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Provisional Peer-Reviewed Toxicity Values for

Soluble Zirconium Compounds
(CASRN 7440-67-7)

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR SOLUBLE ZIRCONIUM COMPOUNDS (CASRN 7440-67-7)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Zirconium is a metallic element having the atomic number of 40, an atomic weight of 91.22, and the chemical symbol (Zr) (ChemIDplus, 2011). It exists as a soft, malleable ductile solid or gray to gold, amorphous powder. It is resistant to corrosion by water and steam, mineral acids, strong alkalis, organic acids, salt solutions, and molten salts. It forms alloys with almost all metals—except mercury, alkali, and alkaline earth groups (HSDB, 2006). Table 1 provides a table of physicochemical properties. In this document, "statistically significant" denotes a *p*-value of <0.05.

Table 1. Physicochemical Properties Table for Zirconium (CASRN 7440-67-7)[a]

Property (unit)	Value
Boiling point (ºC)	3577
Melting point (ºC)	1857
Density (g/cm^3)	6.5107
Vapor pressure (Pa at 25ºC)	0 mm Hg
pH (unitless)	Data not available
Solubility in water (g/100 mL at 25ºC)	Data not available—Soluble in hot concentrated acid
Relative vapor density (air = 1)	Data not available
Molecular weight (g/mol)	91.224

[a]Values from HSDB (2010) and ChemID plus (2011).

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for zirconium is included in the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) database (U.S. EPA, 2010) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) includes a Health and Environmental Effects Profile (HEEP) for zirconium (U.S. EPA, 1985) that declined to derive noncancer and cancer toxicity values due to inadequate noncancer and cancer data, respectively. The toxicity of zirconium has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011) or the World Health Organization (WHO, 2010). The California Environmental Protection Agency (CalEPA, 2008) has also not derived toxicity values for exposure to zirconium.

Occupational exposure limits for zirconium have been established by the Occupational Safety and Health Administration (OSHA, 2006), the National Institute of Occupational Safety and Health (NIOSH, 1994), and the American Conference of Governmental Industrial Hygienists (ACGIH, 2011). The OSHA permissible exposure limit (PEL) 8-hour time weighted average (TWA) for zirconium is 5 mg/m^3 (OSHA, 2010). NIOSH has set a recommended exposure limit

(REL) TWA of 5 mg/m^3 and a REL short-term exposure limit (STEL) of 10 mg/m^3 that applies to all zirconium compounds—except zirconium tetrachloride for which it has set no REL. The NIOSH IDLH (Immediately Dangerous to Life or Health) concentration for zirconium is 25 mg Zr/m^3 (NIOSH, 1994). The ACGIH has set a threshold limit value (TLV) TWA of 5 mg/m^3 and a STEL of 10 mg/m^3 for zirconium (ACGIH, 2011).

The HEAST (U.S. EPA, 2011) did not report a U.S. EPA (1986) cancer weight-of-evidence (WOE) classification or an oral slope factor for Zirconium. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of zirconium. Zirconium is not included in the *12th Report on Carcinogens* (NTP, 2011). The CAL EPA online database CalEPA (2002) does not include a quantitative estimate of carcinogenic potential for zirconium. ACGIH has classified zirconium in the Group A4: "not classifiable as a human carcinogen" (ACGIH, 2011).

Literature searches were conducted on sources published from 1900 through April 2012, for studies relevant to the derivation of provisional toxicity values for zirconium (elemental), CASRN 7440-67-7, zirconium oxychloride, CASRN 7699-43-6, zirconium tetrachloride, CASRN 10026-11-6, zirconium compounds, no CASRN, zirconium nitrate, CASRN 13746-89-9, zirconium picramate, CASRN 63868-82-6, zirconium acetate, CASRN 7585-20-8, zirconium silicate, CASRN 14940-68-2, zirconium potassium fluoride, CASRN 16923-95-8, and zirconium ammonium fluoride, CASRN 16919-31-6. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications (NSCEP) and National Environmental Publications Internet Site (NEPIS) database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for zirconium and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified by the note PS, and entries for the principal studies are presented in bold.

Table 2. Summary of Potentially Relevant Data for Soluble Zirconium Compounds (CASRN 7440-67-7)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Human								
			1. Oral (mg/kg-day)[a]					
None								
			2. Inhalation (mg/m^3)[a]					
Subchronic	None							
Chronic	22 workers (sex not reported), case report, 1−5 years	Not reported	No abnormalities	None	Not run	None	Reed et al. (1956)	
	32 male, case report, 1−17 yrs	Not reported	No abnormalities	None	Not run	None	Bingham et al. (2001)	
	150 workers (sex not reported), survey, duration not reported	Not reported	Respiratory irritation, dermatitis	None	Not run	None	Thoburn and Straub (NIOSH) (1976)	
	178 male, occupational epidemiology, 10 years (average)	<1 mg/m^3; 1−2.5 mg/m^3; 2.5−10 mg/m^3; >10 mg/m^3;	No abnormalities	>10 mg/m^3	Not run	None	Marcus et al. (1996)	
	1 female, case report, 3.5 years	5.8 ≥30% zirconium silicate with clay	Interstitial inflammation, fibrosis of alveolar walls	None	Not run	None	Liippo et al. (1993)	
	1 male, case report, 39 years	Not reported	Pulmonary fibrosis	None	Not run	None	Bartter, et al. (1991)	
	1 worker (sex not reported), case report, duration not reported	Not reported	Interstitial lung granuloma	None	Not run	None	Romeo et al. (1994)	

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
2. Inhalation (mg/m^3)[a]								
Subchronic	12 Albino rabbit (sex not reported), 20 minutes/day, 6 weeks	49,000 (sodium zirconium lactate)	Bronchiolar abscesses with a lobular type of pneumonia or peribronchial granulomas	None	Not run	None	Prior et al. (1960)	
	10 hamster (strain and sex not reported), 225 days	15, 150 (zirconium lactate), 15 (barium zirconate)	Poor weight gain, pathological changes consistent with chronic interstitial pneumonitis, increase in zirconium content of lung tissue (at all doses)	None	Not run	None	Brown et al. (1963)	
	10 rat (strain and sex not reported), 225 days	15, 150 (zirconium lactate), 15 (barium zirconate)	Poor weight gain, pathological changes consistent with chronic interstitial pneumonitis, increase in zirconium content of lung tissue (at all doses)	None	Not run	None	Brown et al. (1963)	
	10 guinea pig (strain and sex not reported), 225 days	15, 150 (zirconium lactate), 15 (barium zirconate)	Poor weight gain, pathological changes consistent with chronic interstitial pneumonitis, increase in zirconium content of lung tissue (at all doses)	None	Not run	None	Brown et al. (1963)	
	Guinea pig (strain and number not reported), 2 to 6 months	NA	No pulmonary effects	None	Not run	None	Clayton and Clayton (1981−1982)	
	Guinea pig (strain and number not reported), 60 days	6, 75 (zirconium tetrachloride)	Increased mortality (not specified) at 6 mg/m^3, no effect at 75 mg/m^3	None	Not run	None	Seiler et al. (1988)	
	Rat (strain and number not reported), 60 days	6, 75 (zirconium tetrachloride)	Increased mortality (not specified) at 6 mg/m^3, no effect at 75 mg/m^3	None	Not run	None	Seiler et al. (1988)	

Table 2. Summary of Potentially Relevant Data for Soluble Zirconium Compounds (CASRN 7440-67-7)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Subchronic	Dog (strain and number not reported), 60 days	6, 75 (zirconium tetrachloride)	Slight decreases in hemoglobin and red blood cell count at 6 mg/m^3, no effect at 75 mg/m^3	None	Not run	None	Seiler et al. (1988)	
Chronic	Laboratory animals (species, strain, number not reported), 1 year	3.5	No effect	None	Not run	None	Bingham et al. (2001)	

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.

[b]Not reported by the study author, but determined from data.

[c]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, NPR = Not peer reviewed, SS = Secondary source.

[d]Conversions for Schroeder et al. (1970) and Schroeder et al. (1968) are for combined drinking water and feed based on default values for body weights and food consumption rates for male and female rats and mice, per U.S. EPA (1988) and days dosed and total days of study based on average longevity (in days) provided in the study tables in Schroeder et al. (1970) and (1968) (since length of study is given as lifetime). Drinking water exposure was converted from zirconium sulfate to zirconium exposure using the following equation: zirconium sulfate intake (ppm) × MW zirconium ÷ MW zirconium sulfate = 5 ppm × 91.224 g ÷ 355.4 g = 1.28 ppm. (Note, the MW of zirconium sulfate tetrahydrate [355.4 g] was used since that compound is soluble in water.) Dosimetry is calculated using default values for rats and default food and water consumption rates (U.S. EPA, 1988). For example, the default time weighted average body weight for chronically exposed male Long-Evans rats is 0.472 kg, the water intake is .057 (L/day) (water factor 0.121 L water/kg BW/day) and the food intake is 0.034 (kg/day) (food factor 0.072 kg food/kg BW/day).

HUMAN STUDIES

Oral Exposures

The only report on oral exposure to zirconium in humans stated that symptoms from acute ingestion consisted of burning pain in mouth and throat, vomiting, watery or bloody diarrhea, tenesmus, retching, hemolysis, hematuria, anuria, liver damage with jaundice, hypotension, collapse, and convulsions (Dreisbach, 1977). However, no dose information was provided.

Inhalation Exposures

A study of 22 workers (sex not reported) exposed for 1 to 5 years to zirconium along with a variety of other compounds during the zirconium reduction process revealed no abnormalities from the exposure (Reed et al., 1956).

A study of 32 males who had worked for 1 to 17 years as hand finishers of zirconium metal reactor components showed no significant differences from the control group (Bingham et al., 2001). Bingham et al. (2001) noted that pulmonary granuloma in a different set of zirconium workers had been reported after long-term exposure to zirconium, but the reports did not specify whether the granuloma was due to zirconium metal or a specific compound of zirconium.

Thoburn and Straub (NIOSH, 1976) conducted a health hazard investigation of 150 workers (sex not reported) in a facility that produced nuclear-reactor-grade zirconium and hafnium from crude zirconium tetrachloride. Based on medical interviews and cutaneous examination of the workers, the study authors determined that respiratory tract irritation and dermatitis existed in the workers and that these health effects were associated with the company's production of zirconium and hafnium. No further information was provided on these studies—including the concentrations of zirconium—and, therefore, neither NOAELs nor LOAELs could be determined.

A study was reported by Marcus et al (1996) on 178 male workers (average age = 37.6 years) working with zirconium compounds in England. The men had been employed at a facility for an average length of employment of 10 years where they were exposed to zirconium compounds. Chest radiographs were done in 1975, 1978, and 1982 and lung-function measurements were carried out at regular intervals. An estimate of cumulative exposure was computed from job titles and the likely exposures in each time period. Four exposure categories were estimated: no dust: <1 mg/m^3; low dust: 1−2.5 mg/m^3; medium dust: 2.5−10 mg/m^3; high dust: >10 mg/m^3. The number of years spent in each job was multiplied by the score on the dust scale and a cumulative dust exposure score calculated for each man. At the start of the study 51.1% were in low dust jobs, 44.8% in medium dust jobs, and 4.1% in high dust jobs. The mean cumulative exposure (years × dust level) was 12.9 'dust years' at the start and 22.3 at the end of the study. Those exposures and categories were examined in relationship to the chest radiographs and impaired lung function of the workers. No evidence was found that zirconium exposure resulted in abnormal chest radiographs or impaired lung function. A NOAEL or LOAEL could not be determined from this study because this is a retrospective study in which the exposures was not adequately quantified.

A number of case reports have reported pulmonary effects from zirconium exposure. Liippo et al. (1993) reported on a case of hypersensitivity pneumonitis in a 25-year old female ceramic tile worker exposed to zirconium. The woman had worked for 3.5 years in a ceramic tile factory as a glazer and sorter and generally had not used protective equipment. Up to 30% zirconium silicate was found in the glazing material used in the tile factory and dust concentrations were up to 5.8 mg/m^3. She developed a worsening dry cough and dyspnea and the woman died one week after an open lung biopsy, which revealed interstitial inflammation and fibrosis of the alveolar walls. Analysis of lung tissue samples showed inhaled dust consisting primarily of clay particles and zirconium-silicate that was almost 100 times that of the normal background level. The authors concluded that zirconium exposure caused an acute allergic alveolitis-like hypersensitivity reaction.

Bartter et al. (1991) reported on a 62-year old man with dyspnea that had gradually increased during the preceding 25 years. He was diagnosed with pulmonary fibrosis. The man had worked for 39 years in the lens grinding department of an optical company where he had been involved in the grinding, polishing, pitting, and blocking of lenses and had been exposed to a variety of compounds—including Zirox B (zirconium oxide and respirable quartz). He had not worn protective equipment at work. Analysis of the lung tissue showed significant elevations of various zirconium compounds—including zirconium oxide, zirconium silicate, and zirconium aluminum silicate. The authors concluded that zirconium was the probable cause of the patient's pulmonary fibrosis. A NOAEL or a LOAEL could not be determined from these studies because these are case reports and there is no dose-response information available.

Romeo et al. (1994) reported on a case of interstitial lung granuloma in a worker exposed to zirconium compounds. Histological examination of transbronchial biopsy tissue showed small interstitial nonconfluent granulomas with epithelioid and giant cells showing no central necrosis. No further information was provided.

Additionally, two case reports on interstitial lung disease related to zirconium exposure were presented by Bingham et al. (2001). The first case was a 49-year old man who had been employed at a refractory brick production factory for 20 years. Chest X-rays showed diffuse bilateral opacities and a histological study of biopsy tissue showed fibrosis and hyperplasia and weakly birefringent particles in alveolar and interstitial histiocytes. Neutron activation analysis of particles showed zirconium levels of 715 ppm. The second case was a 29-year old man who had worked as a coremaker in a foundry for 8 years. X-rays showed diffuse opacities and histology revealed granulomas and birefringent particles in histiocytes. Because no exposure information was provided, neither a NOAEL nor a LOAEL could be determined from these case reports.

Other Exposures

Bingham et al. (2001) reported dermal granulomatous lesions, probably of allergic epithelioid origin, after dermal exposure to deodorant sticks and poison ivy lotions containing zirconium. In a case study of two subjects (gender not specified), daily application of an aluminum deodorant stick did not produce an adverse reaction, but the subjects showed a granulomatous response to intracutaneous injection of a dilute aqueous solution of sodium zirconium lactate (Browning, 1969). Dermal lesions were reported in a 15-year old girl

following treatment of poison ivy dermatitis with 4% zirconium oxide cream. No granulomas appeared on intact skin areas (National Poisons Information Service, 1998).

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to zirconium have been evaluated in two chronic-duration studies that also examined carcinogenic effects (Schroeder et al., 1970; and Schroeder et al., 1968). Kanisawa and Schroeder (1969) summarized the results from Schroeder et al. (1970) and Schroeder et al. (1968) with more details on the carcinogenicity of zirconium than were provided in Schroeder et al. (1970) or Schroeder et al. (1968).

Chronic Studies

A study that administered one of five trace elements (zirconium, niobium, antimony, vanadium, or lead) to 603 rats (approximately 50/gender/chemical) in both drinking water and feed, simultaneously, is chosen as the principal study (Schroeder et al., 1970). This study was performed before Good Laboratory Practice (GLP) guidance was established. The test drinking water containing 5 ppm zirconium sulfate was provided to 56 male and 58 female Long-Evans rats (the offspring of pregnant Long-Evans rats purchased for the study) from weaning to natural death (a maximum of 1347 days). An equal number of rats served as controls. The experimental rats also were fed a diet containing 2.66 µg/g zirconium (thus zirconium was in the food and water). Using time-weighted average body weight and default water consumption in Long-Evans rats, the dose of 5 ppm zirconium sulfate in drinking water was converted to 0.60 mg/kg-day for males (0.057 L/day × 5 mg/L/0.472 kg = 0.60 mg/kg-day) and 0.67 mg/kg-day for females. The dose of 2.66 mg/kg zirconium in feed was converted (also using time-weighted average body weights and food consumption) to 0.19 mg/kg-day for males and 0.22 mg/kg-day for females. These doses were also adjusted for the fraction of zirconium sulfate that is zirconium as shown in Footnote d of Table 2. Actual food consumption data was not shown. Data related to the differential bioavailability between drinking water and dietary zirconium was not available. Because the rats ingested both drinking water and feed, the doses were summed for a total equivalent dose (TED) of 0.79 mg/kg-day in males and 0.89 mg/kg-day in females. The rats were weighed weekly from weaning until 6 weeks of age, and then monthly. As the rats died, they were weighed and dissected to identify grossly visible tumors and other lesions in the heart, lung, kidney, liver, and spleen. During the study, an epidemic of virulent pneumonia struck the rat colony, and killed 19 males and 12 females (controls) and 5 males and 4 females (zirconium-exposed) in a 3-week period. According to the authors, these animals were removed from the series and survival numbers were corrected for that time period.

Zirconium did not consistently affect the growth rates of the rats (Schroeder et al., 1970). Males administered zirconium were significantly heavier than controls at 30, 150, and 180 days and lighter than controls at 360 and 540 days, while females were significantly heavier than controls at 30, 150, and 540 days (see Table B.1). There was no significant difference in survival of the zirconium-administered rats compared to controls (see Table B.2). Females administered zirconium showed significantly higher fasting serum glucose levels than controls and males administered zirconium had significantly higher cholesterol levels. Glycosuria (glucose in the urine) was noted in 23% of the controls and in 52% of 56 rats (study does not say whether in males or females) administered zirconium (significantly different by chi-square analysis at $p < 0.01$) (see Table B.3). No differences were observed in the mean body weights of

the rats administered zirconium compared to controls, while the hearts of males administered zirconium weighed 14.6% less than controls, the hearts of females weighed 7.4% more (see Table B.4). No significant increase was reported in the number of tumors in rats administered zirconium compared to the controls (Schroeder et al., 1970; Kanisawa and Schroeder, 1969) (see Table B.4). The study authors did not identify a NOAEL or LOAEL from this study. A LOAEL of 0.79 mg/kg-day (males) and 0.89 mg/kg-day (females) is identified based on significantly increased incidence of glycosuria, higher fasting glucose levels in females and higher cholesterol levels in males. A NOAEL is not determined because only one dose (in addition to controls) was tested.

Schroeder et al. (1968) administered one of four trace elements (i.e., zirconium, niobium, antimony, or fluorine) to different groups of mice in both drinking water and feed. The test drinking water containing 5 ppm zirconium sulfate was administered to 54 male and 54 female Charles River CD-1 mice (born from random-bred pregnant females) over the lifetime (from weaning until death) of the mice. An equal number of mice served as controls. The experimental mice also were fed a diet reported to contain 2.66 µg/g zirconium. Using standard assumptions for body weight and water consumption in mice, 5 ppm zirconium sulfate in drinking water was calculated to be equivalent to 1.23 mg/kg-day for males and 1.26 mg/kg-day for females. The dose of 2.66 µg/g zirconium in feed was calculated, also using standard assumptions, to represent 0.48 mg/kg-day for males and 0.49 mg/kg-day for females. Because the experimental mice ingested both drinking water and feed, the doses were summed for a total equivalent dose of 1.71 mg/kg-day in males and 1.75 mg/kg-day in females. This study was conducted before GLP guidance was developed by EPA in 1983. The mice were weighed weekly for 8 weeks and then at monthly intervals (see Table B.5). The dead animals were dissected, grossly visible tumors and other lesions were noted, and abnormal tissues were sectioned. For the elemental analysis, hearts, lungs, kidneys, livers, and spleens were pooled in samples of 5 to 15 from the various age groups and analyzed.

Significantly decreased body weights were noted in male mice at 90 and 540 days and female mice at 540 days. Schroeder et al. (1968) reported a significant increase in body weights in females at 60 days (see Table B.5). The study authors noted that administration of zirconium was associated with shortened life spans by 27 to 47 days in males and 67 to 85 days in females, at 5 out of 6 intervals, and that the difference in females was statistically significant. As in Schroeder et al. (1970), the study continued until natural death of each animal (see Table B.6). Schroeder et al. (1968; Kanisawa and Schroeder, 1969) noted a significant change in body weights of males at 540 days. No significant increase was noted in the number of tumors compared with control mice (see Table B.7). The study authors did not identify a NOAEL or LOAEL from this study. A LOAEL is identified by EPA because the decrease in body weight was greater than 10%. The LOAEL in male mice is 1.71 mg/kg-day while the FEL (based on significantly increased mortality) in female mice is 1.75 mg/kg-day.

Inhalation Exposures

The effects of inhalation exposure of animals to zirconium have been evaluated in four subchronic studies (Seiler et al., 1988; Brown et al., 1963; Prior et al., 1960; Clayton and Clayton, 1981−1982), and one chronic (Bingham et al., 2001) study. The aerodynamic diameters of the particles/suspensions were generally not available, so direct comparisons between studies

is difficult. The subchronic-duration data are summarized in Table 2 based on animal species; however, they are discussed in the text below based on study reports.

Short-term Studies

No studies regarding the effects of short term inhalation exposure of animals to zirconium were identified.

Subchronic Studies

Rats, guinea pigs, and dogs were exposed by inhalation to zirconium tetrachloride at 6 and 75 mg/m^3 for 60 days (Seiler et al., 1988). Dogs showed slight decreases in hemoglobin and red blood cell counts and rats and guinea pigs demonstrated increased mortality (unspecified) at 6 mg/m^3. No effects were noted with zirconium oxide at 75 mg/m^3 (Seiler et al., 1988). No further details were provided in the secondary source (HSDB, 2006) for this study. Because equivocal effects were noted at the low dose but not the high dose, neither a NOAEL nor a LOAEL is identified.

Prior et al. (1960) exposed 12 Albino rabbits to 0 or 0.049 mg sodium zirconium lactate per cubic centimeter (49,000 mg/m^3) of air, for 20 minute exposures per day for 6 weeks. All exposed animals exhibited either bronchiolar abscesses with a lobular type of pneumonia or peribronchial granulomas. These effects were not seen in the control animals. These data suggest a LOAEL of 49,000 mg/m^3 with no NOAEL.

In another study, guinea pigs exposed continuously to several steps in the zirconium reduction process for 2 to 6 months did not exhibit any pulmonary changes after a histological examination (Clayton and Clayton, 1981−1982). No further details were provided.

Chronic Studies

Zirconium tetrachloride inhaled by laboratory animals (unspecified) for 1 year at 3.5 mg/m^3 showed no adverse effects (Bingham et al., 2001). No further details were provided in the secondary source (HSDB, 2006) for this study. A NOAEL or LOAEL could not be determined due to the lack of data available on this study

Brown et al. (1963) exposed groups of 10 rats, 10 hamsters, and 10 guinea pigs for 225 days to either 15 or 150 mg/m^3 zirconium lactate, 15 mg/m^3 barium zirconate, or to room air (controls). The animals exposed to the compounds showed reduced weight gain, pathological changes consistent with chronic interstitial pneumonitis, very little deposition of fibrous tissue, no granuloma, and an increase in the zirconium content of the lung tissue.

Developmental Studies

No studies regarding the effects of inhaled zirconium on the fetal development of animals were identified.

Reproductive Studies

No studies regarding the effects of inhaled zirconium on the reproduction of animals were identified.

Other Routes of Exposure

The effects of injection exposure of animals to zirconium have been evaluated in six short-term studies (Stookey et al., 1967; Harding, 1948; Shima et al., 1987; Shelley and Raque, 1971; Ikarashi et al., 1996; Kang et al., 1977). The effects of implant exposure have been evaluated in one chronic study (Takamura et al., 1994).

Injection

Stookey et al. (1967) determined the toxic reaction of rats and guinea pigs to zirconium silicate (20% concentration) or sodium zirconium lactate injections (20% and 45% concentration). In rats, zirconium silicate injections resulted in a mild inflammatory reaction in the oral mucosa, subcutaneous tissues, and intramuscular tissues. Sodium zirconium lactate injections resulted in a destructive granulomatous reaction in the above tissues, and also in the periosteal tissue. In guinea pigs, zirconium silicate injections resulted in a mild inflammatory reaction in the oral mucosa, subcutaneous tissues, periosteal tissue, and intramuscular tissue, while sodium zirconium lactate injections resulted in a destructive granulomatous reaction in the above tissues. In another study by Stookey et al. (1967), rats were injected with 50 mg zirconium silicate to muscle tissue. A mild inflammatory reaction was noted in the subcutaneous and intramuscular tissues, with no necrosis identified. In a third study, Stookey et al. (1967) histologically examined gingival tissue in rats administered an oral paste containing 75% zirconium silicate and 25% distilled water. No unusual tissue response was observed and only an occasional mild local inflammatory response was reported. No NOAEL or LOAEL are established because of lack of relevance of this route of exposure to oral or inhalation routes.

Six rats were injected intratracheally with 1 mL of a 10% solution of zirconium silicate (Harding, 1948). Three rats were killed after 7 and 9 months and their lungs examined microscopically. Most of the zirconium silicate was found within the alveoli and lymph vessels of the lungs and a small amount was noted within phagocytic cells. Swollen histiocytes were observed in a few alveoli. Fibrosis was not noted. In another study by Harding (1948), a rabbit received 4 doses intravenously over 1 week of a 5 mL suspension of a 10% solution of zirconium silicate. The rabbit was killed 33 weeks later. Clumps of crystals were observed in the Kupfer cells. Smaller clumps were also noted in the spleen and alveolar walls and fibrosis was detected.

Shima et al. (1987) studied the effects of zirconium oxychloride on the humoral immune system in mice. This was done in two different experiments by measuring IgM antibody production against sheep red blood cells by the method of hemolytic plaque formation. For both experiments, splenic cells were collected from mice immunized with 10% sheep red blood cells and cell suspensions were prepared. In the first experiment, male mice were injected intraperitoneally once with 0, 1.7, 3.4, 17, or 34 mg/kg zirconium oxychloride. The mean IgM production at each dose was increased compared to controls, and was statistically significant at 1.7, 3.4, and 34 mg/kg. In the second experiment, male mice were injected with 0, 2.125, 4.25, or 8.5 mg/kg zirconium oxychloride every other day for 2 or 4 weeks. The mean IgM production in each dose showed an increase over the controls, but only the group injected with 2.125 mg/kg was statistically significantly different than the controls. The study authors suggested that long-term exposure to low levels of zirconium dust in the workplace of zirconium industries could enhance the humoral immune response, or at least the IgM immune response, and could induce a state of hypersensitivity in exposed workers.

CBA/J mice were injected intradermally in the foot pads or intraperitoneally with zirconium lactate or sodium zirconium lactate (Shelley and Racque, 1971). A biopsy at 1 week showed a nonspecific inflammatory round cell infiltrate and after 6 months, varying degrees of a granulomatous response were noted, consisting primarily of macrophages. However, none of the mice showed evidence of a delayed immune type of epithelioid cell granulomatous hypersensitivity.

A study assessed the contact sensitizing capability of zirconium chloride in guinea pigs and mice (Ikarashi et al., 1996). No sensitization responses were observed in the guinea-pig sensitization test (at an injection of 0.1 mL of 1% zirconium chloride) or in the sensitive mouse lymph node assay (at an initial intradermal injection of 50 µL of various concentrations of zirconium chloride, followed by a topical application of 25 µL of 5% zirconium chloride in 70% dimethylsulphoxide on both ears 5 days later).

In a study designed to assess the potential sensitizing ability of selected compounds, rabbits were injected with zirconium aluminum glycinate and sodium zirconium lactate (100 µg in saline solution) intradermally two times a week for 6 weeks (Kang et al., 1977). The rabbits were skin tested within 7 days following the last inoculation. Rabbits administered sodium zirconium lactate showed some marginally positive macrophage migration inhibition and skin reactivity. No positive skin reactivity was noted with zirconium aluminum glycinate. The study authors stated that delayed hypersensitivity does not appear to be associated with zirconium compounds, under the conditions of this experiment.

Implant

Solid rods containing zirconium oxide with yttrium oxide were implanted in the left thigh muscle of mice for 24 months (Takamura et al., 1994). Histological examination of the lungs, liver, heart, kidneys, spleen, pancreas, brain, adrenals, gonads, thyroid, and thighs was carried out. No increase in tumors at the implantation site was reported. In Olmedo et al. (2002) dental implants were placed in rats to observe distribution over time. The histological analysis revealed the presence of abundant intracellular aggregates of metallic particles of Ti and Zr in peritoneum, liver, lung, and spleen. No health effects were noted.

OTHER DATA

A few studies on the short-term toxicity, toxicokinetics, and genotoxicity of zirconium are available.

Short-Term Studies

The oral LD_{50} was reported to be 1688 mg/kg in rats and 655 mg/kg in mice for zirconium tetrachloride (O'Neil, 2001). The oral LD_{50} in rats was reported to be 3500 mg/kg for zirconium oxychloride (O'Neil, 2001), >10,000 mg/kg for zirconium lactate and 1980 mg/kg for barium zirconate (Brown et al., 1963).

Stookey et al. (1967) administered doses ranging from 70 to 200 g/kg body weight zirconium silicate by oral intubation to 80 albino mice, with the purpose of determining the LD_{50} for zirconium silicate. A dosage of 200 g/kg of body weight resulted in a 37.5% mortality rate in the mice. Doses greater than 200 g/kg were not tested due to limitations of the mouse gastrointestinal tract, so the LD_{50} was not determined.

Toxicokinetics

A few studies on the toxicokinetics of zirconium are available. Schroeder et al. (1970) administered 5 ppm zirconium in the drinking water and 2.66 µg/g in the feed to rats over a lifetime, and examined the accumulation in the kidney, liver, heart, lung, and spleen. Accumulation in the organs was not observed, except for male rats where significant accumulation in the spleen was noted. Schroeder et al. (1968) administered 5 ppm zirconium in the drinking water and 2.66 µg/g in the feed to mice over a lifetime and determined that zirconium accumulated in the spleen and heart.

A recent study investigated the behavior of zirconium tritide (a radioactive compound) particles in rat lungs (Zhou et al., 2010). Zirconium tritide particles (approximately 43 µg based on a 0.5 mL instillate of a 3 mg ZrT/35 mL saline solution) were instilled in the lungs of rats and the tritium clearance time was obtained by sacrificing 44 rats at 1 hour, and 1, 2, 3, 7, 14, 30, 60, 120, and 180 day postexposure to collect lungs, bronchial lymph nodes (BLN), blood, liver, kidney, and muscle tissues. While the volume surface diameter (VSD) was given, the ZrT particles was a respirable 1.73 µm, this is not directly relevant since the particles were instilled. A biokinetic model of zirconium tritide particles in the rat lung was developed and the predicted retention curves with various phases of tritium in each organ agreed with the experimental data.

Genotoxicity

Table 3 presents a summary of the genotoxicity studies on zirconium. Zirconium oxychloride was negative when tested in *Salmonella typhimurium* TA97, TA98, TA1535, TA1537, and TA100, with and without rat and hamster liver S-9 metabolic activation (Mortelmans et al., 1986). Zirconium tetrachloride also was negative in *Salmonella typhimurium* TA98, TA100, TA102, TA1537, and TA2637, without metabolic activation. When it was combined with 9-amino-acridine, it was positive for mutagenicity (Ogawa et al., 1987). Ghosh et al. (1990, 1991) administered oral doses of zirconium oxychloride at 225, 750, or 2250 mg/kg in male mice and 220, 734, or 2200 mg/kg in female mice to study the effects on bone marrow chromosomes. No increase in mitotic division frequency or in chromosomal aberrations and breaks per cell were noted at the lowest dose, while the division frequency and the number of chromosomal aberrations was increased at the higher doses, in both males and females, as compared to controls. The frequency of chromosomal aberrations was slightly higher in females than in males, but was not statistically significant. The study authors concluded that zirconium oxychloride was potentially clastogenic, the effect being directly proportional to the dose used (Ghosh et al., 1991). In a study on human peripheral blood lymphocytes (Ghosh et al., 1992), aqueous solutions of zirconium oxychloride (20 µg/mL) were added to cultures from male and female volunteers ranging in age from newborns to 60 years old. The endpoints screened were chromosome and chromatid breaks, dicentrics, and rearrangements. The frequencies of chromosomal aberrations and sister chromatid exchanges were compared between the different age groups, in both males and females. The frequency of sister chromatid exchanges increased with the age of the female volunteers, but not the males.

Table 3. Other Studies for Soluble Zirconium Compounds (CASRN 7440-67-7)

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	Zirconium oxychloride: *Salmonella typhimurium* TA97, TA98, TA1535, TA1537, TA100 (with and with S-9 metabolic activation) (In vitro)	Negative	None	Mortelmans et al. (1986)
	Zirconium tetrachloride: *Salmonella typhimurium* TA98, TA100, TA102, TA1537, TA2637 (without S-9 metabolic activation) (In vitro)	Negative	None	Ogawa et al. (1987)
	Zirconium oxychloride: Oral exposure of Swiss albino mice to 225, 750, 2,250 mg/kg (males), 220, 734, 2,200 mg/kg (females) (In vivo)	Mitotic divisional frequency not increased at 220−225 mg/kg, increased at higher doses	The percentages of total abnormalities was increased in both sexes at all doses	Ghosh et al. (1990)
	Zirconium oxychloride: Oral exposure of Swiss albino mice to 225, 750, 2,250 mg/kg (males), 220, 734, 2,200 mg/kg (females) (In vivo)	Increase in chromosomal aberrations directly proportional to dose	Zirconium as zirconium oxychloride is potentially clastogenic	Ghosh et al. (1991)
	Zirconium oxychloride: Human peripheral blood lymphocyte culture from males and females (In vitro)	Frequency of sister chromatid exchanges increased with age of female volunteers, (not male,) the frequency of other chromosomal aberrations was not related to age in either males or females	Molecular mechanism for increase in sister chromatid exchanges is not known	Ghosh et al. (1992)

DERIVATION OF PROVISIONAL VALUES

Table 4A presents a summary of noncancer reference values. Table 4B presents a summary of cancer values for zirconium.

Table 4A. Summary of Noncancer Reference Values for Soluble Zirconium Compounds (CASRN 7440-67-7)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Dose	POD Method	POD	UFc	Principal Study
Screening chronic p-RfD (mg/kg-day)	Rat/M,F	Glycosuria in urine, increased glucose and cholesterol levels	8×10^{-5}	LOAEL	0.79 mg/kg-day	10,000	Schroeder et al. (1970)
Screening subchronic p-RfD (mg/kg-day)	Rat/M,F	Glycosuria in urine, increased glucose and cholesterol levels	8×10^{-5}	LOAEL	0.79 mg/kg-day	10,000	Schroeder et al. (1970)
Subchronic p-RfC (mg/m^3)	N/A						
Chronic p-RfC (mg/m^3)	N/A						

N/A = not available

Table 4B. Summary of Cancer Reference Values for Soluble Zirconium Compounds (CASRN 7440-67-7)

Toxicity Value	Reference Value	Tumor Type or Precursor Effect	Species/Sex	Principal Study
p-OSF	N/A			
p-IUR	N/A			

N/A = not available

DERIVATION OF ORAL REFERENCE DOSES

There are no human oral studies available on zirconium and no animal subchronic studies. There are two oral chronic studies available in animals. Schroeder et al. (1970) administered 5 ppm zirconium sulfate in drinking water and 2.66 µg/g zirconium in the feed to rats over a lifetime, with a significantly increased incidence of glycosuria (study did not say if

this effect was noted in males or females or both), higher fasting serum glucose levels in females and higher serum cholesterol levels in males (see Table B.3). In mice, Schroeder et al. (1968), administered the same 5 ppm zirconium sulfate in drinking water and 2.66 µg/g zirconium in the feed over a lifetime, resulting in a significant difference in the survival rate in female mice, significantly decreased body weight in male mice at 90 and 540 days and in female mice at 540 days, and significantly increased body weight in female mice at 60 days (see Table B.5) was observed. Both studies used a single dose only (in addition to controls), and it is not clear in Schroeder et al. (1970) whether the increased incidence of glycosuria occurred in male or female rats. In Schroeder et al. (1970), there was an epidemic of virulent pneumonia in the rat colony, killing a number of animals. The authors stated that these animals were removed from the series and survival curves corrected from that time. However, the epidemic of pneumonia presents additional uncertainty about the results. The authors stated that the results from both of these studies "reveal no evidence that zirconium as fed has any biological activity, except possibly to affect body weight of older animals inconsistently". The basis of this statement is unclear given that there was increased mortality in mice. Glycosuria and higher fasting glucose levels in females and higher cholesterol levels in males were noted in the rats after zirconium exposure (Schroeder et al., 1970), and LOAELs of 0.79 mg/kg-day (males) and 0.89 mg/kg-day (females) are identified.

Due to the limitations of the database, and these studies, as discussed above, the use of these studies to derive a chronic p-RfD would result in the application of four full areas of uncertainty. EPA practice is not to develop a p-RfD with these limitations. However, Appendix A of this document contains screening values that may be useful in certain instances. Please see the attached Appendix for details.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

Due to insufficient data, no subchronic p-RfD can be derived. However, Appendix A of this document contains a screening value that may be useful in certain instances.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

Due to insufficient data, no chronic p-RfD can be derived. However, Appendix A of this document contains a screening value that may be useful in certain instances.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There are several chronic-duration inhalation studies in humans on zirconium (Bingham et al., 2001; Thoburn and Straub, 1976; Marcus et al., 1996; Liippo et al., 1993; Bartter et al., 1991; Romeo et al., 1994). However, the concentration of the zirconium in air was not reported in most of these studies or they were case reports on a single individual. Marcus et al. (1996) estimated cumulative exposure to zirconium compounds by dividing exposure into four general categories based on job titles and likely exposures in each time period. However, this exposure data is insufficient to calculate a p-RfC.

There are four subchronic inhalation studies (i.e., Seiler et al., 1988; Prior et al., 1960; Clayton and Clayton, 1981-1982; Brown et al., 1963) and one chronic (Bingham et al., 2001) inhalation study in animals for zirconium. However, for three of these studies (Seiler et al., 1988; Clayton and Clayton, 1981−1982; Bingham et al., 2001), the primary study was unavailable, and there were very few details available in the secondary sources (such as the

Hazardous Substances Data Bank [HSDB, 2006]). No details of the experimental design and few details of the results, including the numbers of animals exposed, are reported in this secondary source. The primary studies were obtained and reviewed for Prior et al. (1960) and Brown et al. (1963). However, few details are reported in these studies, including the sex of the animals in Prior et al. (1960) and the strain and the sex of the animals in Brown et al. (1963). Therefore, neither a subchronic or chronic p-RfC—nor screening values—can be derived.

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

Due to insufficient data, no subchronic p-RfC can be derived.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

Due to insufficient data, no chronic p-RfC can be derived.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No human data are available on the carcinogenicity of zirconium. Two animal studies reported no increase in tumor incidence after exposure to zirconium in the feed and drinking water for a lifetime in rats and mice (Schroeder et al., 1968, 1970; Kanisawa and Schroeder, 1969) (see Table B.7). According to the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is ***"Inadequate Information to Assess Carcinogenic Potential" of zirconium*** (see Table 5).

Table 5. Cancer WOE Descriptor for Zirconium (CASRN 7440-67-7)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	N/A	N/A	
"Likely to Be Carcinogenic to Humans"	N/A	N/A	
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No human cancer studies are available for zirconium, and two animal studies are inadequate to assess the carcinogenic potential of zirconium**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

Due to a lack of carcinogenicity data, no p-OSF can be derived.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

Due to a lack of carcinogenicity data, no p-IUR can be derived.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for zirconium. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING ORAL REFERENCE DOSES

There are no adequate subchronic- or chronic-duration studies regarding the toxicity of oral exposure to zirconium on which to derive provisional toxicity values. However, Schroeder et al. (1970) administered 5 ppm zirconium sulfate in the drinking water and 2.66 µg/g zirconium in the feed over a lifetime to rats. A significantly increased incidence of glycosuria (study did not say if this effect was noted in male or females or both) was noted. In addition, higher fasting glucose levels in females and higher cholesterol levels in males were observed (see Table B.3). In a second experiment, Schroeder et al. (1970) administered the same 5 ppm zirconium sulfate in the drinking water and 2.66 µg/g zirconium in the feed for a lifetime to mice. The health effects noted were a significant difference in the survival rate in female mice (reported in the text but not in the study table, see Table B.6). Significantly decreased body weight was observed in male mice at 90 and 540 days and female mice at 540 days, while a significant increase was observed in female mice at 60 days (see Table B.5). However, these studies used only a single dose (in addition to controls), and there was an epidemic of virulent pneumonia in the rat colony which killed a number of animals, and using these studies to derive a p-RfD also results in the application of a composite UF (UF_C) of 10,000. Thus, only a screening chronic p-RfD can be developed based on the effects noted in rats and mice after exposure to zirconium in drinking water and feed over a lifetime (Schroeder et al., 1968, 1970). While the critical effect may appear to be of minor biological significance, there is clear treatment-related mortality at higher doses. The dose provided in the study for exposure to zirconium sulfate in drinking water (i.e., 5 ppm) was converted to mg/kg-day based on standard values for body weights and food and water consumption in both male and female rats and mice (U.S. EPA, 1988), and the exposure to zirconium in feed (2.66 µg/g) was also converted to mg/kg-day using these standard values (see Table 2, see footnote d). Because the rats were exposed via drinking water and feed, the converted values in mg/kg-day were added together to obtain the total dose for both male and female rats and mice. A LOAEL of 0.79 mg/kg-day (males) and 0.89 mg/kg-day (females) is identified based on significantly increased glycosuria in the urine and higher fasting serum glucose levels in female rats and higher cholesterol levels in male rats in Schroeder et al. (1970). A LOAEL in male mice of 1.71 mg/kg-day is identified from Schroeder et al. (1968) for reduced mean body weight that was greater than 10% compared to concurrent controls. The male mouse LOAEL of 1.71 mg/kg-day strengthens the decision to use the male rat LOAEL of 0.79 mg/kg-day as the POD which, importantly, is also protective

against frank effects observed in female mice. The screening chronic p-RfD for zirconium is therefore derived based on the LOAEL in male rats (0.79 mg/kg-day) since this value was slightly lower than that in female rats (0.89 mg/kg-day) (Schroeder et al., 1970) as follows:

Adjust for daily exposure:

$LOAEL_{ADJ}$ = LOAEL × [conversion to daily dose]
= 0.79 mg/kg × (days dosed ÷ 7 days in week)
= 0.79 mg/kg × (7 ÷ 7)
= 0.79 mg/kg-day × 1
= 0.79 mg/kg-day

Screening Chronic p-RfD = $LOAEL_{ADJ} \div UF_c$
= 0.79 mg/kg-day ÷ 10,000
= **8×10^{-5} mg/kg-day Zirconium**

Table A.1 summarizes the uncertainty factors for the screening chronic p-RfD for Zirconium.

Table A.1. Uncertainty Factors for Screening Chronic p-RfD of Zirconium (CASRN 7440-67-7)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to the toxicity of zirconium.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproductive or developmental toxicity studies.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	10	A UF_L of 10 is applied because the POD was developed using a LOAEL.
UF_S	1	A UF_S of 1 is applied for using data from a chronic study to assess potential effects from chronic exposure.
UF_C	10,000	

DERIVATION OF SCREENING SUBCHRONIC ORAL REFERENCE DOSE

In the absence of data from subchronic-duration studies, the chronic screening p-RfD of 8×10^{-5} mg/kg-day is adopted as the provisional screening subchronic p-RfD.

APPENDIX B. DATA TABLES

Table B.1. Body Weights of Long-Evans Rats Administered Zirconium[a] (CASRN 7440-67-7)

Age (Days)	Control (Grams)[b]	Zirconium (Grams)[b]
Males		
30	72.1 ± 4.2	88.5 ± 2.3[c]
60	189.5 ± 6.0	204.0 ± 4.7
90	270.0 ± 8.9	285.7 ± 6.2
120	312 ± 9.3	313.7 ± 8.7
150	341.5 ± 8.9	377.5 ± 6.32[c]
180	364.7 ± 8.7	392.0 ± 6.44[e]
360	443.8 ± 14.9	405.2 ± 8.45[f]
540	507.4 ± 16.4	469.0 ± 8.13[d]
Females		
30	64.7 ± 2.1	82.1 ± 2.12[c]
60	154.2 ± 6.0	159.3 ± 1.9
90	197.1 ± 5.4	204.4 ± 1.9
120	225.2 ± 5.3	232.0 ± 2.7
150	238.8 ± 4.0	250.0 ± 2.5[e]
180	250.5 ± 4.9	263.7 ± 4.3
360	262.6 ± 5.9	267.0 ± 4.2
540	262.4 ± 9.8	299.2 ± 5.32[c]

[a]Schroeder et al. (1970).
[b]Mean ± SEM.
[c]$p < 0.005$.
[d]$p < 0.025$.
[e]$p < 0.01$.
[f]$p < 0.05$.

Table B.2. Survival and Longevity of Rats Administered Zirconium[a]

	No. Rats	Mean Age (Days)	50% Dead (Days)	75% Dead (Days)	90% Dead (Days)	Last Dead (Days)	Longevity[b] (Days)
Control male	52	819	872	974	1057	1232	1160 ± 27.8
Zirconium male	56	870	881	1019	1077	1189	1127 ± 23.0
Control female	54	910	912	1050	1157	1347	1304 ± 36.0
Zirconium female	58	935	947	1099	1187	1291	1247 ± 17.4

[a]Schroeder et al. (1970).
[b]Mean ± SEM of last 10% of animals surviving.

Table B.3. Serum Glucose and Cholesterol Levels in Rats Administered Zirconium[a]

	Age (Days)	Glucose[b] Fasting (mg/100 mL)[c]	Glucose[b] Nonfasting (mg/100 mL)[c]	Cholesterol (mg/100 mL)[c]
Control males	718	106.5 ± 3.6	134.4 ± 5.1	77.5 ± 2.1
Zirconium males	921	106.1 ± 9.9	133.3 ± 4.7	89.7 ± 5.6[d]
Control females	698	79.6 ± 8.2	114.2 ± 5.4	116.0 ± 6.0
Zirconium females	921	111.4 ± 5.6[e]	120.5 ± 3.3	100.7 ± 9.0

[a]Schroeder et al. (1970).
[b]Difference between fasting and nonfasting levels of glucose were significant in all groups of males.
[c]Mean ± SEM.
[d]$p < 0.01$.
[e]$p < 0.005$.

Table B.4. Mean Heart and Body Weights of Rats and Gross Tumors[a]

	No. Rats Autopsied	Weight at Death (Grams)	Heart Weight (mg)	Ratio × 1000 (Heart Wt/ Body Wt)	Tumors (No.)	Tumors (%)
Control males	50	334	1498	4.49	10	20.0
Zirconium males	46	324	1280	3.95	7	15.2
Control females	39	234	949	4.06	14	35.9
Zirconium females	53	244	1019	4.18	20	37.7

[a]Schroeder et al. (1970).

Table B.5. Body Weights of Mice Administered Zirconium[a]

Age (Days)	Control (Wt−Grams)[b]	Zirconium (Wt−Grams)[b]
Males		
30	26.0 ± 0.68	26.6 ± 1.19
60	39.1 ± 0.68	39.2 ± 0.93
90	45.2 ± 0.75	42.8 ± 0.90[c]
120	49.3 ± 1.06	48.2 ± 0.93
150	52.0 ± 1.42	51.0 ± 0.75
180	51.6 ± 1.38	51.1 ± 1.06
360	56.8 ± 2.16	54.7 ± 1.40
540	58.0 ± 1.91	50.3 ± 2.59[d]
Females		
30	22.1 ± 0.42	20.1 ± 0.49
60	28.6 ± 0.54	30.4 ± 0.55[c]
90	35.1 ± 0.56	35.1 ± 1.29
120	38.2 ± 0.89	39.0 ± 1.03
150	44.0 ± 0.98	42.6 ± 1.52
180	45.2 ± 0.80	43.8 ± 0.94
360	54.3 ± 1.48	53.5 ± 1.12
540	55.2 ± 1.45	50.7 ± 1.20[d]

[a]Schroeder et al. (1968).
[b]Mean ± SEM.
[c]$p < 0.025$.
[d]$p < 0.01$.

Table B.6. Life Span of Mice Administered Zirconium[a]

	No. Mice	Mean Age (Days)	Median Age (Days)	75% Dead (Days)	90% Dead (Days)	Last Dead (Days)	Longevity[b] (Days)
Control male	54	540	570	637	692	913	805 ± 34.3
Zirconium male	54	520	543	599	645	832	760 ± 17.4[c]
Control female	54	618	625	745	770	951	855 ± 29.3
Zirconium female	53	580	558	660	800	955	901 ± 21.0

[a]Schroeder et al. (1968).
[b]Mean ± SEM.
[c]$p < 0.025$.

Table B.7. Tumors in Mice Administered Zirconium[a]

	Control	Zirconium
No. of mice	71	72
Type of tumor		
Benign epithelial	16	10
Malignant epithelial	4	4
Benign nonepithelial	0	0
Malignant nonepithelial	4	1
Pretumorous, liver	1	0
Total lesions	25	15
Location of tumor		
Lung	15 (3)	9 (3)
Liver	4	3 (1)
Mammary gland	1 (1)	
Other	4 (4)	3 (1)
Total tumors	24 (8)	15 (5)
% with tumors	33.8	20.8

[a]Kanisawa and Schroeder (1969).

Note: Numbers in parentheses indicate number malignant.

APPENDIX C. BMD OUTPUTS

Appendix C is not applicable.

APPENDIX D. REFERENCES

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