severe kidney and liver damage was observed at 1000 ppm 2,4-DB in the diet (80-100 mg/kg bw/day). A NOEL of about 25-30 mg/kg/day was established.

2,4-DB does not appear to be teratogenic, but the data are very limited. Structurally related compounds (2,4-D and 2,4,5-T) are teratogenic. No data on carcinogenicity are available. 2,4-DB has not been shown to be mutagenic.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

Confidence in the critical study is medium because of the moderate number of animals and large number of dose groups employed, but not high, because some data are lacking. Confidence in the data base is low, because of the general lack of data, but tends toward medium because one moderately supportive study is available. Confidence in the RfD is low because of the weak data base.

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Documentation of RfD and Review:

The ADI in the 1984 Health and Environmental Effects Profile has had a limited Agency review with the help of two external scientists.

U.S. EPA. 1984. Health and Environmental Effects Profile for 2,4-DB. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P060AP.

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Agency RfD Review:

First Review: 05/31/85
Second Review: 06/19/85
Verification Date: 06/19/85

U.S. EPA Contact:

Primary: M.L. Dourson
FTS/684-7544 or 513/569-7544
Secondary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: 1,2-Dichlorobenzene CAS #: 95-50-1

Carcinogenicity:

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)

Last minute information prevented the release of these values.

Endpoint and Experimental Doses:

Preparation Date:

Uncertainty Factors (UFs):

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Modifying Factors (MFs):

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Additional Comments:

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Confidence in the RfD:

Study: Data Base: RfD:

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Documentation of RfD and Review:

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary:
FTS/684-75 or 513/569-75

Secondary:
FTS/684-75 or 513/569-75

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Dichlorofluoromethane CAS #: 75-71-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Sherman (1974)	15 mg/kg/day (NOEL)	100	-	0.2 mg/kg/day or 10 mg/day for a 70 kg man
Rat chronic oral study				
Reduced body weight	150 mg/kg/day (LOAEL)			

Endpoint and Experimental Doses:

Sherman, H. 1974. Long-term feeding studies in rats and dogs with dichlorodifluoromethane (Freon 12 Food Freezant). Haskell Laboratory for Toxicology and Industrial Medicine Report No. 24-74.

The study reported by the Haskell Laboratory (Sherman et al., 1974) involved 2-year feeding studies in which dogs and rats received 300 ppm or 3000 ppm of dichlorodifluoromethane. This report contained data on clinical biochemical, urine analytical, hematological or histopathological evaluations. Additionally, carcinogenic and three-generation reproductive studies were conducted in rats. Except for decreased weight gain in rats (about 20% in females) which received 3000 ppm (150 mg/kg/day) dichlorodifluoromethane in the diet, no other adverse effects were attributable to this compound in either rats or dogs.

The Haskell Laboratory study reported above is sufficiently complete to derive an ADI for adequate protection against adverse human health effects. The high dose (3000 ppm or 150 mg/kg/day) caused decreased body weights in rats and thus considered as a LOAEL; whereas the low dose (300 ppm or 15 mg/kg/day) in rats produced no adverse effects attributable to the oral administration of dichlorodifluoromethane (Freon 12).

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

The NOEL from the 2-year rat study (15 mg/kg/day) and an uncertainty factor of 100 (10 for species extrapolation and 10 for sensitive individuals) were used to derive the ADI of 0.2 mg/kg/day or 10 mg/day for a 70 kg human being.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: High Data Base: Low RfD: High

The Haskell Laboratory study is a chronic oral study in two species which incorporated extensive clinical and toxicological parameters. Therefore, a high level of confidence in study is appropriate. Confidence in the data base is low because of the lack of other data. Confidence in the RfD follows at high to medium.

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Documentation of RfD and Review:

This document has undergone a limited Agency review.

U.S. EPA. 1982. Errata: Halomethanes Ambient Water Quality Criteria Document for the Protection of Human Health. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-D023.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	07/08/85	Primary:	C.T. DeRosa
Second Review:	07/22/85		FTS/684-7534 or 513/569-7534
Verification Date:	07/22/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Dimethoate CAS #: 60-51-5

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Edson et al. (1967) Short-term feeding study in humans Decreases in cholinesterase (ChE) activity	NOEL: 0.2 mg/kg/day LOAEL: 0.4 mg/kg/day	10	-	0.02 mg/kg/day

Endpoint and Experimental Doses:

Edson, E.F., K.H. Jones and W.A. Watson. 1967. Safety of dimethoate insecticide. Br. J. Med. 4: 554-555.

Thrity-six male and female adult volunteers without occupational exposure to organophosphate insecticides were arranged in groups and given repeated doses of dimethoate. The dimethoate was administered as a flavoured aqueous solution. Venous blood samples were taken twice before and once or twice/week after dimethoate dosage started. ChE in whole blood was measured and its depression taken as the critical first response to dimethoate. Activity in red cells and plasma were also determined separately. The study was under close medical supervision, and inquiry was also made for any effects other than ChE depression, though none was detected.

The results show that no significant change occurred with 0.068 or 0.202 mg/kg/day. ChE values at 0.434 mg/kg/day began to show a slow downward trend by day 20, and this continued to the end of the test at 57 days. Higher doses showed the same effects at an earlier stage, and a somewhat faster rate. The rate and extent of red cell ChE depression closely paralleled those of whole-blood ChE. No localized gastrointestinal or other clinical effects occurred in any group.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 10 accounts for the expected interhuman variability to the toxicity of this chemical in lieu of specific data. An additional uncertainty factor of 10-fold to adjust the results found after short-term to chronic exposures is not considered necessary here because the critical toxic effect, cholinesterase inhibition is immediate and occurs regardless of exposure duration.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

The study is given a confidence rating of high because it was conducted in humans with a fair amount of subjects at each of five doses. Cholinesterase inhibition, the critical toxic effect was measured. The supporting animal data base is given a confidence rating of high because it is extensive and yields similar RfD values. High confidence in the RfD follows.

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Documentation of RfD and Review:

The ADI has been through the Registration Standard process of the OPP.

Gessert, R.A. 1982. Memorandum to P. Parsons. Dimethoate Registration Standard; Toxicology Assessment. Office of Pesticide Programs, U.S. EPA, Washington, DC, August 31.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	07/08/85	Primary:	R. Engler
Second Review:	07/22/85		FTS/537-7490 or 202/557-7490
Verification Date:	07/22/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Dinoseb CAS #: 88-85-7

Carcinogenicity: Limited data are negative.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
CBI	NOEL: None	1000	-	0.001 mg/kg/day
Rat chronic oral bioassay	LOAEL: 1 mg/kg/day			
Decreased body and thyroid weights				

Endpoint and Experimental Doses:

CBI (Confidential Business Information)

Sixty rats/sex/group were fed diets containing dinoseb at 0, 1, 3 or 10 mg/kg bw/day for up to 104 weeks. Ten animals/sex were sacrificed at 1 year for interim results. Clinical signs of toxicity attributed to dinoseb were evident in all treated groups (hunched posture and urine staining of coat). A statistically significant and dose-related reduction in body weight gain was observed at 3 and 10 mg/kg/day. This effect was evident within the first year of treatment, and occurred despite increased food consumption. Decreased mean relative absolute thyroid weights in all treated males and decreased relative thyroid weights in mid-dose males were observed at the 104-week terminal kill. No consistent dose-related effects were observed for hematology, selected blood chemistries or urinalysis values.

Ilivicky and Casida (1969) suggested that the mechanism of toxicity for dinoseb involved an elevated metabolic rate associated with uncoupling of oxidative phosphorylation. The observation of decreased growth rate with increased food consumption, concurrent with decreased thyroid weight is consistent with this hypothesis.

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intra- and inter-species variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation from a LOAEL to it hypothesized NOAEL.

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Modifying Factors (MFs):

None.

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Additional Comments:

Body weight losses due to dinoseb treatment have also been reported for rats treated at 9.1 mg/kg/day for 11 weeks and at 10 mg/kg/day for 6 months. A 90-day dog study showed reversible heart and liver effects at 5.3 mg/kg/day with a NOEL of 3 mg/kg/day.

Dinoseb was not carcinogenic in one rat study, and has not been found to be mutagenic. Dinoseb was teratogenic by i.p. and s.c. administration to mice, but not by the oral route. Male reproductive toxicity was observed for rats fed dinoseb at 15.6 mg/kg/day for 11 weeks.

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium

The confidence in the chosen study is high because of the large number of animals/sex in three dose groups, the large number of parameters measured, and because of the interim kill. The data base is rated medium because the supporting studies are only subchronic in duration. Confidence in the RfD is not higher than medium because a NOAEL was not established.

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Documentation of RfD and Review:

The ADI in the 1984 Health and Environmental Effects Profile has received limited Agency review with the help of two scientists.

U.S. EPA. 1984. Health and Environmental Effects Profile for Dinoseb. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P0-87AP.

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Agency RfD Review:

First Review: 07/08/85
Second Review: 07/22/85
Verification Date: 07/22/85

U.S. EPA Contact:

Primary: M.L. Dourson
FTS/684-7544 or 513/569-7544
Secondary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Ethylbenzene CAS #: 100-41-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Wolf et al. (1956) Rat subchronic to chronic oral bioassay Liver and kidney toxicity	136 mg/kg/day (NOEL); 408 mg/kg/day (LOAEL) Conversion Factor: 5 days/7 days; thus, 136 mg/kg/day x 5 days/7 days = 97.1 mg/kg/day	1000	-	0.1 mg/kg/day

Endpoint and Experimental Doses:

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

The chosen study is a rat 182-day oral bioassay where ethylbenzene was given 5 days/week at doses of 13.6, 136, 408 or 680 mg/kg/day in olive oil gavage. There were 10 albino female rats/dose group with 20 controls.

The criteria considered in judging the toxic effects on the test animals were growth, mortality, appearance and behavior, hematological findings, terminal concentration of urea nitrogen in the blood, final average organ and body weights, histopathological findings, and bone marrow counts. The LOAEL of 408 mg/kg/day is associated with histopathological changes in liver and kidney.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting data base is low because other oral toxicity data are not found. A low confidence in the RfD follows.

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Documentation of RfD and Review:

A recent ORD document reaffirms the ADI from the ODW criteria document. Both documents have extensive Agency review with the help of selected outside scientists review.

An identical ADI was publicly reviewed during the 1980 Ambient Water Quality Criteria series.

U.S. EPA. 1980. Ambient Water Quality Criteria for Ethylbenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-048.

U.S. EPA. 1985. Drinking Water Criteria Document for Ethylbenzene. Office of Drinking Water, Washington, DC. (Public review draft)

U.S. EPA. 1985. Health Effects Assessment for Ethylbenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H008.

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Agency RfD Review:

First Review: 05/20/85
Second Review: -
Verification Date: 05/20/85

U.S. EPA Contact:

Primary: M.L. Dourson
FTS/684-7544 or 513/569-7544
Secondary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Fluoride CAS #: 7782-41-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Hodge (1950) Cited in: Underwood (1977)	1 ppm (NOAEL converted to 0.05 mg/kg/day	1		0.05-0.2 mg/kg/day or 1 mg/day for a 20 kg child excess fluoride intake over background
Children epidemiological study	2 ppm (LOAEL)			
Dental mottling				
	Coversion Factor: 1 mg/L (NOAEL) x 1 L/day / 20 kg child = 0.05 mg/kg/day			

Endpoint and Experimental Doses:

Hodge, H.C. 1950. The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. J. Am. Dent. Assoc. 40: 436. Cited in: Underwood, E.J. 1977. Trace Elements in Human and Animal Nutrition. Academic Press, NY.

Fluoride related compounds are used in the prevention of dental caries. Extensive human epidemiological studies with large populations have been carried out over the last 40 years. The NOAEL (1 ppm) and LOAEL (2 ppm) in drinking water are defined within a narrow dose range. Underwood (1977) is the secondary reference cited for RfD (ADI) basis. Hodge (1950) is the primary reference cited in Underwood (1977).

Hodge (1950) studied children consuming fluoride in their drinking water. Fluoride levels of 0-14 ppm were investigated. Dental mottling was the parameter of interest. Fluoride levels of 2-10 ppm produced a linear dose response curve (increasing mottling with increasing dose). Fluoride levels of 0.1-1.0 ppm produced no observable effect. An assumption of 20 kg bw for children was used as the children studied were 12-14 years old.

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

Uncertainty factors were not deemed necessary since the NOAEL is that of the critical toxic effect (i.e., dental fluorosis) in a sensitive population of humans (i.e., children for a length of exposure that encompasses both the critical toxic effect and the sensitive population.

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Modifying Factors (MFs):

None.

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Additional Comments:

A range of RfD of 0.05-0.2 mg/kg/day is given. The upper limit is based on the Surgeon General's statement that no adverse medical effects occur at excess fluoride exposures of 4 ppm of drinking water or less (i.e., 4 mg/L x 1 L/day / 20 kg = 0.2 mg/kg/day).

.....

Confidence in the RfD:

Study: Medium Data Base: High RfD: High

Confidence in the study is medium because the exposures represent excess fluoride intake and not total doses. Confidence in the data base is high because of the large number of studies conducted in children all support the chosen NOAEL. Confidence in the RfD is high because little uncertainty remains in the toxicity data base.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Flourine: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Formic Acid CAS #: 64-18-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Malorny (1969) Rat oral chronic study	200 mg/kg/day (NOAEL) 0.2% drinking water	100	-	2 mg/kg/day or 140 mg/day for a 70 kg man
Solmann (1921) Rat oral subchronic bioassay Body weight	0.5% drinking water (LOAEL)			

Endpoint and Experimental Doses:

Malorny, G. 1969. Acute and chronic toxicity of formic acid and formate. Z. Ernachrungswiss. 9: 332-339.

Formic acid is a normal component of human tissues and foods and is important in intermediary metabolism. Ingested formic acid is rapidly metabolized and excreted (Malorny, 1969). The best information on which to base an ADI is the study of Malorny (1969) in which no adverse effects were observed in several generations (5) of rats that consumed 150-200 mg/kg/day (author's estimated range) of formic acid. None of the other information available suggests that toxic effects would occur at lower levels. Solmann (1921) reported a series of studies in which rats received 0.25% formic acid in drinking water (mean dosage of 160 mg/kg) for 15 week without showing any effects on growth or food and water consumption. Solmann (1921) also reported a study in which men consumed sodium formate in doses of 10 g/day (150 mg/kg/day) for some time without any harmful effects. On the other hand, formate doses of 2-3 g several times daily has been reported to cause nausea and albuminuria in men (von Oettingen, 1969).

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

The TLV for formic acid vapor in the atmosphere is 5 ppm (ACGIH, 1984), the same as the OSHA standard (CFR, 1981). Formic acid is "generally recognized as safe" as a synthetic flavoring substance and an indirect food substance (Guest et al., 1982).

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Uncertainty Factors (UFs):

Based on the information available, the NOEL of 200 mg/kg/day (Malorny, 1969) can be divided by an uncertainty factor of 100 (10 for intraspecies extrapolation and 10 for sensitive population) to derive an ADI of 2 mg/kg/day for protection against adverse human health effects.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The study is given a medium confidence because of the extensive length of testing (i.e., 5 generations), several parameters were measured. The data base is rated medium because several studies are available that support the choice of NOAEL. A medium rating in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Formic Acid: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/19/85
Second Review: -
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Hydrogen Cyanide CAS #: 74-90-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat oral chronic study	10.8 mg/kg/day CN (NOAEL)	100	5	0.02 mg/kg/day or 2 mg/day for a 70 kg man
Philbrick et al. (1979) Rat subchronic to chronic oral bioassay Decreased body and thyroid weights and myelin degeneration	30 mg/kg/day CN (LOAEL)			
	Conversion Factor: Molecular weight of HCN/CN is 27/26; thus 10.8 mg/kg/day CN x 27/26 = 11.2 mg/kg/day HCN			

Endpoint and Experimental Doses:

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

Since hydrogen is present in very high levels physiologically an ADI of 1.5 mg/day is recommended based on cyanide content.

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 author's data for concentration at the

Preparation Date: 01/06/86

Endpoint and Experimental Doses (cont.):

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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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. Thus,

Additional Comments (cont.):

until additional chronic studies are available, an ADI of 2 mg/day for a 70 kg man is recommended. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H011.

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

The Drinking Water Criteria document and the Health Effects Assessment document have undergone an extensive Agency and limited external review.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Hydrogen Sulfide CAS #: 7783-06-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Watterau et al. (1964-1965) Pig oral toxicity study (subchronic)	3.1 mg/kg/day (NOAEL)	1000	-	0.003 mg/kg/day or 0.2 mg/kg/day for a 70 kg man
GI disturbance	15 mg/kg/day (LOAEL)			
	Dose Conversion: 0.200 kg of diet/day x 1210 mg H2S/kg of diet / 78 kg bw = 3.1 mg/kg bw/day			

Endpoint and Experimental Doses:

Watterau, H., W. Ockert and U.G. Knape. 1964-1965. In: Toxicity of Hydrogen Sulfide in Animal Feeding. Survey of the literature. (Westermann et al., 1975. Landwirtsch. Forsch. 28: 70-80)

Data regarding chronic/subchronic toxicity of H2S was limited and H2S is not scheduled for carcinogenicity testing by the NTP (1985). The oral toxicity data (Watterau et al., 1964-1965) may be used to calculate an ADI. Although lacking in some detail, Watterau et al. (1964-1965) suggest that adult pigs showed digestive disorders when their diet was replaced by a high percentage of dried greens containing H2S at an approximate intake of 15 mg/kg/day. This effect was not reproduced in a second experiment. This dose may be considered a LOAEL.

Watterau et al. (1964-1965) also tested pigs for 105 days at three lower doses. An intermediate dose of approximately 3.1 mg/kg/day (determined from information given in the critical study) was associated with no changes in body weight gain when compared to control.

Preparation Date: 01/10/86

Uncertainty Factors (UFs):

The uncertainty facotr of 1000 represents 10 for interspecies extrapolation, 10 for sensitive population and 10 for subchronic exposure. An ADI of 0.003 mg/kg/day may be recommended for adequate protection against adverse human health effects.

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Modifying Factors (MFs):

None.

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Additional Comments:

Based on epidemiological data (Poda, 1966) the ACGIH (1980) has recommended a TLV-TWA of 10 ppm (13.9 mg/cu. m) for hydrogen sulfide. However, citing evidence of eye injury, headaches, nausea and insomnia after exposure to H_2S at low concentrations for several hours, NIOSH (1977) adopted a ceiling occupational exposure limit of 10 ppm with a 10-minute maximum exposure to this concentration. More rigorous epidemiological evidence, however, is limited. Until further chronic/reproductive data available, a low confidence in the RfD is recommended.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

The confidence in the study is rated low because the number of animals/dose group was unspecified and the study was designed to test for only minimal toxic responses. The supporting oral toxicity data base is rated low because it does not exist. Low confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Interanl Review, August 1985.

U.S. EPA. 1985. Hydrogen Sulfide: Review and Evaluation of ADI. Contract No. 68-03-3228, Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/19/85
Second Review:
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Linuron CAS #: 330-55-2

Carcinogenicity:

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)

Information to be provided by the Office of Pesticide Programs

Endpoint and Experimental Doses:

Preparation Date:

Uncertainty Factors (UFs):

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Modifying Factors (MFs):

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Additional Comments:

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Confidence in the RfD:

Study: Data Base: RfD:

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Documentation of RfD and Review:

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary:
FTS/684-75 or 513/569-75

Secondary:
FTS/684-75 or 513/569-75

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Malathion CAS #: 121-75-7

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Rider et al. (1959); Moeller and Rider (1962)	0.23 mg/kg/day (NOEL);	10	-	0.02 mg/kg/day
Human subchronic oral bioassay	0.34 mg/kg/day (LOEL)			
Cholinesterase inhibition				

Endpoint and Experimental Doses:

Rider, J.A., H.C. Moeller, J. Swader and R.G. Devereaux. 1959. A study of the anticholinesterase properties of EPN and malathion in human volunteers. Clin. Res. 1: 81.

Moeller, H.C. and S.A. Rider. 1962. Plasma and red blood cell cholinesterase activity as indications of the threshold of incipient toxicity of ethyl-p-nitrophenylthionobenzenephosphonate (EPN) and malathion in human being. Toxicol. Appl. Pharmacol. 4: 123-130.

Malathion was administered by gelatin capsules to groups of five healthy male volunteers ranging in age from 23-63 years at doses of either 8 mg/day for 32 days, 16 mg/day for 47 days or 24 mg/day for 56 days. Cholinesterase activity was determined twice weekly before, during and after administration of the chemical. The intermediate dose was a NOEL. The high-dose was associated with a depression in plasma and RCB cholinesterase activity with no clinically manifested side effects.

The choice of human study for derivation of the ADI is well supported by animal studies. Although the clinical study appears to have been well

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

conducted with five male volunteers in each of three dose groups, the duration of the study is rather short (32-56 days), investigators only looked for one type of effect and body weights were not given.

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Uncertainty Factors (UFs):

The 10-fold factor accounts for the expected interhuman variability to the toxicity of this chemical in lieu of specific data. Note that the usual factor of 10S to estimate a chronic effect level from a subchronic effect level is not considered necessary here because the critical toxic effect (i.e., cholinesterase inhibition) is thought to be independent of exposure duration.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: High RfD: Medium

Confidence in the chosen study is rated medium because only one sex was tested and the duration was rather short. Confidence in the supporting data base is rated high because several animal studies support the chosen effect level. Confidence in the RfD is rated medium to high.

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Documentation of RfD and Review:

The ADI in this 1984 Health and Environmental Effects Profile has received a limited Agency review with the help of two external scientists.

U.S. EPA. 1984. Health and Environmental Effects Profile for Malathion. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P101.

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Agency RfD Review:

First Review: 07/22/85
Second Review: -
Verification Date: 07/22/85

U.S. EPA Contact:

Primary: M.L. Dourson
FTS/684-7544 or 513/569-7544
Secondary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: MCPA CAS #: 94-74-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Reuzel et al. (1980)	1.0 mg/kg/day (NOEL)	1000	-	0.001 mg/kg/day
Dog subchronic oral bioassay	3.0 mg/kg/day (LOAEL)			
Kidney and liver toxicity				

Endpoint and Experimental Doses:

Reuzel et al. 1980. CBI (Confidential Business Information)

Two 13-week studies were conducted in dogs by Reuzel et al. (1980). Collectively five doses were given to groups of four dogs/sex. A clinical syndrome which included icterus, diarrhea, corneal ulcers, severe dermatitis, dehydration and severe weight loss led to the death or humane kill of 7/8 high-dose dogs. Elevated blood creatinine and urea nitrogen were observed in a dose-related fashion at the three highest doses, suggesting impaired kidney function. (The lowest of these doses was 3.0 mg/kg/day.) The two lowest doses showed no effects outside normal limits. (The highest of these doses was 1.0 mg/kg/day.)

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

Confidence in the chosen study is medium because the study appears to be well conducted with four beagle dogs/sex in each of five dose groups. Confidence in the data base is medium because the CBI study for the derivation of the ADI is moderately well supported by studies in the open literature. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

The ADI in the 1984 Health and Environmental Effects Profile has received a limited Agency review with the help of two external scientists.

U.S. EPA. 1984. Health and Environmental Effects Profile for MCPA and MCPB. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P082AP.

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Agency RfD Review:

First Review: 07/22/85
Second Review: -
Verification Date: 07/22/85

U.S. EPA Contact:

Primary: M.L. Dourson
FTS/684-7544 or 513/569-7544
Secondary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Mercury Fulminate CAS #: 628-86-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Fitzhugh et al. (1950) Rat oral chronic study	NOEL: A well defined level was not available	1000	-	0.003 mg/kg/day or 0.2 mg/day for a 70 kg man
Renal and kidney damage	40 ppm Hg or 2 mg Hg/kg/day (LOAEL) converted to 2.83 mg/kg/day mercury fulminate Conversion Factors: 5% food consumption/g body weight; molecular weight of mercury fulminate ($C_2HgN_2O_2$) to mercury (Hg) is 285/201; thus, 40 mg/kg of diet (i.e., 40 ppm) x 0.05 kg of diet/kg bw/day x 285/201 = 2.83 mg/kg bw/day			

Endpoint and Experimental Doses:

Fitzhugh, O.G., A.A. Nelson, E.P. Lang and F.M. Kunze. 1950. Chronic toxicities of mercuric phenyl and mercuric salts. Arch. Ind. Hyg. Occup. Med. 2: 433-441.

This is the only chronic ingestion study designed to evaluate the toxicity of inorganic mercury salts. In this study, rats of both sexes (20-24/group) were given 0.5, 2.5, 10, 40 or 160 ppm mercury as mercury acetate for up to 2 years. Assuming food consumption was equal to 5% bw/day, the daily intake of Hg was 0.025, 0.125, 0.5, 2.0 or 8.0 mg/kg/day, respectively. Detailed microscopic evaluation of various tissues indicated that only the kidney was affected to any degree with lesions in the proximal convoluted tubules and cortex. Treatment related changes did not appear to be present at doses

Preparation Date: 01/10/86

Endpoint and Experimental Doses (cont.):

greater than 40 ppm. However, the description of effects occurring at the lower doses was not well characterized. Therefore, 40 ppm (2.0 mg/kg) was identified as a LOAEL in the study.

There is no information concerning the toxicity of mercury fulminate. Assuming that the toxicity of this compound is due primarily to its mercury component, it is appropriate to derive an ADI for mercury fulminate based on analogy to mercury. This assumption is supported by the fact that cyanates do not exhibit the high toxicity of cyanides and that mercury compounds are considerably more toxic. Therefore, using the LOAEL 2 mg/kg/day provided by the Fitzhugh et al. (1950) study, an ADI of 0.003 mg/kg/day or 0.2 mg/day is derived.

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Uncertainty Factors (UFs):

An uncertainty factor of 1000 was used to account for interspecies extrapolation, differences in sensitivity among humans and for the conversion of a LOAEL to a NOAEL.

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Modifying Factors (MFs):

None.

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Additional Comments:

No data are available on the toxicity of mercury fulminate.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

Confidence in the study is rated medium as a medium amount of animals/sex was used in each of five dose groups and several parameters were measured. The NOAEL, however, was not well defined. Confidence in the supporting data base and RfD are both low; since the toxicity of mercury fulminate has not been tested, this RfD is based on analogy to inorganic mercury.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Mercury Fulminate: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH,

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/19/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/19/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Mercury (inorganic) CAS #: 7439-97-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Fitzhugh et al. (1950) Rat oral chronic study	NOAEL: None	1000	-	0.002 mg/kg/day or 0.1 mg/day for a 70 kg man
Renal and kidney damage	40 ppm Of diet converted to 2 mg/kg bw/day (LOAEL) Conversion Factor: Food consumption 5% body weight; thus, 40 mg/kg of diet (i.e., 40 ppm) x 0.05 kg of diet/kg bw/day = 2 mg/kg/day			

Endpoint and Experimental Doses:

Fitzhugh, O.G., A.A. Nelson, E.P. Laug and F.M. Kunze. 1950. Chronic toxicities of mercuric phenyl and mercuric salts. Arch. Ind. Hyg. Occup. Med. 2: 433-441.

This is the only chronic ingestion study designed to evaluate the toxicity of inorganic mercury salts. In this study, rats of both sexes (20-24/ group) were given 0.5, 2.5, 10, 40 or 160 ppm mercury as mercury acetate for up to 2 years. Assuming food consumption was equal to 5% bw/day, the daily intake was equal to 0.025, 0.125, 0.5, 2.0 and 8.0 mg/kg bw, respectively. Detailed microscopic evaluation of various tissues indicated that only the kidney was affected to any degree with lesions in the promixal convoluted tubules and cortex. Treatment-related changes did not appear to be present at doses less than 40 ppm.

Also, it was noted that the damage occurring at these lower doses was present to some degree in older control animals. The 40 ppm feeding level was

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

identified as a LOAEL in this study. Although it appears that the 10 ppm feeding level, as well as the two lower doses, may have been a NOAEL the descriptive manner in which the data are presented makes it difficult to adequately evaluate the histopathological data for these doses. As a result of this uncertainty and since the use of the 40 ppm LOAEL will result in a somewhat more protective estimate than a 10 ppm NOAEL, the 40 ppm LOAEL is chosen as the basis for an ADI calculation.

Short-term and subchronic studies were conducted by Bariety et al. (1971), Druet et al. (1978), Weening et al. (1978) and Makker and Aikawa (1979). A NOAEL of 50 ug/kg for antibody formation could be derived from the study of Druet et al. (1978). However, this study is not chosen because the route of exposure was subcutaneous injection, the immune response occurred only in a genetically susceptible strain of rats and the duration of the study was only 8-12 weeks.

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Uncertainty Factors (UFs):

Based upon these factors the Fitzhugh et al. (1950) study was considered most appropriate for the development of an ADI. This study established a LOAEL of 2 mg/kg bw/day. Applying scaling factors of 100 to account for extrapolation from animals to humans and differences in sensitivity among human population and an additional 10 for conversion of a LOAEL to a NOAEL an ADI or 0.002 mg/kg/day or 0.1 mg/day for a 70 kg human was derived.

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Modifying Factors (MFs):

None.

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Additional Comments:

The data base for this chemical is characterized by only one chronic ingestion study with a small number of animals surviving past 18 months (20-24 animals/group). Short-term and subchronic studies by i.p. or s.c. exposures and supporting epidemiological data are not well characterized.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

Confidence in the study is rated medium as a medium amount of animals/sex was used in each of five dose groups and several parameters were measured.

Confidence in the RfD (cont.):

The NOAEL, however, was not well defined. Confidence in the data base is medium because a small number of studies lends some support. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

Limited peer review and Agency-wide internal review, 1984.

U.S. EPA. 1984. Health Effects Assessment Document for Mercury. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa FTS/684-7534 or 513/569-7534
Second Review:	-		
Verification Date:	08/05/85	Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Methylene Chloride CAS #: 75-09-2

Carcinogenicity: CAG, U.S. EPA - Category B2.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
National Coffee Association (1982)	NOEL: 5.85 and 6.47 mg/kg/day for males and females, respectively	100	-	0.06 mg/kg/day
2-year rat drinking water bioassay Liver toxicity	LOAEL: 52.58 and 58.32 mg/kg/day for males and females, respectively			

Endpoint and Experimental Doses:

National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazelton Laboratories America, Inc., Vienna, VA, August 11.

The chosen study appears to have been very well conducted with 85 rats/sex at each of four dose groups. A high-dose recovery group of 25 rats/sex, as well as two control groups of 85 and 50 rats/sex, was also tested. Many effects were monitored.

The supporting data base, in addition to this study, is limited with an inhalation NOEL of 87 mg/cu. m (Haun et al., 1972). [The equivalent oral dose is about 28 mg/kg bw/day (i.e., 87 mg/cu. m x 0.5 x 0.223 cu. m/day / 0.35 kg; these exposure values are for rats).]

Preparation Date: 01/06/86

Uncertainty Factors (UFs):

The 100-fold factor accounts for both the expected intra- and inter-species variability to the toxicity of this chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium

The study is given a high confidence rating because a large number of animals was tested of both sexes in four dose groups, with a large number of controls. Many effects were monitored and a good dose-severity was obtained. The data base is rated medium to low because only a few studies support the chosen NOAEL. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

The ADI has only been reviewed by the U.S. EPA's ADI Work Group during the summer of 1985.

U.S. EPA. 1985. Drinking Water Criteria Document for Methylene Chloride. Office of Drinking Water, Washington, DC. (Draft)

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Agency RfD Review:

First Review: 06/24/85
Second Review: 07/08/85
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: K. Khanna
FTS/382-7588 or 202/382-7588
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Methyl Ethyl Ketone CAS #: 78-93-3

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
LaBelle and Brieger (1955) Rat inhalation/sub-chronic study	235 ppm (693 mg/ cu. m) converted to 46 mg/kg/day (NOAEL)	1000	-	0.05 mg/kg/day or 3 mg/day for a 70 kg man
Schwetz et al. (1974) Teratology bioassay Fetotoxicity teratogenicity	130.5 mg/kg/day (estimated LOAEL)			
	Conversion Factors: 7 hour/24 hour, 5 days/7 days, 0.223 cu. m/day/0.35 kg (rat breathing rate/rat body weight) 0.5 absorption rate; thus, 693 mg/cu. m x 7 hour/24 hour x 5 days/7 days x 0.223 cu. m/day / 0.35 kg x 0.5 = 46 mg/kg/day			

Endpoint and Experimental Doses:

LaBelle, W. and H. Brieger. 1955. The vapor toxicity of a composite solvent and its principal components. Am. Med. Assoc. Arch. Ind. Health. 12: 623-627.

Adequate chronic toxicity testing has not been performed with methyl ethyl ketone. Although several more recent subchronic studies have been conducted (Freddi et al., 1982; Cavender et al., 1983; Takeuchi et al., 1983), only the NOAEL of the LaBelle and Brieger (1955) provides the lowest and most protective dose for deriving an ADI. In this study, 25 rats were exposed to 235 ppm of methyl ethyl ketone for 7 hour/day, 5 days/week for 12 weeks. No effects were observed, but only a few parameters were measured. Methyl ethyl ketone has also been tested for teratogenicity (Schwetz et al., 1974; Deacon et al.,

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

1981) and the observed LOAELs for fetotoxicity are higher than the NOAELs of LaBelle and Brieger (1955). The animal NOAEL of 693 mg/cu. m was converted to a human NOAEL of 46 mg/kg/day to derive an ADI of 0.05 mg/kg/day.

The route extrapolation raises a level of uncertainty due to differences in pharmacokinetic parameters, notably. absorption and elimination.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

No oral chronic studies are available at this time. Several subchronic inhalation studies provided adequate data in support of a RfD with a medium level of confidence.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The study is given medium to low confidence because only 25 rats were exposed to only one dose, and the sex, strain and amount of control animals were unspecified. The data base is given a medium rating because four different studies lend some support to the chosen NOAEL. Medium to low confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May 1985.

U.S. EPA. 1985. Methyl Ethyl Ketone: Review and Evaluation of ADI. Contract NO. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 07/08/85
Second Review: -
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Methyl Ethyl Ketone Peroxides CAS #: 1338-23-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
ACGIH (1984)	1.5 mg/cu. m (TLV) converted to 0.077 mg/kg/day	10	-	0.008 mg/kg/day or 0.5 mg/day for a 70 kg man

Conversion Factors:

x 5 days/7 days
x 10 cu. m/day (human breathing rate in 8 work hours)
0.5% absorption / 70 kg; thus, 1.5 mg/cu. m x 5 days/7 days x 10 cu. m/day x 0.5 / 70 kg = 0.077 mg/kg/day

Endpoint and Experimental Doses:

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. Methyl Ethyl Ketone Peroxides. Documentation of Threshold Limit Values, 4th ed. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984-1985. p. 279-280.

The ACGIH (1984) has set a ceiling limit TLV of 0.2 ppm for methyl ethyl ketone peroxides, by analogy to hydrogen peroxide. Floyd and Stokinger (1958) conducted inhalation and oral acute testing of this compound establishing its LD50 and LC50 in rats and mice. The results of this study indicated that methyl ethyl ketone peroxide was more toxic than benzozyl peroxide (TLV=5 mg/cu. m) and similar in toxicity to hydrogen peroxide (TLV=1.4 mg/cu. m). Based on these findings the ACGIH (1984) recommended a TLV for methyl ethyl ketone peroxide as 1.5 mg/cu. m (0.2 ppm).

As of April 1985, the NTP (1985) has been conducting skin painting tests and histopathology assays on this chemical. The results are not yet available.

Preparation Date: 01/07/86

Endpoint and Experimental Doses (cont.):

Limited carcinogenic and mutagenic data studies have been conducted, but results are inconclusive (Koten and Falk, 1963). Using the TLV of 0.2 ppm (1.5 mg/cu. m) an ADI of 0.076 mg/kg/day can be derived. This ADI should be used only until the results of the NTP (1985) testing becomes available, at which time it should be revised.

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Uncertainty Factors (UFs):

The 10-fold factor accounts for the expected interhuman variability to the toxicity of this chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

No adequate chronic or subchronic data are available upon which to base an ADI. No supporting epidemiological data are available.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

The confidence in the chosen effect level, supporting data base, and resulting RfD are all low. TLV-based RfDs are only estimated when sufficient oral or inhalation toxicity data are not available.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Methyl Ethyl Ketone Peroxide: Review and Evaluation of ADI. Contract No. 68-03-3228, Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/19/85	Primary:	C.T. DeRosa FTS/684-7534 or 513/569-7534
Second Review:	-		
Verification Date:	08/19/85	Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Nickel Cyanide CAS #: 557-19-7

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Ambrose et al. (1976) Rat oral chronic study	100 ppm of diet (NOAEL) converted to 1.89 mg/kg/day nickel cyanide	100	-	0.02 mg/kg/day or 1 mg/day for a 70 kg man
Decreased body weight	1000 ppm of diet (50 mg/kg bw/day) nickel (LOAEL)			
	Conversion Factors: 5% food consumption/g body weight; 0.2% assumed difference in nickel absorption in water vs. diet; molecular weight Ni(CN)2/Ni: x 110.74/58.69; thus, 100 mg/kg of diet (ppm) x 0.05 mg/kg of diet/kg bw/day x 0.2 x 110.74/58.69 = 1.89 mg/kg bw/day			

Endpoint and Experimental Doses:

Ambrose, A.M., P.S. Larson, J.R. Borselleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

Nickel cyanide is 47% cyanide and 53% nickel. Therefore, if nickel cyanide were to completely dissociate in water or dilute acids, approximately equal amounts would be released on a weight basis.

Based on recommended ADI for nickel (0.7 mg/day, U.S. EPA, 1985), the toxicity of nickel is approximately 2 times greater than the currently reported toxicity of Cyanide (ADI of 1.5 mg/day, U.S. EPA, 1985). It is apparent, therefore that an ADI for nickel cyanide based on the toxicity of cyanide might not be protective for adverse effects caused by nickel.

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

Ambrose et al., (1976) reported the results of a 2-year study in groups of 25 rats/sex given 0, 100, 1000 or 2500 ppm nickel (estimated as 0, 5, 50 and 125 mg Ni/kg bw) in the diet. Consistently, body weights in both high dose male and female rats were significantly decreased compared with controls. Groups of females on the 1000 or 2500 ppm nickel diets had significantly higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. No significant effects were reported at 100 ppm nickel (5 mg/kg bw). The dose of 1000 ppm (50 mg Ni/kg bw) represents a LOAEL from this study, while the 100 ppm (5 mg Ni/kg bw) dose is a NOAEL. The fact that nickel was administered in the diet rather than in water caused some problem. Nickel in the diet is absorbed at a different rate than Ni in water; therefore, Foulkes (1984) recommeded an absorption factor of 0.2 to be applied to the dietary data to derive an ADI for nickel in water.

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Uncertainty Factors (UFs):

The 100-fold factor accounts for both intra- and interspecies variability to the toxicity of the chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

By applying an uncertainty factor of 100 (10 for intraspecies extrapolation and 10 for sensitive population) and an absorption factor of 0.2 to the NOAEL of 5 mg/Ni/kg bw an ADI of 0.7 mg/day for nickel was derived. Because nickel cyanide is not soluble in water and is slightly soluble in dilute acids, ingestion of nickel cyanide would expose an individual to nickel cyanide as well as small amounts of cyanide and nickel. Based on toxicity data an ADI of 6 mg/day for nickel cyanide (ADI CN 1.5/0.47CN x 2 moles CN) may not provide adequate protection when compared to an ADI of 1 mg/day for nickel cyanide (ADI Ni 0.7/0.53 Ni). Therefore, an ADI of 1 mg/day for nickel cyanide is recommended.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

Medium confidence in the study is chosen because three doses were administered to a moderate number of animals and several parameters were measured. Dogs were also tested. Low confidence is chosen for both the supporting data base and RfD since nickel cyanide has not been tested for toxicity and thus, the RfD is by analogy. Until additional chronic/reproductive toxicity data are is available a low confidence in the RfD is recommended.

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Documentation of RfD and Review:

Extensive Agency-wide and Peer review, 1985.

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

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Nitric Oxide CAS #: 10102-43-9

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Walton (1951)	10 ppm of drinking water or 10 mg/L (NOEL) converted to 1.0 mg/kg/day	1	10	0.1 mg/kg/day or 1 mg/day for a 10 kg child
Infant chronic exposure to drinking water Methemoglobinemia	11-20 ppm (LOAEL)			
	Conversion Factor: 1 L drinking water/day 10 kg child; thus, 10 mg/L x 1 L/day / 10 kg = 1.0 mg/kg/day			

Endpoint and Experimental Doses:

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41: 986-996.

This is an epidemiological study on the formation of methemoglobinemia in infants routinely fed milk prepared from nitrate contaminated water. This study analyzed all known cases of infant methemoglobinemia occurring in 37 U.S. states irrespective of date or type of water supply. Nitrate (nitrogen) content ranged from 10 ppm to over 100 ppm. No incidences of methemoglobinemia were found to occur in drinking water containing greater than 10 ppm (10 mg/L) nitrate (nitrogen). A NOEL of 10 mg/L was derived from these studies.

Nitric oxide in water generates NO2 (nitrite). Methemoglobinemia is formed by the oxidation of hemoglobin to methemoglobinemia by nitrite. Infants are particularly susceptible to the formation of methemoglobin.

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

Several more recent studies support Walton's (1951) 10 mg/L NOAEL for infant methemoglobinemia formation (NAS, 1977; Winton, 1971; Calabrese, 1978).

Using the NOAEL from the Walton study, the ADI for nitric oxide was calculated (U.S. EPA, 1985) for a 10 kg child drinking 1 L of water/day and a modifying factor of 10. An ADI of 0.1 mg/kg/day or 1 mg/day was, therefore, derived for nitric oxide.

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Uncertainty Factors (UFs):

No uncertainty factor was used in the derivation of the RfD because the NOEL was of the critical toxic effect (i.e., methemoglobinemia) in the sensitive human population (i.e., infants). The length of exposure encompassed both the critical effect and the sensitive population.

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Modifying Factors (MFs):

A modifying factor of 10 was applied because of the direct toxicity of nitrite.

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Additional Comments:

An RfD of 0.2 mg/kg/day could be calculated using the body weight of 4 kg and fluid consumption of 0.64 L/day from the Walton (1951) study. The lower value of 0.1 mg/kg/day is maintained, however, due to the uncertainties in the changing fluid consumption and body weight as a neonate (4 kg) ages to a 2-year-old child (10 kg), and the varying lengths of weaning time among families.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

Confidence in the study, data base and RfD are all considered high because the NOEL is determined in the known sensitive human population. The data base contains several recent supporting epidemiological studies.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Nitric Oxide: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/19/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/19/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Nitrobenzene CAS #: 98-95-3

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
CIIT (1984) Rat/mice subchronic inhalation study	NOAEL: None	10,000	-	0.0005 mg/kg/day or 0.03 mg/day for a 70 kg man
Hematologic, adrenal, renal and hepatic lesions	25 mg/cu. m (mice converted to 4.6 mg/kg/day LOAEL)			
	Conversion Factors: 6 hour/24 hour, 5 days/7 days, 0.039 cu. m/day/0.03 kg (mice breathing rate/body weight) and 0.8 absorption factor; thus, 25 mg/cu. m x 6 hour/24 hour x 5 days/7 days x 0.039 cu. m/day / 0.03 kg x 0.8 = 4.6 mg/kg/day			

Endpoint and Experimental Doses:

CIIT (Chemical Industry Institute of Toxicology). 1984. Ninety day inhalation toxicity study of nitrobenzene in F344 rats and B6C3F1 mice. CIIT, Research Triangle Park, NC. FYI-OTS-0874-0333.

The CIIT study provides the most appropriate data currently available to derive an ADI. Ten animals/sex/species/dose group were administered nitrobenzene at] of 3 doses in a 90-day inhalation study. Other than increased incidence of hemolytic anemia in rats at 25 mg/cu. m and vacuolization of adrenal cortical cells in female mice at 25 mg/cu. m and higher, adverse effects of nitrobenzene exposure in mice and rats were comparable to unexposed controls at this dose. Mice and rats exposed to nitrobenzene at 81 mg/cu. m showed increased incidence and severity of liver and kidney lesions.

Environ, Inc. (1984) recommended an ADI of 0.057 mg/kg/day or 4 mg/day which is based on the TLV of 1 ppm, a predicted level to protect workers

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

against cyanogenic and hematologic effects. Absorption coefficients of 0.8 and dermal to inhalation absorption ratio of 7:18, based on pharmacokinetic data of Piotrowski (1967, 1977) and Salmowa et al. (1963) were employed to derive the daily exposure level of nitrobenzene.

Data regarding the effects of nitrobenzene in humans are limited to symptoms and observations in workers including headaches, vertigo, methemoglobinemia (ACGIH, 1980). The ADI derived from the TLV appears adequate to protect workers from above adverse effects; however, the effects of occupational exposure to nitrobenzene on the liver and/or kidneys have not been adequately evaluated. The CIIT (1984) study indicates that the liver and kidney may be target organs of chronic/subchronic nitrobenzene exposure, and the ADI based on the TLV may not be protective for the toxic effects of nitrobenzene on the liver and/or kidney. Therefore, until more definitive chronic data are available, the ADI of 0.0005 mg/kg/day is recommended to protect against adverse health effects of nitrobenzene.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 represents two 10-fold factors for both intra- and interspecies variability to the toxicity of this chemical in lieu of specific data, a 10-fold factor for estimating a chronic effect level from its subchronic equivalent and a 10-fold factor for estimating a RfD from a LOAEL rather than a NOAEL.

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Modifying Factors (MFs):

None.

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Additional Comments:

Subchronic animal inhalation study provided adequate data over the recommended TLV (ACGIH, 1985) to derive an ADI. Further chronic studies are needed to recommend an ADI at a higher level of confidence.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

Medium confidence in the study is recommended because a limited number of animals/sex/dose was tested and a NOEL for the critical toxic effect (i.e., adrenal toxicity) was not determined; however, two species were used and many

Confidence in the RfD (cont.):

parameters were measured. Medium confidence in the data base is recommended because many unpublished studies support the chosen LOAEL. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May 1985.

U.S. EPA. 1985. Health and Environmental Effects Profile for Nitrobenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P145.

U.S. EPA. 1985. Nitrobenzene: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	07/08/85	Primary:	C.T. DeRosa FTS/684-7534 or 513/569-7534
Second Review:	-		
Verification Date:	07/08/85	Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Nitrogen Dioxide CAS #: 10102-44-0

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Walton (1951)	10 ppm of drinking water or 10 mg/L (NOEL) converted to 1.0 mg/kg/day	1	-	1 mg/kg/day or 10 mg/day for a 10 kg child
Infant chronic exposure drinking water	11-20 ppm (LOAEL)			
Methemoglobinemia				
	Conversion Factor: 1 L water consumed/day 10 kg child; thus, 10 mg/L x 1 L/day / 10 kg = 1.0 mg/kg/day			

Endpoint and Experimental Doses:

Walton, G. 1951. Survery of literature relating to infant methemoglobinemia due to nitrate - contaminated water. Am. J. Public Health. 41: 986-996.

This is an epidemiologic study on the formation of methemoglobinemia in infants who routinely consumed milk prepared from water containing various levels of nitrate. The study analyzed all cases of infant methemoglobinemia occuring in 37 U.S. states irrespective of date of occurrence or type of water supply. Nitrate (nitrogen) content ranged for 10 ppm to greater than 100 ppm. No incidences of methemoglobinemia were found to occur in drinking waters containing less than 10 ppm (10 mg/L) nitrate (nitrogen). Therefore, a NOEL of 10 ppm (10 mg/L) was derived.

Several more recent epidemiological studies support Walton's (1951) threshold for infant methemoglobinemia (NAS, 1977; Winton, 1971; Calabrese, 1978).

Nitrogen dioxide in water dissociates to form nitrates and nitrite. Nitrate toxicity appears to be due to its conversion to nitrites which results

Preparation Date: 01/07/86

Endpoint and Experimental Doses (cont.):

in the oxidation of hemoglobin to methemoglobin in humans. Animals are not a good model for methemoglobin formation because many species lack nitrate reducing bacteria. Infants are, however, particularly susceptible due to the high nitrate reducing bacteria content, their lower enzymatic capacity to reduce methemoglobin to hemoglobin and finally to the presence of hemoglobin F which is more susceptible to oxidation.

An ADI of 1.0 mg/kg/day (U.S. EPA, 1985) for nitrate/nitrogen was derived based on the NOEL of 10 mg/L (Walton, 1951).

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Uncertainty Factors (UFs):

No uncertainty factor was used in the derivation of the RfD because the NOEL was of the critical toxic effect (i.e., methemoglobinemia) in the sensitive human population (i.e., infants). The length of exposure encompassed both the critical effect and the sensitive population.

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Modifying Factors (MFs):

None.

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Additional Comments:

A RfD of 2 mg/kg/day could be calculated using the body weight of 4 kg and fluid consumption of 0.64 L/day from the Walton (1951) study. The lower value of 1 mg/kg/day is maintained, however, due to the uncertainties in the changing fluid consumption and body weight as a neonate (4 kg) ages to a 2-year-old child (10 kg), and the varying lengths of weaning time among families.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

Confidence in the study, data base and RfD are all considered high because the NOEL is determined in the known sensitive human population. The data base contains several recent supporting epidemiological studies.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Nitrogen Dioxide: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/19/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/19/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Pentachloronitrobenzene (PCNB) CAS #: 82-68-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Borzelleca and Larson (1968)	NOEL: 30 mg/kg of diet converted to 0.75 mg/kg bw/day	100	-	0.008 mg/kg/day
2-year feeding study in dogs	LOAEL: 180 mg/kg of diet			
Liver toxicity				
	Conversion Factor: x 0.025 kg of diet/kg of bw/day (an assumed factor); thus, 30 mg/kg of diet x 0.025 kg of diet/kg bw/day = 0.75 mg/kg/day			

Endpoint and Experimental Doses:

Borzelleca, J.F. and P.S. Larson. 1968. Toxicity study of the effect of adding Terraclor to the diet of Beagle dogs for a period of two years. Unpublished report prepared by the Dept. of Pharmacology, Medical College of Virginia. Submitted by Olin Corp. as Report No. 2490. EPA Acc. No. 248283, June 10.

Groups of four male and four female beagle dogs (4.5 months of age) were given diets containing 0, 5, 30, 180 or 1080 ppm of the test substance for 2 years. "Minimal" cholesteral hepatosis with secondary bile nephrosis was observed in all dogs in the 180 ppm groups (LOAEL). The dose of 30 ppm was the highest NOEL in this study.

Chronic feeding studies need to be done in another species (rats). The small sample size of Borzelleca and Larson (1968) reduces the statistical validity of the study. PCNB may act synergistically with oncogenic HCB.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 100 accounts for both intra- and interspecies variability to the toxicity of this chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Medium

The confidence in the chosen study is medium because only eight animals/dose were used; however, four doses were tested, several effects were monitored and a dose-severity was observed. The data base is rated low because of the general lack of supporting data. The RfD is rated medium to low.

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Documentation of RfD and Review:

This ADI has been internally reviewed by the Office of Pesticide Programs, U.S. EPA.

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Agency RfD Review:

First Review: 05/20/85
Second Review: -
Verification Date: 05/20/85

U.S. EPA Contact:

Primary: T. Farber
FTS/557-3710 or 513/557-3710
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Pentachlorophenol CAS #: 87-86-5

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Schwetz et al. (1978) Rat oral chronic study	3 mg/kg/day (NOEL)	100	-	0.03 mg/kg/day or 2 mg/day for a 70 kg man
Liver and kidney pathology	10 mg/kg/day (LOEL)			

Endpoint and Experimental Doses:

Schwetz, B.A., J.F. Quast, P.A. Keelev, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

Only one chronic study regarding oral exposure (Schwetz et al., 1978) was located in the available literature. Twenty-five rats/sex were administered 1 of 3 doses in the diet. At the 30 mg/kg/day level of treatment, a reduced rate of body weight gain and increased specific gravity of the urine were observed in females. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg/day or higher levels and in males exposed to 30 mg/kg/ day. The 3 mg/kg/day level of exposure was reported as a chronic NOEL.

A number of studies that have investigated the teratogenicity of orally administered pentachlorophenol in rodents are available in the literature. Although these studies (Larsen et al., 1975; Schwetz and Gehring, 1973; Schwetz et al., 1978; Hinkle, 1973), did not reveal teratogenic effects feto-maternal toxicity were seen at 30 mg/kg/day. Since pentachlorophenol apparently does not cross the placental barrier, the observed fetotoxicity may be a reflection of maternal toxicity (Larsen et al., 1975). The NOEL in these studies was 3.0 mg/kg, which is the same as for the chronic study reported earlier.

Preparation Date: 01/07/85

Uncertainty Factors (UFs):

The 100-fold factor accounts for the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium

The confidence in the chosen study is rated high because a moderate number of animals/sex were used in each of three doses, a comprehensive analysis of parameters was conducted, and a reproductive study was also run. Confidence in the supporting data base is rated medium because only one chronic study is available. Other subchronic studies provide adequate but weaker supporting data. The confidence in the RfD is medium. More chronic/reproductive studies are needed to provide a higher confidence in the RfD.

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Documentation of RfD and Review:

Limited Peer Review and Agency-wide Internal Review, 1984.

U.S. EPA. 1984. Health Effects Assessment for Pentachlorophenol. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H043.

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

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Agency RfD Review:

First Review: 05/20/85
Second Review:
Verification Date: 05/20/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Phenol CAS #: 108-95-2

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Dow Chemical (1976) Rat oral subchronic study	NOAEL: None	500	-	0.1 mg/kg/day or 7 mg/day for a 70 kg man
Kidney and liver pathology	50 mg/kg/day (135 doses) (LOAEL)			

Endpoint and Experimental Doses:

Dow Chemical Co. 1976. References and literature review pertaining to toxicological properties of phenol. Toxicol. Res. Lab. Unpublished Report.

This study reported slight kidney damage in rats treated by gavage at 50 mg/kg/day of phenol for 6 months. Higher doses produced moderate kidney and slight liver damage. However, no effects on liver, kidneys or any other organs were observed in 90-day studies in rats (780 mg/kg/day of phenol) and mice (1700 mg/kg/day of phenol) which received various doses of phenol in the drinking water (NCI, 1980). In this study, when extended for 2 more weeks, rats and mice treated with 153 and 313 mg/kg/day phenol, respectively, showed decreased weight gain and reduced water intake. In addition, male and female rats at 344 mg/kg/day dose had a significantly increased incidence of chronic kidney inflammation.

The difference in LOAELs of the NCI (1980) study (344 mg/kg) and the Dow Chemical (1976) study (50 mg/kg) are plausibly attributed to differences in mode of administration with the gavage study of Dow Chemical producing the lowest LOAEL.

Diechmann and Oespar (1940) noted no effects on water consumption and weight gain at phenol concentrations as high as 1600 mg/L. Further, in studies using rats and spanning 3-5 generations, Heller and Purcell (1938)

Preparation Date: 01/07/86

Endpoint and Experimental Doses (cont.):

observed normal growth and reproduction at phenol concentrations up to 5000 mg/L. Taking the drinking water consumption data provided by Deichmann and Oesper (1940) for the 1600 mg/L group, this NOEL represents an average dose of 49 mg/kg/day which is equivalent to that used in the derivation of the ADI.

Consideration of all these factors suggest that the previously estimated ADI of 7 mg/day (U.S. EPA, 1980) based on the LOAEL of 50 mg/kg/day from the Dow Chemical (1976) study should provide adequate protection.

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Uncertainty Factors (UFs):

A 500-fold uncertainty factor was applied to the LOAEL of 50 mg/kg/day (10 for subchronic data, 10 for species extrapolation and 5 for use of LOAEL). A factor of 500 was used because it was judged that the existing data did not justify the use of a factor of 100, but were better than the requirements for a factor of 1000.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Low Data Base: Medium RfD: Medium

The chosen study is given a confidence rating of low because few animals were used, a NOEL was not established and the study was never published. The data base is given a medium confidence rating because several studies support the chosen effect level. Until other chronic studies are available, a medium confidence in the RfD is recommended.

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Documentation of RfD and Review:

The Health and Environmental Effects Profile has had a limited peer review and Agency-wide internal review during 1985. The Ambient Water Quality Criteria document was extensively reviewed by the Agency and underwent public comments during 1980.

Documentation of RfD and Review (cont.):

U.S. EPA. 1985. Health and Environmental Effects Profile for Phenol. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-P125.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Phenol. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-066.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Phenyl Mercuric Acetate CAS #: 62-38-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Fitzhugh et al. (1950) Rat oral chronic study	0.1 ppm Hg diet or 0.0084 mg/kg/day phenyl mercuric acetate (NOAEL)	100	-	0.08 ug/kg/day or 6 ug/day for a 70 kg man
Renal damage	0.5 ppm Hg or 0.042 mg/kg/day phenyl mercuric acetate (LOAEL)			
	Conversion Factor: Food consumption 5% bw/day, molecular weight PMA/Hg is 337/201; thus, 0.1 mg/kg of diet (ppm) x 0.05 kg of diet/kg bw/day x 337/201 - 0.0084 mg/kg bw/day			

Endpoint and Experimental Doses:

Fitzhugh, O.G, A.A. Nelson, E.P. Laug and I.M. Kunze. 1950. Chronic oral toxicities of mercuric phenyl and mercuric salts. Arch. Ind. Hyg. Occup. Med. 2: 433-442.

Phenyl mercuric acetate was administered to rats (10-24/group/sex) at levels of 0, 0.1, 0.5, 2.5, 10, 40 and 160 mercury in their diet for 2 years. Detailed microscopic examinations of the liver and kidney were performed at 1 and 2 years of age. Microscopic examination of the viscera was also performed at the 2-year mark. As little as 0.5 ppm mercury as phenyl mercuric acetate resulted in detectable kidney damage in females after 2 years. No differences were seen between controls and females receiving 0.1 ppm mercury. At higher doses (greater than 2.5 ppm) renal lesions were observed in both males and females. A NOEL of 0.1 ppm was determined from these results.

Fitzhugh et al. (1950) is the only chronic study regarding the oral toxicity of phenyl mercuric acetate. Therefore, assuming that the rat consumed

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

the equivalent of 5% of its body weight in food/day, the 0.1 ppm Hg NOEL is equivalent to 0.005 mg/kg/day Hg or 0.0084 mg/kg bw phenyl mercuric acetate.

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Uncertainty Factors (UFs):

An ADI of 0.08 ug/kg/day or 6 ug/kg/day for a 70 kg human was derived by dividing the NOEL by an uncertainty factor of 100 to account for species extrapolation and differences in human sensitivity.

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Modifying Factors (MFs):

None.

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Additional Comments:

The data base contains very little information on the oral toxicity of phenyl mercuric acetate. Some subchronic testing has been conducted. Limited data are available on the mutagenic and teratogenic effects of this compound. No relevant carcinogenic data is available.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Medium

The chosen study is given a medium confidence rating because a moderate number of animals/sex were tested at each of six doses; several parameters were measured. The data base is given a low confidence rating because little or no supporting data exist. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Phenyl Mercuric Acetate: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/19/85
Second Review: -
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534

Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Phosphine CAS #: 7803-51-2

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Hackenburg (1972) Rat chronic oral study	0.51 mg/kg food converted to 0.026 mg/kg/day (NOEL)	100	-	0.0003 mg/kg/day or 0.02 mg/day for a 70 kg man
Body weight and clinical parameters	LOAEL: None			
	Conversion Factor: Food consumption of 5% bw/day; thus, 0.51 mg/kg of diet x 0.05 kg of diet/kg bw/day = 0.026 mg/kg bw/day			

Endpoint and Experimental Doses:

Hackenburg, U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphate. Toxicol. Appl. Pharmacol. 23(1): 147-153.

This study reported a no effects dose level for rats fed diet fumigated with phastoxin over a 2-year period. The mean phosphine concentration during that time period was 0.51 mg/kg of feed. Based on an average 5% food consumption and average rat body weight of 610.4 g (reported in the study), the phosphine dose can be calculated as 0.026 mg/kg bw/day. Hackenburg (1972) found a slight, yet statistically insignificant, tendency for test females to gain weight faster than their control counterparts. There were no other differences between controls and treated rats in hemoglobin content, hematocrit, differential white blood cell count, glucose levels, SGPT, serum urea, prothrombin time, organ weights or tissue histopathology. Survival rates and tumor incidences were similar between controls and experimental animals.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

Application of an uncertainty factor of 100 (10 for intraspecies extrapolation and 10 for sensitive population) to the rat NOEL of 0.026 mg/kg yields an ADI of 0.02 mg/day.

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Modifying Factors (MFs):

None.

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Additional Comments:

The ACGIH (1984) has recommended a TLV of 0.3 ppm (0.42 mg/cu. m) for phosphine, based principally upon an epidemiological study by Jones (1964). In this study, workers exposed intermittently to about 10 ppm phosphine gas experienced GI, cardiorespiratory and CNS symptomatology. Based on the TLV, an ADI of 0.021 mg/kg/day can be recommended. However, the Hackenburg (1972) study was a 2-year study in rats which explored a number of functional and morphological endpoints. This study forms a better basis for an RfD.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

The confidence in the study was rated high because of the moderate number of animals/dose, the extensive methodology employed to assure proper administration of the test compound, and the extensive number of parameters measured. The data base was rated high because of the effectiveness and safety of this chemical has been long reported. The overall rating for the RfD is, thus, high.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Phosphine: Review and Evaluation of ADI. Contract No. 68-03-3228, Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/19/85
Second Review:
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Potassium Cyanide CAS #: 151-50-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat oral chronic study	10.8 mg/kg/day CN (NOAEL) converted to 27.0 mg/kg/day of potassium cyanide	100	5	0.05 mg/kg/day or 4 mg/day for a 70 kg man
Philbrick et al. (1979) Rat chronic oral bioassay Decreased body and thyroid weights, myelin degeneration	30 mg/kg/day CN (LOAEL)			
	Conversion Factors: Molecular weight of KCN/CN is 65/26; thus, 10.8 mg/kg/day x 65/26 = 27.0 mg/kg/day			

Endpoint and Experimental Doses:

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

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

Since potassium is present in very high levels in food and the environment, an ADI of 3.8 mg/day for potassium cyanide, based on cyanide content is recommended.

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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.

Additional Comments (cont.):

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. Thus, until additional chronic studies are available, an ADI of 3.8 mg/day for a 70 kg human is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, 1985. Limited peer review and Agency-wide review, 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H011.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Potassium Silver Cyanide CAS #: 506-61-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat oral chronic study Philbrick et al. (1979) Rat chronic oral bioassay Decreased body and thyroid weights, myelin degeneration	10.8 mg/kg/day CN (NOAEL) converted to 82.7 mg/kg/day potassium silver cyanide 30.0 mg/kg/day CN (LOAEL)	100	5	0.2 mg/kg/day or 10 mg/day for a 70 kg man

Conversion Factor: Molecular weight KAg(CN)2/CN: x 199/26; thus, 10.8 mg/kg/day x 199/26 = 82.7 mg/kg/day

Endpoint and Experimental Doses:

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

Because of potassium, silver cyanide dissociates to form potassium, cyanide and silver cyanide, only 1 molar equivalent of cyanide is generated (Windholz, 1983). Based on free cyanide liberated by the dissociation of potassium silver cyanide an ADI of 12 mg/day for 70 kg man is recommended.

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 concentra-

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

tions were estimated based on the author's 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

A modifying factor of 5 was used for apparent tolerance of cyanide when it is ingested with food than when administered by gavage or drinking water.

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 12 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Pyridine CAS #: 110-86-1

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Encyclopedia of Occupational Safety and Health (1983) Rats subchronic to chronic inhalation bioassay	NOEL: None	1000	-	0.002 mg/kg/day or 0.2 mg/day for a 70 kg man
Reduced liver weight	10 ppm (32.35 mg/cu. m) converted to 2.15 mg/kg/day (LOEL) Conversion Factors: 7 hour/24 hour, 5 days/7 days, 0.223 cu. m/day/0.35 kg (rat breathing rate/rat body weight) 0.5 absorption rate; thus, 32.35 mg/cu. m x 7 hour/24 hour x 5 days/7 days x 0.223 cu. m/day / 0.35 kg x 0.5 = 2.15 mg/kg/day			

Endpoint and Experimental Doses:

Encyclopedia of Occupational Safety and Health. 1983. Vol. II: L-Z. International Labour Office, Geneva. p. 1810-1811.

The study reported in the above encyclopedia contains data taken from a rat inhalation study in which the exposure chamber contained 10-50 ppm pyridine vapor over 7 hours/day, 5 days/week for a 6-month period. The lower dose, 10 ppm pyridine (2.15 mg/kg/day) had no effect upon growth rate and mortality, but an increase in the relative liver weights was observed. Further details of the study were unavailable from the data base. The 2.15 mg dose was considered a LOEL.

Preparation Date: 01/07/86

Uncertainty Factors (UFs):

The 1000-fold represents 10 for both intra- and interspecies variability to the toxicity of this chemical in lieu of specific data and an additional 10 because the RfD is based on a LOAEL and not a NOAEL.

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Modifying Factors (MFs):

None.

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Additional Comments:

Chronic oral studies for a RfD of high level of confidence are unavailable. Need data base on chronic/reproductive studies.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

The confidence in the chosen study is low because many details were unavailable and a NOEL was not determined. Confidence in the data base is low because of the general lack of information. Low confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May and July 1985.

U.S. EPA. 1985. Pyridine: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 07/08/85
Second Review: -
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Selenious Acid CAS #: 7783-00-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Yang et al. (1983) Human epidemiology study	0.750 mg/day (NOAEL)	10	1.5	0.003 mg/kg/day or 0.2 mg/day for a 70 kg man
Selenosis	3.2 mg/day or 0.046 mg/kg/day (LOAEL)			

Endpoint and Experimental Doses:

Yang, G., S. Wang, R. Zhou and S. Sun. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37: 872-881.

In solution selenium from selenious acid and selenite salts is present predominantly as the biselenite ion (NAS, 1976). The toxicity of selenite salts and selenious acid would therefore be expected to be similar at sub-lethal doses. It would thus be appropriate to derive a selenious acid ADI by analogy to selenium.

The effects of oral selenium exposure have been relatively thoroughly studied in experimental animals and man. The NAS (1980) has determined an adequate and safe range for selenium intake of 0.05-0.2 mg/day for an adult man.

The effects of selenium deficiency are potentially as serious as those of selenium toxicity. Selenosis has been reported in high selenium areas where the average intake was 5 mg/day (range 3.2-6.7), but no selenosis occurred when the average intake was 0.750 mg/day (range 0.240-1.51) (Yang et al., 1983). Therefore, care must be exercised in deriving an ADI to insure that minimum dietary requirements are met.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

An uncertainty factor of 10 for the LOAEL for selenosis (3.2 mg/day) was applied to derive an ADI of 0.2 mg selenious acid/day for adequate protection against adverse health effects in humans. Since the LOAEL is from a large population of humans the usual uncertainty factor of 10 for interhuman variability is not thought to be necessary.

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Modifying Factors (MFs):

A modifying factor of 1.5 is used based on information suggesting that selenium in water is absorbed more efficiently than selenium in food (U.S. EPA, 1985).

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: High RfD: High

Confidence in the chosen study is medium because doses are given as ranges. Confidence in the data base and RfD are both high because many supportive animal studies (reviewed by NAS, 1977) and epidemiological studies exist.

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Documentation of RfD and Review:

Office of Drinking Water and ECAO-Cincinnati Internal Reveiw, 1985.

U.S. EPA. 1985. Health Effects Assessment for Selenium (and Compounds). Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H058.

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Agency RfD Review:

First Review: 08/19/85
Second Review:
Verification Date: 08/19/85

U.S. EPA Contact:

Primary: C.T. DeRoa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Selenourea CAS #: 630-10-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Yang et al. (1983)	0.750 mg/day (NOAEL)	10	1.5	0.005 mg/kg/day or 0.3 mg/day for a 70 kg man
Human epidemiology study	3.2 mg/day Se or 0.046 mg/kg/day converted to 0.072 mg/kg/day equivalent exposure of selenourea by analogy to selenium (LOAEL)			
Selenosis	Conversion Factor: Molecular weight of $Se(NH_2)_2/Se(-2)$ is 123.03/78.96; thus, 0.046 mg/kg/day x 123.03/78.96 = 0.072 mg/kg/day			

Endpoint and Experimental Doses:

Yang, G., S. Wang, R. Zhou and S. Sun. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37: 872-881.

There is little information regarding the toxicity of selenourea. Cummins and Kimura (1971) reported a rat oral LD50 of 50 mg/kg, compared with 7 mg/kg for sodium selenite. It was postulated that the lower toxicity of selenourea was probably due to its lower water solubility and consequent poorer GI absorption compared with sodium selenite. Because of the lack of data regarding the toxicity of selenourea, the best approach in deriving an ADI for selenourea is by analogy to selenium.

The NAS (1980) has determined an adequate and safe range for selenium intake of 50-200 ug/day for an adult man. The effects of selenium deficiency are potentially as serious as those of selenium toxicity. Selenosis has been reported in high selenium areas where the average intake was 5 mg/day (range 3.2-6.7), but no selenosis occurred when the average intake was 0.75 mg/day (range 0.24-1.51; Yang et al., 1983). U.S. EPA (1985) recommended an ADI of

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

0.21 mg/day for selenium by applying an uncertainty factor of 15 to the LOAEL of 3.2 mg/day (Yang et al., 1983). This ADI was derived on the intake of selenium in drinking water, and an uncertainty factor of 15 rather than 10 was applied because of information that selenium in water is absorbed more efficiently than selenium in food.

This ADI should be adjusted for differences in molecular weight between selenourea (123.03) and selenium (78.96) and, thus, an ADI of 0.005 mg/kg/day (0.003 mg Se x 1.6) or 0.33 mg/day for selenourea is recommended to provide adequate protection against adverse health effects.

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Uncertainty Factors (UFs):

An uncertainty factor of 10 for the LOAEL for selenosis (3.2 mg/day) was applied to derive an ADI of 0.2 mg selenious acid/day for adequate protection against adverse health effects in humans. Since the LOAEL is from a large population of humans the usual uncertainty factor of 10 for interhuman variability is not thought to be necessary.

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Modifying Factors (MFs):

A modifying factor of 1.5 is used based on information suggesting that selenium in water is absorbed more efficiently than selenium in food (U.S. EPA, 1985).

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: High RfD: High

Confidence in the chosen study is medium because doses are given as ranges. Confidence in the data base and RfD are both high because many supportive animal studies (reviewed by NAS, 1977) and epidemiological studies exist.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, August 1985.

U.S. EPA. 1985. Selenourea: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1985. Health Effects Assessment for Selenium (and Compounds). Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H058.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/19/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/19/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Silver Cyanide CAS #: 506-64-9

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Rat oral chronic bioassay	10.8 mg/kg/day CN (NOAEL) converted to 55.66 mg/kg/day silver cyanide	100	5	0.1 mg/kg/day or 8 mg/day for a 70 kg man
Philbrick et al. (1979) Rat chronic oral bioassay Decreased body and thyroid weights, myelin degeneration	30.0 mg/kg/day (LOAEL)			

Conversion Factor: Molecular weight of AgCN/CN is 134/26; thus, 10.8 mg/kg/day x 134/26 = 55.66 mg/kg/day

Endpoint and Experimental Doses:

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

Silver cyanide is not soluble in water or dilute acid (Windholz, 1983). Currently the data base does not provide any toxicity information on silver cyanide. It is, therefore, recommended that an ADI of 8 mg/day for a 70 kg human based on cyanide will provide adequate protection against an adverse health effects. Note that this is a conservative protective assumption in light of silver cyanide's lack of solubility.

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

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 7.8 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

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 low because this chemical has not been tested. The confidence in the RfD is low because it is based on analogy. Chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Sodium Cyanide CAS #: 143-33-9

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Chronic rat feeding study as HCN	10.8 mg/kg/day CN (NOAEL) converted to 20.4 mg/kg/day of sodium cyanide	100	5	0.04 mg/kg/day or 3 mg/day for a 70 kg man
Philbrick et al. (1979) Rat chronic oral bioassay Body weight loss, myelin degeneration, thyroid effects	30.0 mg/kg/day CN (LOAEL)			
	Conversion Factor: Molecular weight of NaCN/CN is 49/26; thus, 10.8 mg/kg/day x 49/26 = 20.4 mg/kg/day			

Endpoint and Experimental Doses:

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

Since sodium is present in very high levels physiologically, an ADI for sodium cyanide of 0.04 mg/kg/day or 3 mg/day can be calculated based on the maximum molar equivalents (1) of cyanide generated in aqueous solution or dilute acids.

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 concentra-

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

tions 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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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,

Additional Comments (cont.):

these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 2.8 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Strychnine CAS #: 57-24-9

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Seidl and Zbinden (1982) Rat oral short-term to subchronic study	NOAEL: None	10,000	-	0.0003 mg/kg/day or 0.02 mg/day for a 70 kg man
Toxicity/histopathology	2.5 mg/kg/day LOAEL/FEL			

Endpoint and Experimental Doses:

Seidl, I. and G. Zbinden. 1982. Subchronic oral toxicity of strychnine in rats. Arch. Toxicol. 51(3): 267-271.

This is the only oral subchronic study reported, in which rats received daily doses of 0 through 10 mg/kg of strychnine by gavage for 28 days. Data recorded for the surviving animals included blood cell count, electrocardiograms, eye examinations, urine chemistry, weight gain, tissue histology, organ weights, behavioral tests, and food and water consumption. Mortality was observed in 5/12 male rats receiving 10 mg/kg, 1/12 in each of the 5 mg and 2.5 mg/kg groups. All deaths occurred 0.5-6 hours after oral doses. While one rat that died in the 2.5 mg/kg/day group showed signs of poisoning, no symptoms were exhibited by survivors, nor did any of the survivors differ from controls histologically or in any of the parameters monitored. The systemic level of this rapidly degradable toxicant [based on pharmacokinetics data, Sgaragli and Mannaion (1973)] was probably much higher than in normal oral intake with food and water because it was administered all at once by gavage. Thus, 2.5 mg/kg/day could be considered a subchronic LOAEL for rats.

Additional studies (Gritzelmann et al., 1978) reported that a 6-month-old human patient received strychnine doses of 0.3-1.1 mg/kg/day over an 18-month period without any adverse effects. However, the patient may have had a

Preparation Date: 01/12/86

Endpoint and Experimental Doses (cont.):

higher strychnine tolerance as a result of nonketotic hyperglycinemia. The Oil and Hazardous Materials-Technical Assistance Data Systems (1984) reported that "adults may safely drink daily 0.078-0.25 gallons of water containing 10 mg/L of strychnine" (equivalent to 2.9-9.5 mg/day). This corresponds to 0.041-0.136 mg/kg.

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Uncertainty Factors (UFs):

An ADI of 0.0003 mg/kg/day or 0.02 mg/day for a 70 kg man is derived from the Seidl and Zbinden (1982) short-term to subchronic study by applying an uncertainty factor of 1000 to account for extrapolation from a subchronic to a chronic exposure study, extrapolation from animals to humans and differences in sensitivity among the human population. An additional 10 is used because a LOAEL/FEL (2.5 mg/kg/day) was utilized in the estimation of the RfD instead of a NOAEL. In view of this concern and the limitations in the data base, the derived ADI should be viewed as an interim estimate. Despite the limitations of the data base the additional factor of 10 should result in a sufficiently protective level.

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Modifying Factors (MFs):

None.

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Additional Comments:

The data base contained only one rat subchronic study for ADI with supportive clinical data. Until further chronic/reproductive studies are available, a low confidence in the RfD is recommended.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low because a small number of animals was tested, a NOEL was not established, and the study is extremely short. Confidence in the data base is low because of the limited supporting studies. Low confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Strychnine: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Tetrachloroethylene CAS #: 127-18-4

Carcinogenicity: CAG, U.S. EPA - Category B2.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Carpenter (1937)	NOAEL: 70 ppm inhalation converted to an oral dose of 19.4 mg/kg/day	1000	-	0.02 mg/kg/day
Rat inhalation, 7 months at 8 hour/day, 5 days/week	LOAEL: 230 ppm			
Kidney and liver changes	Conversion Factors: 70 ppm = 475 mg/cu. m x 1 cu. m/hour (assumed ventilation rate) x 8 hours/day x 5 days/7 days x 0.5 (assumed inhalation retention factor) / 70 kg (assumed human body weight) = 19.4 mg/kg/day			

Endpoint and Experimental Doses:

Carpenter, C.P. 1937. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 19: 323-336.

Carpenter (1937) exposed groups of 24 rats (12/sex) to 1 of 3 doses by inhalation for 8 hours/day, 5 days/week for 7 months. No significant changes were observed at the low dose of 70 ppm. At 230 ppm, renal congestion and swelling were noted. At 470 ppm, the liver aslo was congested and exhibited cloudy swelling, which remained for 46 days after termination of exposure. The kidney showed increased secretion, cloudy swelling and desquamation; the spleen was congested and showed an increase in pigment content.

The study showed good dose-response, but the U.S. EPA was obligated to use the inhalation route of exposure since no good oral data are available.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: High RfD: Medium

Confidence in the chosen study is medium because while only a small number of animals/sex were tested at each dose, the number of parameters measured was large. Confidence in the supporting data base is high to medium because several inhalation studies support the chosen effect level. Medium to high confidence in the RfD normally would follow, but medium is chosen because the data are from inhalation exposures.

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Documentation of RfD and Review:

Extensive internal (i.e., Red Border) and Steering Committee review. Public comment period was June 12 to September 15, 1984.

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

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	05/20/85	Primary:	P. Fenner-Crisp FTS/382-7589 or 513/382-7589
Second Review:			
Verification Date:	05/20/85	Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: 2,3,4,6-Tetrachlorophenol CAS #: 58-90-2

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Hattula et al. (1981) Rat oral short-term to subchronic study	10 mg/kg/day (NOEL)	1000	-	0.01 mg/kg/day or 0.7 mg/day for a 70 kg man
Liver necrosis	50 mg/kg/day (LOAEL)			

Endpoint and Experimental Doses:

Hattula, M.L., V.M. Wasenius, R. Krees, A.N. Arstila and M. Kihlstrom. 1981. Acute and short-term toxicity of 2,3,4,6-tetrachlorophenol in rats. Bull. Environ. Contam. Toxicol. 26: 795-800.

The reported study is a short-term toxicity study in which body weight changes and organ histopathology were observed. There is concern about the duration of exposure (55 days) which could be mitigated by rapid rate of urinary elimination of the compound. Based on the data the 10 mg/kg/day is considered as a NOEL and application of an uncertainty factor of 1000 (10 for subchronic study, 10 for interspecies conversion and 10 for sensitive population) was used to derive the ADI of 0.01 mg/kg/day. Additional data are presented to substantiate the above ADI.

Schwetz et al. (1974) incorporated an acute range finding toxicity study which resulted in the selection of an MTD of 30 mg/kg/day for the reproduction study. The lower dose (10 mg/kg) was a NOAEL, although subcutaneous edema in exposed fetuses was considered a chance alone incidence. The subcutaneous edema was not observed in the high-dose group. High dose exposure (30 mg/kg) caused significant delayed ossification of the skull bones; however, this anomaly normally occurs in all control populations. No other maternal or fetal toxicity was reported in any of the doses tested in this study. Since subcutaneous edema was a chance alone incidence, it is recommended that the 10 mg/kg dose may be used as a NOEL.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Chronic studies are not available. Subchronic and reproductive studies provided adequate data for a RfD of medium level confidence.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

Medium confidence in the critical study is selected because although only a few animals were tested/dose and sex was unspecified, dosing was conducted 7 days/week, and several parameters were measured. Medium confidence in the data base is selected as two bioassays are available that support the chosen NOEL. Medium confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May 1985.

U.S. EPA. 1985. 2,3,4,6-Tetrachlorophenol: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 07/08/85
Second Review:
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Tetraethyl Lead CAS #: 78-00-2

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Schepers (1964) Rat subchronic study/ gavage 5 days/7 days	NOAEL: None	10,000	-	0.0001 ug/kg/day or 0.008 ug/day for a 70 kg man
Histopathology of liver and thymus	1.7 ug/kg/day (LOAEL) converted to 1.2 ug/ kg/day Conversion Factor: 5 days/7 days; thus, 1.7 ug/kg/ day x 5 days/7 days = 1.2 ug/kg/day			

Endpoint and Experimental Doses:

Schepers, G.W. 1964. Tetraethyl and tetramethyl lead. Arch. Environ. Health. 8: 277-295.

In a 20-week study, Schepers (1964) administered tetraethyl lead in peanut oil by gavage to groups of 12 CD rats (6/sex) at 1.7 and 170 ug/kg/bw 5 days/ week. Gross observations revealed swollen livers and fatty plaques in the thymus at both dose groups. Histological preparations revealed hepatocyte vacuolization, cytoplasmic degeneration and neuronal damage among low-dose rats. Rats exposed to the higher dose developed similar, but more severe, histopathologies. Based on these findings a LOAEL of 1.2 ug/kg/day (1.7 ug/kg/day x 5 days/7 days) was determined.

A subchronic inhalation study by Davis et al. (1963) in rats and dogs supports these findings. However, the equivalent oral doses derived from this study are substantially higher than the LOAEL derived from the Schepers (1964) study. Therefore, a human ADI of 0.0001 ug/kg/day was derived based on the LOAEL of 1.2 ug/kg/day from Schepers (1964) and on a standard scaling factor of 10,000.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 10,000 represents 10 to extrapolate from animal to human, 10 to convert subchronic to chronic exposure and 10 to protect for sensitive humans, and an additional factor of 10 to convert a LOAEL to a NOAEL.

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Modifying Factors (MFs):

None.

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Additional Comments:

The data base contained limited long-term oral studies, as well as limited subchronic inhalation and oral data. Reproductive, carcinogenic and teratogenic data are available but inconclusive. Limited epidemiological data are also available.

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The chosen study is given medium confidence because although only a few animals/sex/dose were tested, a good histopathology was conducted, and a dose-severity was observed. The data base was considered to have medium to low confidence because some supporting information was available. Medium (that tends to low) confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Tetraethyl Lead: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallic Oxide CAS #: 563-68-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding	5 ppm in diet thallium acetate (NOEL) converted to 0.39 mg/kg/day as thallium or 0.43 mg/kg/day thallic oxide	1000	-	0.0004 mg/kg/day thallium or 0.0004 mg/kg/day thallic oxide or 0.03 mg/day thallic oxide for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet as thallium acetate (LOAEL) converted to 1.16 mg/kg/day thallium or 1.30 mg/kg/day thallic oxide			
	Conversion Factor: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O is 204/263; molecular weight of Tl2O3/2 Tl is 456/408; thus, 5 mg/kg of diet (ppm) x 0.1 kg of diet/kg bw/day x 204/263 x 456/408 = 0.433 mg/kg/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology. In addition, other groups of rats (10/sex/dose) were fed thallic oxide at dietary levels of 20, 35, 50, 100 and 500 ppm for 15 weeks. All animals fed greater than or equal to 50 ppm died. Increased mortality was seen at 35 ppm. At 20 ppm males showed weight depression, both sexes showed alopecia and both sexes showed increased kidney weight. These data indicate that the toxicity of thallic oxide is substantially similar to thallium acetate. Unfortunately, lower feeding levels corresponding to a NOAEL were not utilized for this salt. It is proposed that the NOEL for thallium acetate, 5 ppm (0.39 mg/kg/day as thallium), be used to calculate an ADI for thallic oxide. A feeding level of 0.43 mg/kg/day thallic oxide would provide an equivalent thallium intake.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallium Acetate CAS #: 563-68-8

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding study	5 ppm in diet (NOEL) converted to 0.5 mg/kg/day	1000	-	0.0005 mg/kg/day or 0.04 mg/day for a 70 kg human
Increased kidney weight, alopecia	15 ppm in diet (LOAEL) converted to 1.5 mg/kg/day			
	Conversion Factor: Young rat food consumption 10% bw/day; thus, 5 mg/kg of diet (ppm) x 0.1 kg of diet/kg bw/day = 0.5 mg/kg bw/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallium Carbonate CAS #: 6533-73-9

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding study	5 ppm in diet as thallium acetate (NOEL) converted to 0.39 mg/kg/day thallium or 0.44 mg/kg/day thallium carbonate	1000	-	0.0004 mg/kg/day thallium or 0.0004 mg/kg/day thallium carbonate or 0.03 mg/day thallium carbonate for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet (LOAEL) converted to 1.2 mg/kg/day as thallium or 1.3 mg/kg/day thallium carbonate			
	Conversion Factors: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O2 is 204/263; molecular weight of Tl2CO3/2 Tl is 467/408; thus, 5 mg/kg of diet (ppm) x 0.1 kg of diet/kg bw/day x 204/263 x 467/408 = 0.44 mg/kg/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm)

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

was added partway through (time not specified). Animals were allowed ad lib access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology.

Data concerning the toxicity of thallium carbonate per se were not located. The toxicity of thallium acetate and thallium carbonate should be substantially similar. This assumes that gastrointestinal absorption of the two compounds is also substantially similar. An interim ADI is proposed by analogy to thallium acetate based upon the feeding level of 5 ppm thallium acetate which corresponds to a NOEL. This feeding level provided a thallium equivalent of 0.39 mg/kg/day corresponding to a feeding level of 0.44 mg/kg/day thallium carbonate.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD are low because no supporting data are available.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallium Chloride CAS #: 7791-12-0

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding study	5 ppm in diet thallium acetate (NOEL) converted to 0.39 mg/kg/day thallium or 0.45 mg/kg/day thallium chloride	1000	-	0.0004 mg/kg/day thallium or 0.0005 mg/kg/day thallium chloride or 0.03 mg/day thallium chloride for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet as thallium acetate (LOAEL) converted to 1.16 mg/kg/day thallium or 1.36 mg/kg/day thallium chloride			

Conversion Factor: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O3 is 204/263; molecular weight of TlCl/Tl is 239/204; thus, 5 mg/kg of diet (ppm) x 0.1 kg of diet/kg bw/day x 204/263 x 239/204 = 0.454 mg/kg/day

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib

Preparation Date: 01/09/86

Endpoint and Experimental Doses (cont.):

access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology.

No data were located concerning the toxicology of thallium chloride per se. The toxicity of thallium chloride should be substantially similar to that of thallium acetate. This presumes that absorption by the gastrointestinal tract is also substantially similar for the two compounds. Utilizing the no-observable effect feeding level from the thallium acetate study an interim ADI may be calculated for thallium chloride by correcting for differences in thallium content. Thallium acetate (5 ppm) contributes 0.39 mg/kg/day thallium which would be equivalent (in terms of thallium content) to 0.45 mg/kg/day thallium chloride.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallium Nitrate CAS #: 10102-45-1

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Down et al. (1960) Rat subchronic feeding study	5 ppm in diet as thallium acetate (NOEL) converted to 0.39 mg/kg/day thallium or 0.51 mg/kg/day thallium nitrate	1000	-	0.0004 mg/kg/day thallium or 0.0005 mg/kg/day thallium nitrate or 0.04 mg/day thallium nitrate for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet (LOAEL) converted to 1.16 mg/kg/day as thallium or 1.52 mg/kg/day thallium nitrate			
	Conversion Factor: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O2 is 204/263; molecular weight of TlNO3/Tl is 266/204; thus, 5 mg/kg of diet (ppm) x 0.1 kg of diet/kg bw/day x 204/263 x 266/204 = 0.506 mg/kg/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology.

No data were located concerning the toxicity of thallium nitrate per se. The toxicity of thallium nitrate and thallium acetate should be substantially similar. This presumes that absorption of these compounds from the gastrointestinal tract is similar. By analogy an ADI for thallium nitrate may be calculated from the NOEL for thallium acetate. The thallium nitrate feeding level equivalent to the NOEL dose was 5 ppm. This corresponds to 0.39 mg/kg/day thallium, which would be equivalent (in terms of thallium content) to 0.51 mg/kg/day thallium nitrate.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

Limited in-house review by ECAO-Cincinnati, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review:
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

Chemical: Thallium Selenite CAS #: 12039-52-0

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding study	5 ppm in diet as thallium acetate (NOEL) converted to 0.39 mg/kg/day thallium or 0.54 mg/kg/day thallium selenite	1000	-	0.0004 mg/kg/day thallium or 0.0005 mg/kg/day thallium selenite or 0.04 mg/day thallium selenite for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet (LOAEL) converted to 1.16 mg/kg/day thallium or 1.62 mg/kg/day thallium selenite			
	Conversion Factor: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O2 is 204/263; molecular weight of TlSe/Tl is 284/204; thus, 5 mg/kg of diet (5 ppm) x 0.1 kg of diet/kg bw/day x 204/263 x 284/204 = 0.540 mg/kg/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology.

No toxicological data were located concerning thallium selenite per se. It is possible to develop an ADI based on equivalent thallium exposure from data concerning thallium acetate. However, this extrapolation is considered more uncertain than extrapolations among the simple thallium salts.

The no-effect feeding level for thallium acetate was 5 ppm which contributed 0.39 mg/kg/day thallium. The dietary thallium selenite intake which would provide an equivalent thallium intake is 0.54 mg/kg/day thallium selenite. The exposure to selenium from this compound, based upon the proposed interim ADI of 38 µg/day, should be well below the toxic range for selenium alone.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

ECAO-Cincinnati limited Internal Review, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	08/05/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Thallium Sulfate CAS #: 7446-18-6

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Downs et al. (1960) Rat subchronic feeding study	5 ppm in diet as thallium acetate (NOEL) converted to 0.39 mg/kg/day thallium or 0.48 mg/kg/day thallium sulfate	1000	-	0.0004 mg/kg/day thallium or 0.0005 mg/kg/day thallium sulfate or 0.03 mg/day thallium sulfate for a 70 kg man
Increased kidney weight, alopecia	15 ppm in diet (LOEL) converted to 1.16 mg/kg/day thallium or 1.44 mg/kg/day thallium sulfate			
	Conversion Factor: Young rat food consumption 10% bw/day; molecular weight of Tl/TlC2H3O2 is 204/263; molecular weight of Tl2SO4/2 Tl is 504/408; thus, 5 mg/kg of diet (ppm) x 0.1 of diet/kg bw/day x 204/263 x 504/408 = 0.479 mg/kg/day			

Endpoint and Experimental Doses:

Downs, W.L., J.K Scott, L.T. Steadman and E.A. Maynard. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. 21: 399-406.

Groups of rats (5/sex/dose) were fed diets containing nominal concentrations of thallium acetate of 0, 5, 15 or 50 ppm. An additional group (30 ppm) was added partway through (time not specified). Animals were allowed ad lib access to these diets for 15 weeks. The 50 ppm level resulted in 100% mortality by week 5. The 30 ppm level resulted in 100% mortality by week 9. Four

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

of 10 control animals died (2/sex) by week 15 making interpretation of survival in the remaining dose groups difficult (15 ppm 3/5 males died, 1/5 females; 5 ppm 2/6 males died, 0/4 females). At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The authors state there was a slight increase in kidney weight (doses not specified, data not shown). The authors reported that histopathological evaluations did not indicate treatment-related pathology.

No data concerning the toxicity of thallium sulfate per se were located. The toxicity of thallium sulfate and thallium acetate should be substantially similar. This presumes that gastrointestinal absorption is substantially similar. An ADI for thallium sulfate may be estimated by analogy to thallium acetate. The no-effect feeding level for thallium acetate was 5 ppm which provided 0.39 mg/kg/day thallium. A thallium sulfate intake providing a corresponding thallium intake would be 0.48 mg/kg/day.

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Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

Downs et al. (1960) is the only subchronic study available for the oral route. There appear to be no chronic data. An abstract of a Russian study was located which reported administration of thallium sulfate or carbonate by i.p. or s.c. injection. However, in the absence of data for oral absorption efficiency, it is difficult to compare these doses. Further chronic/reproductive toxicity data are needed for a higher level of confidence in the RfD.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study is low. This study is flawed by small group sizes, mortality in the control group, failure to monitor food consumption and lack of detail in the reported results. However, four doses were tested and were preceded by a short-term bioassay that tested six doses. Confidence in both the data base and the RfD is low because no supporting data are available.

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Documentation of RfD and Review:

Limited in-house review by ECAO-Cincinnati, July 1985.

U.S. EPA. 1985. Thallium Compounds: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
Secondary: M.L. Dourson
FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Toluene CAS #: 108-88-3

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
CITT (1980) Rat chronic inhalation study	300 ppm (1130 mg/cu. m) converted to 29 mg/kg/day (NOAEL)	100	-	0.3 mg/kg/day or 20 mg/day for a 70 kg man
Clinical chemistry and hematological parameters	LOAEL: None			
	Conversion Factors: 5 days/7 days, 6 hour/24 hour; 0.5 absorption factor, 20 cu. m human breathing rate; 70 kg; thus, 1130 mg/cu. m x 5 day/7 days x 6 hours/24 hours x 0.5 x 20 cu. m/day / 70 kg = 28.8 mg/kg/day			

Endpoint and Experimental Doses:

CIIT (Chemical Industry Institute of Toxicology). 1980. A twenty-four month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. CIIT, Research Triangle Park, NC.

Toluene is most likely a potential source of respiratory hazard. The only chronic toxicity study on toluene was conducted for 24 months in male and female F344 rats (CIIT, 1980). Toluene was administered by inhalation at 30, 100 or 300 ppm (113, 377 or 1130 mg/cu. m) to 120 male and female F344 rats for 6 hours/day, 5 days/week. The same number of animals (120 male and female) was used as a control. Clinical chemistry, hematology and urinalysis testing was conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene.

Based on these findings, a NOAEL of 300 ppm or 1130 mg/cu. m was derived. An oral ADI of 20 mg/day can be derived using route-to-route extrapolation.

Preparation Date: 01/08/86

Endpoint and Experimental Doses (cont.):

This was done by expanding the exposure from 6 hours/day, 5 days/week to continuous exposure and multiplying by 20 cu. m/day and 0.5 to reflect a 50% absorption factor.

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Uncertainty Factors (UFs):

An uncertainty factor of 100 (10 for sensitive individuals and 10 for intraspecies extrapolation was also applied.

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Modifying Factors (MFs):

None.

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Additional Comments:

The only oral study found in the data base (Wolf et al., 1956) contains subchronic data in which no adverse effects of toluene were reported at the highest dose tested (590 mg/kg/day).

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Confidence in the RfD:

Study: High Data Base: Medium RfD: Medium

A high confidence is chosen for the critical study because a large number of animals/sex were tested in each of three dose groups and many parameters were studied. Interim kills were performed. The data base is rated medium because several studies support the chosen effect level. The confidence of the RfD is not any higher than medium because the critical study was by the inhalation route.

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Documentation of RfD and Review:

Limited Peer Review and Agency-wide Internal Review, 1984.

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

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	05/20/85	Primary:	C.T. DeRosa
Second Review:	08/05/85		FTS/684-7534 or 513/569-7534
Verification Date:	08/05/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Trichloromonofluoromethane CAS #: 75-69-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
NCI (1978)	NOAEL: None	1000	-	0.3 mg/kg/day or 20 mg/day for a 70 kg man
Cancer bioassay studies in rats and mice				
Survival and histopathology	488 mg/kg/day (LOAEL) converted to 349 mg/kg/day			
	Conversion Factor: 5 days/7 days; thus, 488 mg/kg/day x 5 days/7 days = 349 mg/kg/day			

Endpoint and Experimental Doses:

NCI (National Cancer Institute). 1978. Bioassay of trichlorofluoromethane for possible carcinogenicity. Report. No. 106, PHS/NIH, DHEW Publ. No. 78-1356.

The NCI bioassay was performed on rats and mice exposed to various doses of trichloromonofluoromethane by gavage over a period of 78 weeks (50 animals/species/sex/dose for each of two doses with 20 animals/species/sex for each of two control groups. A statistically significant positive association between increased dosage and accelerated mortality by the Tarone test in male and female rats and female mice was observed. In treated rats of both sexes there were also elevated incidences of pleuritis and pericarditis not seen in controls. Inhalation studies which employed multispecies exposures to higher levels of the compound than used by NCI (Leuschner et al., 1983; Colman et al., 1981; Hansen et al., 1984), reported no adverse clinical/pathological signs of toxicity due to subchronic or short-term exposures.

The LOAEL of 488 mg/kg/day (mortality in rats) was converted to 349 mg/kg/day on a 7-day exposure basis.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

An uncertainty factory of 1000 (10 for LOAEL, 10 for species conversion, and 10 for sensitive human population), results in an ADI of 0.3 mg/kg/day.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: High Data Base: High RfD: High

The chosen study is given a high to medium confidence because large numbers of animals/sex were tested in two doses for chronic exposures. One difficult was the study did not establish a NOEL. The data base is given a high confidence because multi-species inhalation studies provide supporting data. High to medium confidence in the RfD follows.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May 1985.

U.S. EPA. 1985. Trichloromonofluoromethane: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	07/08/85	Primary:	C.T. DeRosa
Second Review:	-		FTS/684-7534 or 513/569-7534
Verification Date:	07/08/85	Secondary:	M.L. Dourson
			FTS/684-7544 or 513/569-7544

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: 2,4,5-Trichlorophenol CAS #: 95-95-4

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
McCollister et al. (1961) Rat oral subchronic study	100 mg/kg/day (1000 ppm) (NOEL)	1000	-	0.1 mg/kg/day or 7 mg/day for a 70 kg man
Liver and kidney pathology	300 mg/kg/day (3000 ppm) (LOAEL)			
	Conversion Factor: Food consumption 10% of body weight young adult animals; thus, 1000 mg/kg of diet x 0.1 kg of diet/kg bw/day = 100 mg/kg/day			

Endpoint and Experimental Doses:

McCollister, D.D., D.T. Lockwood and V.K. Rowe. 1961. Toxicologic information on 2,4,5-trichlorophenol. Toxicol. Appl. Pharmacol. 3: 63-70.

This is the only subchronic (98 days) oral study in rodents available in the literature. Ten rats of each sex were exposed to different levels (from 100 through 10,000 ppm) of 2,4,5-trichlorophenol for 98 days. Mild diuresis and slight degenerative changes in the liver and kidneys were observed in rats of both sexes in the 3000 ppm and higher doses. In this study 1000 ppm (100 mg/kg/day based on food consumption as 10% of body weight in young adults) was considered to be a NOEL, as judged by behavior, mortality, food consumption, growth, body and organ weights and histopathology. Until further chronic/reproductive studies are available, this ADI, 0.1 mg/kg/day, is recommended.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of a subchronic effect level to its chronic equivalent.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Medium

The confidence in the chosen study is medium because five dose groups were tested and several parameters were monitored. It is not higher than medium because only a few animals were tested/dose. Confidence in the data base is low because little, if any, supporting data exist. Confidence in the RfD is medium to low. Additional chronic/reproductive toxicity studies are needed to support a higher confidence in the RfD.

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Documentation of RfD and Review:

Limited Peer Review and Agency-wide Internal Review, 1984.

U.S. EPA. 1984. Health Effects Assessment for 2,4,5-Trichlorophenol. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H034.

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Agency RfD Review:		U.S. EPA Contact:	
First Review:	05/20/85	Primary:	C.T. DeRosa FTS/684-7534 or 513/569-7534
Second Review:	-		
Verification Date:	05/20/85	Secondary:	M.L. Dourson FTS/684-7544 or 513/569-7544

Chemical: 1,1,2-Trichloro-1,2,2-trifluoroethane CAS #: 76-13-1

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Imbus and Adkins (1972) Epidemiologic study: Human occupational exposure Psychomotor impairment	5358 mg/cu. m converted to 273 mg/kg/day (NOAEL)	10	-	30 mg/kg/day or 2000 mg/day for a 70 kg man

Conversion Factors: 10 cu. m (8-hour human breathing volume), 5 days/7 days, 0.5 absorption factor, 70 kg bw; thus, 5358 mg/cu. m x 10 cu. m x 5 days/7 days x 0.5/70 kg = 273 mg/kg/day

Endpoint and Experimental Doses:

Imbus, H.R. and C. Adkins. 1972. Physical examination of workers exposed to trichlorotrifluoroethane. Arch. Environ. Health. 24(4): 257-261.

Several animal inhalation studies reported negative results in dogs, rabbits, and rats chronically exposed to very high concentrations of trichlorotrifluoroethane (U.S. EPA, 1983, Health Assessment Docuement). No apparent adverse effects have been reported in humans occupationally exposed to trichlorotrifluoroethane at either 500 mg/cu. m levels for 11 years or 5358 mg/cu. m levels for 2.77 years (Imbus and Adkins, 1972).

Slight impairment of psychomotor performance was reported in male volunteers exposed to trichlorotrifluoroethane concentrations of 19,161 mg/cu. m for 2.75 hours (Stopps and McLaughlin, 1967). This exposure period was too brief to consider a NOAEL for chronic exposure. Therefore, the ADI of 30 mg/kg/day is considered protective.

Preparation Date: 01/09/86

Uncertainty Factors (UFs):

The uncertainty factor of 10 accounts for the expected interhuman variability to the toxicity of this chemical in lieu of specific data.

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Modifying Factors (MFs):

None.

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Additional Comments:

None.

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Confidence in the RfD:

Study: Low Data Base: Low RfD: Low

Confidence in the chosen study, data base and RfD are all considered low. Although based on human data, and the fact that several chronic studies in animals support the human NOEL, uncertainties in both the exposure levels and route extrapolation preclude a higher confidence rating.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, May 1985.

U.S. EPA. 1985. 1,1,2-Trichloro-1,2,2-trifluoroethane: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 07/08/85
Second Review: -
Verification Date: 07/08/85

U.S. EPA Contact:

Primary: C.T. DeRosa
FTS/684-7534 or 513/569-7534
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REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Zinc Cyanide CAS #: 557-21-1

Carcinogenicity: None.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD (ADI)
Howard and Hanzal (1955) Chronic rat feeding study as HCN	10.8 mg/kg/day CN (NOAEL) converted to 24.3 mg/kg/day zinc cyanide	100	5	0.05 mg/kg/day or 3 mg/day for a 70 kg man
Phibrick et al. (1979) Rat subchronic to chronic oral bioassay Body weight loss, thyroid effects, myelin degeneration	30.0 mg/kg/day CN (LOAEL)			
	Conversion Factor: Molecular weight of Zn(CN)2/(CN)2 is 117/52; thus, 10.8 mg/kg/day x 117/52 = 24.3 mg/kg/day			

Endpoint and Experimental Doses:

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

Since zinc is present at high levels in foods and is considerably less toxic than cyanide, an ADI for zinc cyanide of 0.05 mg/kg/day or 3.4 mg/day can be calculated based on the maximum molar equivalents (2) of cyanide generated in aqueous solution or dilute acids.

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

Preparation Date: 01/09/86

Endpoint and Experimental Doses:

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 histopathological 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 subcutaneous route (Crampton et al., 1979; Lessell, 1971; Herthing et al., 1960). Human data do not provide adequate information from which to derive an ADI 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 ADI 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 ADI is the oral route of administration.

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Uncertainty Factors (UFs):

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

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Modifying Factors (MFs):

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

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Additional Comments:

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

Additional Comments (cont.):

generation and produced 100% mortality in the F2 generation in mice. However, these data are not consistent with the body of available literature. Thus, until additional chronic studies are available, an ADI of 3.4 mg/day for a 70 kg man is recommended.

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Confidence in the RfD:

Study: Medium Data Base: 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. The confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

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Documentation of RfD and Review:

ECAO-Cincinnati Internal Review, July 1985.

U.S. EPA. 1985. Cyanides: Review and Evaluation of ADI. Contract No. 68-03-3228. Environmental Criteria and Assessment Office, Cincinnati, OH.

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Agency RfD Review:

First Review: 08/05/85
Second Review: -
Verification Date: 08/05/85

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