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Integrated Risk Information System

Cadmium (CASRN 7440-43-9)

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Cadmium; CASRN 7440-43-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Cadmium

File First On-Line 03/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/01/1994
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/1992

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Cadmium
CASRN — 7440-43-9
Last Revised — 02/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of

deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Significant proteinuria	NOAEL (water): 0.005 mg/kg/day	10	1	5E-4 mg/kg/day (water)
Human studies involving chronic exposures	NOAEL (food): 0.01 mg/kg/day	10	1	1E-3 mg/kg/day (food)
U.S. EPA, 1985				

* Conversion Factors: See text for discussion

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

U.S. EPA. 1985. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington, DC. (Final draft)

A concentration of 200 ug cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 ug Cd/gm wet human renal cortex; the model assumes that 0.01% day of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 ug Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and ian UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day (see Section VI.A. for references).

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

UF — This uncertainty factor is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals.

MF — None

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

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect.

Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

__I.A.5. Confidence in the Oral RfD

Study — Not applicable
Database — High
RfD — High

The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism and elimination. All of this information considered together gives high confidence in the database. High confidence in either RfD follows as well.

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

Source Document — U.S. EPA, 1985

Other EPA Documentation — None

Agency Work Group Review — 05/15/1986, 08/19/1986, 09/17/1987, 12/15/1987, 01/20/1988, 05/25/1988

Verification Date — 05/25/1988

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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

Substance Name — Cadmium
CASRN — 7440-43-9

Not available at this time.

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Cadmium
CASRN — 7440-43-9
Last Revised — 06/01/1992

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per

(mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification — B1; probable human carcinogen

Basis — Limited evidence from occupational epidemiologic studies of cadmium is consistent across investigators and study populations. There is sufficient evidence of carcinogenicity in rats and mice by inhalation and intramuscular and subcutaneous injection. Seven studies in rats and mice wherein cadmium salts (acetate, sulfate, chloride) were administered orally have shown no evidence of carcinogenic response.

__II.A.2. Human Carcinogenicity Data

Limited. A 2-fold excess risk of lung cancer was observed in cadmium smelter workers. The cohort consisted of 602 white males who had been employed in production work a minimum of 6 months during the years 1940-1969. The population was followed to the end of 1978. Urine cadmium data available for 261 workers employed after 1960 suggested a highly exposed population. The authors were able to ascertain that the increased lung cancer risk was probably not due to the presence of arsenic or to smoking (Thun et al., 1985). An evaluation by the Carcinogen Assessment Group of these possible confounding factors has indicated that the assumptions and methods used in accounting for them appear to be valid. As the SMRs observed were low and there is a lack of clear cut evidence of a causal relationship of the cadmium exposure only, this study is considered to supply limited evidence of human carcinogenicity.

An excess lung cancer risk was also observed in three other studies which were, however, compromised by the presence of other carcinogens (arsenic, smoking) in the exposure or by a small population (Varner, 1983; Sorahan and Waterhouse, 1983; Armstrong and Kazantzis, 1983).

Four studies of workers exposed to cadmium dust or fumes provided evidence of a statistically significant positive association with prostate cancer (Kipling and Waterhouse, 1967; Lemen et al., 1976; Holden, 1980; Sorahan and Waterhouse, 1983), but the total number of cases was small in each study. The Thun et al. (1985) study is an update of an earlier study (Lemen et al., 1976) and does not show excess prostate cancer risk in these workers. Studies of human ingestion of cadmium are inadequate to assess carcinogenicity.

__II.A.3. Animal Carcinogenicity Data

Exposure of Wistar rats by inhalation to cadmium as cadmium chloride at concentrations of 12.5, 25 and 50 ug/cu.m for 18 months, with an additional 13-month observation period, resulted in significant increases in lung tumors (Takenaka et al., 1983). Intratracheal instillation of cadmium oxide did not produce lung tumors in Fischer 344 rats but rather mammary tumors in males and tumors at multiple sites in males (Sanders and Mahaffey, 1984). Injection site tumors and distant

site tumors (for example, testicular) have been reported by a number of authors as a consequence of intramuscular or subcutaneous administration of cadmium metal and chloride, sulfate, oxide and sulfide compounds of cadmium to rats and mice (U.S. EPA, 1985). Seven studies in rats and mice where cadmium salts (acetate, sulfate, chloride) were administered orally have shown no evidence of a carcinogenic response.

__II.A.4. Supporting Data for Carcinogenicity

Results of mutagenicity tests in bacteria and yeast have been inconclusive. Positive responses have been obtained in mutation assays in Chinese hamster cells (Dom and V79 lines) and in mouse lymphoma cells (Casto, 1976; Ochi and Ohsawa, 1983; 0berly et al., 1982).

Conflicting results have been obtained in assays of chromosomal aberrations in human lymphocytes treated in vitro or obtained from exposed workers. Cadmium treatment in vivo or in vitro appears to interfere with spindle formation and to result in aneuploidy in germ cells of mice and hamsters (Shimada et al., 1976; Watanabe et al., 1979; Gilliavod and Leonard, 1975).

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

Not available. There are no positive studies of orally ingested cadmium suitable for quantitation.

_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

__II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 1.8E-3 per (ug/cu.m)

Extrapolation Method — Two stage; only first affected by exposure; extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E-2 ug/cu.m
E-5 (1 in 100,000)	6E-3 ug/cu.m
E-6 (1 in 1,000,000)	6E-4 ug/cu.m

__II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — lung, trachea, bronchus cancer deaths
Test animals — human/white male
Route — inhalation, exposure in the workplace
Reference — Thun et al., 1985

Cumulative Exposure (mg/day/cu.m)	Median Observation	24 hour/ ug/cu.m Equivalent	No. of Expected Lung, Trachea and Bronchus Cancers Assuming No Cadmium Effect	Observed No. of Deaths (lung, trachea, bronchus cancers)
less than or				

equal to 584	280	168	3.77	2
585-2920	1210	727	4.61	7
greater than or equal to 2921	4200	2522	2.50	7

The 24-hour equivalent = median observation x lE+3 x 8/24 x 1/365 x 240/365.

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk should not be used if the air concentration exceeds 6 ug/cu.m, since above this concentration the unit risk may not be appropriate.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

The data were derived from a relatively large cohort. Effects of arsenic and smoking were accounted for in the quantitative analysis for cadmium effects.

An inhalation unit risk for cadmium based on the Takenaka et al. (1983) analysis is 9.2E-2 per (ug/cu.m). While this estimate is higher than that derived from human data [1.8E-3 per (ug/cu.m)] and thus more conservative, it was felt that the use of available human data was more reliable because of species variations in response and the type of exposure (cadmium salt vs. cadmium fume and cadmium oxide).

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

__II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985

The Addendum to the Cadmium Health Assessment has received both Agency and external review.

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

Agency Work Group Review — 11/12/1986

Verification Date — 11/12/1986

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

Substance Name — Cadmium
CASRN — 7440-43-9
Last Revised — 10/01/1989

_VI.A. Oral RfD References

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_VI.B. Inhalation RfC References

None

_VI.C. Carcinogenicity Assessment References

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Varner, M.O. 1983. Updated epidemiologic study of cadmium smelter workers. Presented at the Fourth International Cadmium Conference. Unpublished.

Watanabe, T., T. Shimada and A. Endo. 1979. Mutagenic effects of cadmium on mammalian oocyte chromosomes. Mutat. Res. 67: 349-356.

_VII. Revision History

Substance Name — Cadmium
CASRN — 7440-43-9

Date	Section	Description
05/21/1987	II.C.	Slope factor corrected
03/01/1988	II.A.1.	Text added
03/01/1988	II.C.3.	Text revised
03/01/1988	II.C.4.	Confidence statement revised
03/01/1988	II.D.3.	Secondary contact changed
01/01/1989	IV.C.1.	Water quality human health criteria added
01/01/1989	IV.C.2.	Corrected marine acute criterion
08/01/1989	VI.	Bibliography on-line
10/01/1989	I.A.	Oral RfD summary on-line
10/01/1989	VI.A.	Oral RfD references added

12/01/1989	I.B.	Inhalation RfC now under review
06/01/1990	IV.A.1.	Area code for EPA contact corrected
06/01/1990	IV.F.1.	EPA contact changed
08/01/1990	II.A.1.	Basis statement revised
08/01/1990	II.A.2.	Text revised, paragraph 1
08/01/1990	II.B.	Text revised
01/01/1991	II.	Text edited
01/01/1991	II.C.1.	Inhalation slope factor removed (global change)
03/01/1991	II.A.1.	Text revised
03/01/1991	II.B.	Text revised
01/01/1992	IV.	Regulatory actions updated
04/01/1992	IV.A.1.	CAA regulatory action withdrawn
05/01/1992	II.C.2.	Number correction in data table
06/01/1992	II.A.2.	Text revised, paragraph 1
06/01/1992	II.A.3.	Text clarified
02/01/1994	I.A.7.	Secondary contact changed
08/01/1995	I.B.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
01/02/1998	I., II.	This chemical is being reassessed under the IRIS Program.

_VIII. Synonyms

Substance Name — Cadmium
CASRN — 7440-43-9
Last Revised — 03/31/1987

- 7440-43-9
- C.I. 77180
- Cadmium
- KADMIUM

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