Development Support Document
Final September 2, 2016

Cadmium and Cadmium Compounds

CAS Registry Numbers:

Cadmium 7440-43-9
Cadmium Carbonate 513-78-0
Cadmium Chloride 10108-64-2
Cadmium Oxide 1306-19-0
Cadmium Sulfate 10124-36-4
Cadmium Sulfide 1306-23-6

Prepared by
Joseph T. Haney, Jr., M.S.
Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

TABLE OF CONTENTS

List of Tables

List of Figures

Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ADAF	age-dependent adjustment factor
AEGL	air exposure guideline level
AMAD	activity median aerodynamic diameter
ATSDR	Agency for Toxic Substances and Disease Registry
AMCV	Air Monitoring Comparison Values
BMD	benchmark dose
$BMDL_{10}$	BMD 95% lower confidence limit at the 10% response level
C	concentration
°C	degrees Celsius
CalEPA	California Environmental Protection Agency
Cd	cadmium
DF	deposition fraction in the target region of the respiratory tract
DNA	deoxyribonucleic acid
DSD	development support document
E	expected (number of lung cancer mortalities)
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold (e.g., linear) dose-response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose-response noncancer effect
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
GSD	geometric standard deviation
h	hour(s)
HEC	human equivalent concentration
HQ	hazard quotient
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IRIS	Integrated Risk Information System
LCL	95% lower confidence limit
LEC_{10}	effective concentration 95% lower confidence limit at 10% response level
LMW	low molecular weight
LOAEL	lowest-observed-adverse-effect-level
m^3	cubic meter of air

Acronyms and Abbreviations	Definition
µg	microgram
µm	micrometer
mg	milligram
mL	milliliter
MLE	maximum likelihood estimate
MW	molecular weight
MMAD	mass median aerodynamic diameter
MPPD	multiple pass particle dosimetry
MOA	mode of action
MRL	Minimal Risk Level
NA	not applicable
NOAEL	no-observed-adverse-effect-level
NTP	National Toxicology Program
O	observed (number of lung cancer mortalities)
pHC	human complex-forming glycoprotein
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
PPE	personal protective equipment
RBP	retinol binding protein
RDDR	regional deposited dose ratio
ReV	Reference Value
RfC	Reference Concentration
SE	Standard Error
SMR	standardized mortality ratio
σ_g	geometric standard deviation
T	time or exposure duration
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UCD_{10}	urinary cadmium dose at the 10% response level
UCL	95% upper confidence limit
$UCDL_{10}$	UCD 95% lower confidence limit at the 10% response level
$UCDU_{10}$	UCD 95% upper confidence limit at the 10% response level
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor

Acronyms and Abbreviations	Definition
UNEP	United Nations Environment Programme
USEPA	United States Environmental Protection Agency
V_E	minute ventilation
VE_{ho}	default occupational ventilation rate for an 8-h day
VE_h	default non-occupational ventilation rate for a 24-h day

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from the acute and chronic evaluations of cadmium. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2015) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 presents chemical and physical properties of cadmium and cadmium compounds.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	**Concentration**	**Notes**
Acute ReV [1-h] (HQ = 1.0)	18 µg Cd/m^3 **1-h Short-Term Health**	**Critical Effect(s):** Immunotoxicity (i.e., decreases in specific antibody-producing spleen cells) in mice
Acute ReV [24-h] (HQ = 1.0)	0.55 µg Cd/m^3 **24-h Short-Term Health** [a]	**Critical Effect(s):** Pulmonary effects (i.e., alveolar histiocytic infiltrate and focal inflammation in alveolar septa) in rats
$^{acute}ESL_{odor}$	- - -	Odorless
$^{acute}ESL_{veg}$	- - -	Insufficient Data
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	0.011 µg Cd/m^3 **Long-Term Health**	**Critical Effect(s):** Kidney/renal effects (i.e., β2-microglobulin proteinuria) in humans
$^{chronic}ESL_{nonthreshold(c)}$	0.020 µg Cd/m^3 [b]	**Critical Effect(s):** Lung cancer in industrial workers
$^{chronic}ESL_{veg}$	- - -	Insufficient Data

[a] The acute 24-h ReV will be used for the evaluation of 24-h air monitoring data, although the 1-h ReV may be used as appropriate in the event air sampling is conducted over a comparable duration.
[b] Based on the inhalation unit risk factor (URF) of 4.9E-04 per µg Cd/m^3 and a no significant risk level of 1 in 100,000 excess cancer risk, and applicable to all forms of cadmium compounds.

Abbreviations used in Tables 1 and 2: **µg/m^3**, micrograms per cubic meter; **h**, hour; **HQ**, hazard quotient; **ESL**, Effects Screening Level; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL$_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effects; **^{chronic}ESL$_{threshold(nc)}$**, chronic health-based ESL for threshold dose-response noncancer effects; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL.

Table 2. Air Permitting Effects Screening Levels (ESLs)

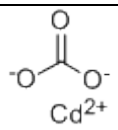
Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1-h] (HQ = 0.3)	5.4 µg Cd/m^3 [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Immunotoxicity (i.e., decreases in specific antibody-producing spleen cells)
$^{acute}ESL_{odor}$	- - -	Odorless
$^{acute}ESL_{veg}$	- - -	Insufficient Data
Long-Term Values [d]	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	0.0033 µg Cd/m^3 [b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Kidney/renal effects (i.e., β2-microglobulin proteinuria) in humans
$^{chronic}ESL_{nonthreshold(c)}$	0.020 µg Cd/m^3 [c]	**Critical Effect(s):** Lung cancer in industrial workers
$^{chronic}ESL_{veg}$	- - -	Insufficient Data

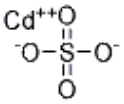
[a] Based on the acute 1-h ReV of 18 µg Cd/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on chronic ReV of 0.011 µg Cd/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[c] Based on the URF of 4.9E-04 per µg Cd/m^3 and a no significant risk level of 1 in 100,000 excess cancer risk, and applicable to all forms of cadmium compounds.

Table 3. Chemical and Physical Properties of Cadmium (Cd) and Compounds [a]

Parameter	Value	Value	Value
Name of Chemical	Cadmium	Cadmium carbonate	Cadmium chloride
Molecular Formula	Cd	$CdCO_3$	$CdCl_2$
Chemical Structure	Cd		
Molecular Weight	112.41	172.42	183.32
Physical State	Lustrous metal	Powder or rhombohedral leaflets	Rhombohedral crystals
Color	Silver-white	White	White
Odor	Odorless	No data	Odorless
CAS Registry Number	7440-43-9	513-78-0	10108-64-2
Synonyms	Colloidal cadmium	Otavite; cadmium monocarbonate; carbonic acid; cadmium salt	Caddy; Vi-Cad; cadmium dichloride; dichlorocadmium
Solubility in water (mg/L)	Insoluble	Insoluble	Soluble
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	7.5E-03 at 257°C	No data	10 at 656°C
Density (g/cm^3)	8.65 at 25°C	4.58 at unspecified °C	4.047 at 25°C
Melting Point	321°C	Decomposes at 357°C	568°C
Boiling Point	765°C	No data	960°C

Parameter	**Value**	**Value**	**Value**
Name of Chemical	Cadmium oxide	Cadmium sulfate	Cadmium sulfide
Molecular Formula	CdO	$CdSO_4$	CdS
Chemical Structure			
Molecular Weight	128.41	208.47	144.48
Physical State at 25°C	Infusible powder or cubic crystals	Monoclinic crystals (hydrate)	Cubic or hexagonal structure
Color	Dark brown	Colorless	Light yellow or orange; brown
Odor	Odorless	Odorless	No data
CAS Registry Number	1306-19-0	10124-36-4	1306-23-6
Synonyms	Aska-Rid; cadmium fume; cadmium monoxide	Cadmium sulphate; sulfuric acid; cadmium (2+) salt	Cadmium monosulfide; cadmium yellow; cadmium orange; cadmopur yellow; greenockite; capsebonb
Solubility in water (mg/L)	Insoluble	Soluble	1.3 at 18°C
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	1 at 1,000°C	No data	No data
Density (g/cm^3)	8.15 (crystals) and 6.95 (amorphous powder) at unspecified °C	4.69 at unspecified °C	4.82 (hexagonal) and 4.5 (cubic) at unspecified °C
Melting Point	Decomposes at 950°C	1,000°C	1,750°C
Boiling Point	No data	No data	No data

[a] Based on Tables 4-1 and 4-2 of ATSDR (2012).

Chapter 2 Major Uses or Sources and Ambient Air Concentrations

2.1 Major Uses and Sources

Most of the following information on the uses and sources of cadmium and cadmium compounds was taken directly from IARC (2012).

2.1.1 Uses

Cadmium metal has specific properties that make it suitable for a wide variety of industrial applications. These properties include: excellent corrosion resistance, low melting temperature, high ductility, and high thermal and electrical conductivity (National Resources Canada 2007). Cadmium is used and traded globally as a metal and component in six classes of products, where it imparts distinct performance advantages. According to the US Geological Survey (USGS), the principal uses of cadmium in 2007 were: nickel-cadmium (Ni-Cd) batteries (83%), pigments (8%), coatings and plating (7%), stabilizers for plastics (1.2%), and other (includes non-ferrous alloys, semiconductors and photovoltaic devices) (0.8%) (USGS 2008). Thus, the primary use of cadmium is in electrodes for Ni-Cd batteries (in the form of cadmium hydroxide). Because of their performance characteristics (e.g., high cycle lives, excellent low- and high-temperature performance), Ni-Cd batteries are used extensively in the railroad and aircraft industry (for starting and emergency power) and in consumer products (e.g., cordless power tools, cellular telephones, camcorders, portable computers, portable household appliances and toys) (ATSDR 2008; USGS 2008).

Cadmium sulfide compounds are used as pigments in a wide variety of applications. These applications include engineering plastics, glass, glazes, ceramics, rubber, enamels, artist colors, and fireworks. Ranging in color from yellow to deep-red maroon, cadmium pigments have good covering power, and are highly resistant to a wide range of atmospheric and environmental conditions (e.g., the presence of hydrogen sulfide or sulfur dioxide, light, high temperature and pressure) (Herron 2001; ATSDR 2008; International Cadmium Association 2011).

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel, aluminum, and other non-ferrous metals. They are particularly suitable for industrial applications requiring a high degree of safety or durability (e.g., aerospace industry, industrial fasteners, electrical parts, automotive systems, military equipment, and marine/offshore installations). This is because they demonstrate good corrosion resistance in alkaline or salt solutions, have a low coefficient of friction and good conductive properties, and are readily solderable (UNEP 2008; International Cadmium Association 2011).

Cadmium salts of organic acids were widely used in the past as heat and light stabilizers for flexible polyvinyl chloride and other plastics (Herron 2001; UNEP 2008). Small quantities of cadmium are used in various alloys to improve their thermal and electrical conductivity, to increase the mechanical properties of the base alloy (e.g., strength, drawability, extrudability, hardness, wear resistance, tensile, and fatigue strength), or to lower the melting point. The metals

most commonly alloyed with cadmium include copper, zinc, lead, tin, silver, and other precious metals. Other minor uses of cadmium include cadmium telluride and cadmium sulfide in solar cells, and other semiconducting cadmium compounds in a variety of electronic applications (Morrow 2001; UNEP 2008; International Cadmium Association 2011).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead, and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement, and phosphate fertilizers (International Cadmium Association 2011). Cadmium is also produced from recycled materials (e.g., Ni-Cd batteries, manufacturing scrap) and some residues (e.g., cadmium-containing dust from electric arc furnaces) or intermediate products. Recycling accounts for approximately 10-15% of the production of cadmium in developed countries (National Resources Canada 2007).

Major uses for some specific cadmium compounds include (Huff et al. 2007):

- Cadmium chloride - preparation of cadmium sulfide, dying and calico printing, electroplating, pigment manufacture, and vacuum tubes (previously used as a fungicide);
- Cadmium hydroxide - alkaline batteries;
- Cadmium nitrate - glass and porcelain colorant and photographic emulsions;
- Cadmium oxide - sliver zinc storage batteries, heat stabilizers for plastics and alloys;
- Cadmium sulfate - intermediate and electroplating;
- Cadmium stearate - lubricant and plastic stabilizer; and
- Cadmium sulfide – pigment.

2.1.2 Sources

In the earth's crust, cadmium appears mainly in association with ores containing zinc, lead, and copper (in the form of complex oxides, sulfides, and carbonates). Elemental cadmium is a soft, silver-white metal, which is recovered as a by-product of zinc mining and refining. The average terrestrial abundance of cadmium is 0.1-0.2 mg/kg, although higher concentrations are found in zinc, lead, and copper ore deposits (National Resources Canada 2007; ATSDR 2008; UNEP 2008).

Particulate cadmium (as elemental cadmium and cadmium oxide, sulfide, or chloride) is emitted to the atmosphere from both natural and anthropogenic sources. Weathering and erosion of cadmium-bearing rocks is the most important natural source of cadmium. Other natural sources include volcanoes, sea spray, and forest fires. However, the majority (85-90%) of airborne cadmium emissions worldwide are from anthropogenic sources. The principal anthropogenic sources are non-ferrous metal production and fossil fuel combustion, followed by ferrous metal production, waste incineration, and cement production (WHO 2000; ATSDR 2008; UNEP 2008). More specifically, major industrial sources of cadmium emissions include zinc, lead, copper, and cadmium smelting operations, coal and oil-fired boilers, other industrial (and urban)

emissions, phosphate fertilizer manufacturing, road dust, and municipal and sewage sludge incinerators. Additional sources that contribute negligible amounts of cadmium are rubber tire wear, motor oil combustion, cement manufacturing, and fertilizer and fungicide application (ATSDR 2012).

2.2 Ambient Air Levels and Other Exposures

Although industrial activities are the main sources of cadmium releases to air, anthropogenic cadmium emissions have decreased by over 90% in the last 50 years. Based on the US facilities required to report to the Toxics Release Inventory in 2009, cadmium and cadmium compound releases to air account for less than 0.5% of the estimated total environmental cadmium releases (Tables 6-1 and 6-2 of ATSDR 2012). Cadmium is emitted into the atmosphere predominantly as elemental cadmium and cadmium oxide, and from some sources as cadmium sulfide (coal combustion and nonferrous metal production) or cadmium chloride (refuse incineration). Once in the air, elemental cadmium is rapidly oxidized to cadmium oxide (WHO 2000). Atmospheric cadmium exists mainly in the forms of cadmium oxide, the primary form in occupational exposures (as dust or fume), and cadmium chloride and sulfate (Morrow 2001; Maret and Moulis 2013; ATSDR 2012; UNEP 2010).

Most of the cadmium that occurs in air is associated with particulate matter in the respirable range (diameter 0.1-1 µm; i.e., < $PM_{2.5}$), and mean cadmium concentrations in ambient air vary (WHO 2000). From 2005-2014, annual averages at ambient air monitoring sites in Texas ranged from not detected to 0.003 µg Cd/m^3 ($PM_{2.5}$ or PM_{10}), with nondetects driving the vast majority of annual site means as well as the statewide mean of approximately 0.0008 µg Cd/m^3. Maximum 24-hour concentrations ranged from not detected to 0.06 µg Cd/m^3, with the vast majority of maximum concentrations being below 0.01-0.02 µg Cd/m^3 (Texas Air Monitoring Information System (TAMIS) data for 2005-2014).

However, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake. For example, vegetables (e.g., particularly leafy vegetables such as lettuce and spinach) have the highest concentrations of cadmium. Peanuts, soybeans, and sunflower seeds also have naturally high levels of cadmium. Additionally, shellfish and organ meats (e.g., liver) have high levels of cadmium as they tend to accumulate cadmium. Smoking is also a significant source of cadmium exposure (e.g., smoking one pack of cigarettes per day results in an absorbed dose ≈ 1-3 µg/day) (ATSDR 2012).

Chapter 3 Acute Evaluation

In addition to deriving a 1-hour (h) acute ReV, a 24-h acute ReV was also developed. The cadmium monitoring data that the TCEQ collects are based on a 24-h sampling duration. Thus, development of a 24-h acute ReV for cadmium will allow the TCEQ to more fully evaluate available monitoring data. Additionally, a longer duration (e.g., 24 h) is consistent with the longer multiple-day, subacute exposure duration studies available in the toxicological database for cadmium. Two studies were identified as key studies for derivation of the acute 1- and 24-h

ReVs for cadmium (Graham et al. 1978; NTP 1995) and are described in the relevant sections below (Sections 3.1 and 3.2).

The TCEQ will develop both acute and chronic values based on the cadmium content of the compound(s) in the key studies (i.e., on a cadmium equivalent basis (μg Cd/m^3)). The cadmium equivalent for a given dose of a cadmium compound is based on the percent of the compound's molecular weight that cadmium comprises (i.e., the compound's concentration in $\mu g/m^3$ × (MW of cadmium in compound / MW of compound)). From a protection of public health perspective, use of cadmium equivalents assumes that other forms are equally as toxic as the compound(s) in the key study on a μg Cd/m^3 basis. This science policy decision is necessary given the lack of available studies to derive separate values for every cadmium compound and is consistent with the approach of other agencies (e.g., ATSDR). However, the derived acute and chronic ReV and ESL values are expected to be sufficiently health-protective regardless of the environmental chemical form (e.g., cadmium oxide, sulfide, or chloride) because they will be based on the cadmium compound(s) that have produced adverse effects at the lowest concentrations (i.e., the most toxic form(s) in the most sensitive species based on a robust database), which is the most conservative health-protective choice.

3.1 Health-Based Acute 1-h ReV and ^{acute}ESL

3.1.1 Physical/Chemical Properties

Cadmium (Cd) is a soft, ductile, silver-white metal with relatively low melting (321°C) and boiling (765°C) points and a relatively high vapor pressure. In the air, cadmium is rapidly oxidized into cadmium oxide. However, when reactive gases or vapor such as carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide or hydrogen chloride are present, cadmium vapor reacts to produce cadmium carbonate, hydroxide, sulfite, sulfate or chloride, respectively. These compounds may be formed in chimney stacks and emitted to the environment. Several inorganic cadmium compounds are quite soluble in water (e.g., cadmium acetate, chloride, and sulfate), whereas cadmium oxide, carbonate, and sulfide are almost insoluble (WHO 2000).

Table 3 provides summary physical/chemical data for cadmium and cadmium compounds (ATSDR 2012). The chemical/physical properties of cadmium and compounds have potential toxicological implications. For example, the deposition of inhaled cadmium in the lungs varies 10-50% depending on the size of airborne particles. Additionally, the absorption of cadmium from the lungs depends on the chemical nature of the particles deposited (e.g., absorption is around 50% for cadmium oxide but considerably less for insoluble salts such as cadmium sulfide) (WHO 2000). These results suggest the potential for greater toxicity by the relatively more soluble cadmium compounds (e.g., cadmium chloride, cadmium oxide fume, cadmium carbonate) compared to the less soluble compounds (e.g., cadmium sulfide) due to higher lung absorption and retention times, and greater mucociliary clearance for the less soluble compounds. For example, for acute exposures, it appears that the relatively more soluble cadmium compounds (e.g., cadmium chloride, cadmium oxide fume, cadmium carbonate compounds) have been reported to be more toxic than the relatively less soluble cadmium

compounds (e.g., cadmium sulfide compounds) (Klimisch 1993; Rusch et al. 1986). However, Glaser et al. (1986) demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide (dust) in biological fluids may be greater than its solubility in water. Thus, although the different forms of cadmium have similar toxicological effects by the inhalation route, quantitative differences may exist from different absorption and distribution characteristics, particularly for the less soluble cadmium pigments such as cadmium sulfide and cadmium selenium sulfide (ATSDR 2012).

More information and discussion on the chemical/physical properties of cadmium and cadmium compounds may be found elsewhere (e.g., see Section 4 of ATSDR 2012).

3.1.2 Key and Supporting Studies for 1-h ReV

3.1.2.1 Key Study (Graham et al. 1978)

Six-week old Swiss albino female mice (20-25 g), strain CD-1, were exposed to aerosolized cadmium chloride for 2 h. On a cadmium content basis, exposure concentrations were 0 (n=20), 110 µg Cd/m^3 (n=17), and 190 µg Cd/m^3 (n=16) (actual metal concentrations determined by atomic absorption spectrophotometry). Exposures took place inside individual containment modules inserted into exposure chambers that only allowed head exposure. Particles were generated using a modified fluid atomization aerosol generator (Environmental Research Corp., St. Paul, Minnesota) and monitored with an aerosol particle monitor (Royco Instruments, Palo, Alto, California). Ninety-nine percent of the particles were ≤ 3 µm in diameter. Two hours after aerosol exposure, all animals, including controls, were immunized with a sheep red blood cell suspension injected intraperitoneally. A direct Jerne plaque assay technique was used to test the immunoglobulin M (IgM) antibody-producing capability of spleen cells harvested on the fourth day after immunization, with cells from each mouse plated in triplicate. The number of plaques per plate was converted to the number of plaques per 10^6 cells for analysis. The number of plaques per 10^6 cells was significantly decreased ($p < 0.05$) at the lowest-observed-adverse-effect-level (LOAEL) of 190 µg Cd/m^3. This LOAEL indicates that a significant decrease in the number of specific antibody-producing spleen cells (i.e., suppression of the primary humoral immune response) is the most sensitive adverse effect for exposure durations relevant to development of the acute 1-h ReV (see Sections 3.1.2.2 and 3.1.2.3). Similarly, 1-h exposure to 880 µg Cd/m^3 as cadmium chloride decreased the humoral immune response in mice in another study (Krzystyniak et al. 1987). No significant difference was reported between the number of plaques per 10^6 cells in the control group versus the mice exposed to the no-observed-adverse-effect-level (NOAEL) of 110 µg Cd/m^3. This NOAEL will serve as the point of departure (POD) for derivation of the acute 1-h ReV (data were not amenable to benchmark dose (BMD) modeling).

3.1.2.2 Supporting Studies

The Takenaka et al. (2004) study is used as the key study for development of AEGL-1 values (AEGL 2010). Since this study provides a higher POD for a longer exposure duration than

Graham et al. (1978), it is used as a supporting study here. The following information on Takenaka et al. (2004) was taken almost verbatim from AEGL (2010).

Twenty-four female Fischer 344 rats were exposed for 6 h to ultrafine particles of cadmium oxide at a concentration of 70 μg Cd/m^3 in whole-body chambers (330 L volume; ventilation 28 exchange of 20 times/h). The mass median aerodynamic diameter (MMAD) was 40 nm with a geometric standard deviation (GSD) of 1.6. Four rats were sacrificed immediately after exposure and on days 1, 4, and 7 for morphology and elemental analysis. Eight rats were sacrificed on day 0 for lung lavage. An additional 16 rats were exposed to 550 μg Cd/m^3 in a similar manner. The MMAD was 51 nm and the GSD was 1.7. Eight rats were sacrificed on day 0 for lung lavage and four rats were sacrificed on days 0 and 1 for morphology and elemental analysis. Twelve animals for each exposure were used as controls, and exposed to clean air only. Just after exposure, cadmium in the lungs of rats exposed to 70 μg Cd/m^3 was 19% of the total inhaled dose and this level remained the same at the other time points. A slight but significant increase of cadmium in the liver was observed only in the rats sacrificed 7 days after exposure. The lung lavage indicated no exposure-related morphological changes in the lungs or inflammatory responses in the low-dose rats. In rats exposed to the higher concentration, 550 μg Cd/m^3, cadmium content was similar in the lungs on day 0 and 1 but was significantly elevated in the liver and kidneys on both days, and 2/4 of the rats had increased blood Cd. Lung lavage of the rats in the high-dose group (550 μg Cd/m^3) showed increased neutrophils, and multifocal alveolar inflammation was observed histologically (AEGL 2010).

Accordingly, AEGL (2010) considers 70 μg Cd/m^3 and 550 μg Cd/m^3 as the 6-h NOAEL and LOAEL values, respectively, for morphological changes in the lungs and inflammatory response in rats. However, the 2-h LOAEL of 190 μg Cd/m^3 from the key study (Graham et al. 1978) adjusted for exposure duration (2-h to 1-h adjustment of 190 μg Cd/m^3 to 239 μg Cd/m^3) and cross-species dosimetry (239 μg Cd/m^3 × regional deposited dose ratio (RDDR) of 4 = 956 μg Cd/m^3 as the LOAEL human equivalent concentration or $LOAEL_{HEC}$) is appreciably (2.4-fold) lower than the 6-h LOAEL from the supporting study (Takenaka et al. 2004) following exposure duration adjustment (6-h to 1-h adjustment of 550 μg Cd/m^3 to 1,000 μg Cd/m^3) and cross-species dosimetric adjustment (1,000 μg Cd/m^3 × RDDR of 2.29 = 2,290 μg Cd/m^3 as the $LOAEL_{HEC}$). This result makes use of the key study more conservative, although the Takenaka et al. (2004) study is supportive.

Likewise, concentrations of 400-450 μg Cd/m^3 as cadmium oxide for 2-3 h resulted in mild hypercellularity (bronchoalveolar junction and adjacent alveoli) and increases in absolute and relative lung weight in rats (Buckley and Bassett 1987; Grose et al. 1987). However, these data are also indicative of decreased humoral immune response as a more sensitive effect for derivation of the 1-h ReV as they correspond to higher $LOAEL_{HEC}$ values (i.e., dosimetrically-adjusted 1-h LOAEL of 577 μg Cd/m^3 × RDDR of 2.42 = 1,396 μg Cd/m^3 as the $LOAEL_{HEC}$ for Buckley and Bassett 1987; similarly, the approximate $LOAEL_{HEC}$ for Grose et al. 1987 is 1,372 μg Cd/m^3). Thus, consideration of these studies supports use of Graham et al. (1978) as the key

study and immunotoxicity (i.e., a decrease in the number of specific antibody-producing spleen cells) as the most sensitive adverse effect for derivation of the acute 1-h ReV.

3.1.2.3 Consideration of Developmental/Reproductive Effects

Based on human data, the potential for cadmium exposure to cause developmental toxicity from pre- or post-natal exposures is not known (ATSDR 2012). In regard to animal inhalation studies, several developmental studies have reported effects following subacute exposure, which are relevant to the potential of short-term exposure to cause such effects. The LOAELs for these developmental studies (with multiple-day exposures on gestational days up to 24 h/day for 21 days) range from 400-1,750 μg Cd/m^3 (NTP 1995; Prigge 1978). For example, decreased fetal body weight occurred in Swiss mice exposed to ≥ 400 μg Cd/m^3 for 6.3 h/day on gestational days 4-17, and decreased fetal body weight and reduced ossification occurred in Sprague-Dawley rats exposed to 1,750 μg Cd/m^3 for 6.3 h/day on gestational days 4-19 (NTP 1995). Decreased fetal body weight also occurred in Wistar rats exposed to 581 μg Cd/m^3 for 21 h/day on gestational days 1-21 (Prigge 1978). These developmental LOAEL values are higher than that identified based on a decreased humoral immune response (2-h LOAEL of 190 μg Cd/m^3 from Graham et al. 1978) for derivation of the 1-h ReV.

Only limited or conflicting evidence is available to evaluate the potential for cadmium exposure to cause reproductive toxicity in humans. However, adverse reproductive effects in animals have been reported due to subacute-to-chronic inhalation exposure (ATSDR 2012). These effects include increased resorptions per litter in mice exposed to 1,750 μg Cd/m^3 for 6.3 h/day on gestational days 4-17 (NTP 1995 as cited by AEGL 2010), increased duration of the estrous cycle at 880-1,000 μg Cd/m^3 in Fischer 344 and Wistar rats exposed 5-6 h/day, 5 days/week, for 13-20 weeks (Baranski and Sitarek 1987; NTP 1995), and decreased spermatid counts at 880 μg Cd/m^3 in Fischer 344 rats exposed 6 h/day, 5 days/week, for 13 weeks (NTP 1995). The NOAEL for effects on the estrous cycle and spermatid count was 220 μg Cd/m^3 (NTP 1995). Fischer 344 rats exposed to 1,060 μg Cd/m^3 6 h/day, 5 days/week, for 62 days experienced increased relative testes weight, but without loss in reproductive success (Kutzman et al. 1986). Therefore, this exposure level is considered a reproductive NOAEL (ATSDR 2012). It is noted that even the chronic exposure reproductive LOAEL values are higher than that identified based on a decreased humoral immune response (2-h LOAEL of 190 μg Cd/m^3 from Graham et al. 1978) for derivation of the 1-h ReV.

In conclusion, LOAEL values relevant to assessing the potential for developmental/reproductive effects due to short-term exposure are higher than the LOAEL value used to identify the critical effect for derivation of the 1-h ReV. For example, the subacute mouse LOAEL of 400 μg Cd/m^3 (exposed 6.3 h/day on gestational days 4-17) for decreased fetal body weight in NTP (1995) is higher than the 2-h mouse LOAEL of 190 μg Cd/m^3 for decreased humoral immune response and would result in a higher $LOAEL_{HEC}$. Consequently, the acute 1-h ReV is expected to be protective of developmental and reproductive effects.

3.1.3 Mode-of-Action (MOA) Analysis and Dose Metric

This section contains MOA information relevant to cadmium-induced adverse effects. Additional MOA information relevant to carcinogenesis is discussed in Section 4.2.2. The following information was taken directly from Section 3.5.2 of ATSDR (2012) or AEGL (2010).

> Cadmium is toxic to a wide range of organs and tissues; however, the primary target organs of cadmium toxicity are the kidneys; bone and lung (following inhalation exposure) are also sensitive targets of toxicity. Changes in the kidney due to cadmium toxicity have been well established. Chronic exposure to cadmium by the oral or inhalation route has produced renal proximal tubule damage, proteinuria (mainly low-molecular weight proteins such as β2-microglobulin), polyuria, glycosuria, amino aciduria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney (Stowe et al. 1972). Cadmium-induced renal injury initially presents as tubular proteinuria which can be quantified by measurement of low molecular weight proteins such as β2-microglobulin, retinol binding protein (RBP), and human complex-forming glycoprotein (pHC, a.k.a. α1-microglobulin). With continued exposure, the progression continues and glomerular damage occurs with a characteristic decrease in the glomerular filtration rate. For the most part, this damage is irreversible (Wittman and Hu 2002). A summary of available information relevant to cadmium's potential mechanisms of toxicity/MOAs is presented below.
>
> Cadmium has been shown to perturb lipid composition and enhance lipid peroxidation (Gill et al. 1989). Depletion of antioxidant enzymes, specifically glutathione peroxidase and superoxide dismutase, has been proposed as the mechanism of cadmium's cardiotoxic effects (Jamall and Smith 1985a), but subsequent studies showed that cardiotoxic mechanisms other than peroxidation are also present (Jamall et al. 1989). Cadmium has been shown to alter zinc, iron, and copper metabolism (Petering et al. 1979) as well as selenium (Jamall and Smith 1985b). Xu et al. (1995) propose that an initiating step in cadmium-induced toxicity to the testes is cadmium interference with zinc-protein complexes that control DNA transcription which subsequently leads to apoptosis. Cadmium sequestration by metallothionein (or a chelator in the case of the Xu et al. 1995 study) prevents cadmium from disrupting zinc-dependent transcriptional controls.
>
> Cardenas et al. (1992) investigated a cadmium-induced depletion of glomerular membrane polyanions and the resulting increased excretion of high-molecular-weight proteins. Interference with glomerular membrane polyanionic charge may precede the tubular damage as a more sensitive and early response to cadmium (Roels et al. 1993). Acute or chronic doses of cadmium have also been reported to reduce hepatic glycogen stores and to increase blood glucose levels. Intralobular fibrosis, cirrhosis, focal mononuclear infiltrates, and proliferation of the smooth

endoplasmic reticulum are among the nonspecific histopathological indicators of cadmium toxicity.

Cadmium complexed with metallothionein from the liver can redistribute to the kidney (Dudley et al. 1985). When metallothionein-bound cadmium is transported to the kidney, it readily diffuses and is filtered at the glomerulus, and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). In the kidneys, exogenous metallothionein is degraded in lysosomes and released cadmium is sequestered by the endogenous metallothionein as well as other proteins (Cherian and Shaikh 1975; Squibb et al. 1984; Vestergaard and Shaikh 1994). This non-metallothionein-bound cadmium can then induce new metallothionein synthesis in the proximal tubule (Squibb et al. 1984).

Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). The rate of metallothionein synthesis in the kidney is lower than in the liver (Sendelbach and Klaassen 1988), and is thought to be insufficient, at some point, to bind the intrarenal cadmium (Kotsonis and Klaassen 1978). Renal damage is believed to occur when the localization of cadmium, or an excessive concentration of cadmium, is unbound to metallothionein. Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage as described above (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present.

Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}cadmium-metallothionein injected (intravenously) into male Swiss mice at a non-nephrotoxic dose (0.1 mg Cd/kg) and concluded that cadmium-metallothionein-induced nephrotoxicity might be due, at least in part, to its preferential uptake of cadmium-metallothionein into the S1 and S2 segments of the proximal tubules, the site of cadmium-induced nephrotoxicity. In a companion study, Dorian et al. (1992b) reported that this preferential renal uptake was also observed after administration of various doses of [^{35}S]cadmium-metallothionein. In contrast to the earlier observed persistency of ^{109}cadmium in the kidney after ^{109}cadmium-metallothionein administration, however, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours); 24 hours after injection of [^{35}S]cadmium-metallothionein, there was very little ^{35}S left in the kidneys. These observations indicate that the protein portion of cadmium-metallothionein is rapidly degraded after renal uptake of cadmium-metallothionein and that the released cadmium is retained in the kidney.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}cadmium-metallothionein at 0.05-1 mg Cd/kg body weight and

^{109}cadmium chloride at 0.1-3 mg/kg in male Swiss mice (Dorian et al. 1995). Cadmium-metallothionein increased urinary excretion of glucose, and protein indicated renal injury, with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by cadmium chloride administration, even at dosages as high as 3 mg Cd/kg. Cadmium-metallothionein distributed almost exclusively to the kidney, whereas cadmium chloride preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after cadmium chloride administration (i.e., the renal cadmium concentration after administration of a high but non-nephrotoxic dose of cadmium chloride was equal to or higher than that obtained after injection of nephrotoxic doses of cadmium-metallothionein). Light microscopic autoradiography studies indicated that cadmium from cadmium-metallothionein preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from cadmium chloride distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after cadmium chloride than after cadmium-metallothionein administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after cadmium chloride than after cadmium-metallothionein administration. The authors suggest that cadmium-metallothionein is nephrotoxic, and cadmium chloride is not nephrotoxic because of a higher concentration of cadmium in the target cells after cadmium-metallothionein. Dorian and Klaassen (1995) evaluated the effects of zinc-metallothionein on ^{109}cadmium-metallothionein renal uptake and nephrotoxicity and concluded that zinc-metallothionein is not only nontoxic to the kidney at a dose as high as 5 μmole metallothionein/kg, but it can also protect against the nephrotoxic effect of cadmium-metallothionein without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a cadmium-metallothionein complex, Liu et al. (1998) exposed metallothionein-null mice to a wide range of cadmium chloride doses, 6 times/week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control mice (i.e., metallothionein normal) with a 150-fold increase in renal metallothionein levels (800 μg metallothionein/g kidney). Renal cadmium was much lower in metallothionein-null mice (10 μg Cd/g), and metallothionein levels were not detectable. The maximum tolerated dose of cadmium (as indicated by routine urinalysis and histopathology measures) was approximately 8 times higher in control mice than in metallothionein-null mice. Lesions were more severe in metallothionein-null mice than in controls.

The critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction also remains a topic of intense investigation. Whether the critical concentration of urinary cadmium is closer to 5 or 10 μg Cd/g creatinine, corresponding to about 100 and 200 μg cadmium/g kidney, respectively, is the

current focus of the debate. In one analysis, the critical concentration producing dysfunction in 10% of a susceptible population has been estimated to be approximately 200 μg cadmium/g kidney; 50% of the susceptible population would experience dysfunction with a kidney concentration of 300 μg/g (Ellis et al. 1984, 1985; Roels et al. 1983).

Studies in humans and animals have demonstrated that the bone is a sensitive target of cadmium toxicity. It is likely that cadmium acts by direct and indirect mechanisms, which can lead to decreased bone mineral density and increased fractures (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Studies in young animals suggest that cadmium inhibits osteoblastic activity, resulting in a decrease in the synthesis of bone organic matrix and mineralization (Brzóska and Moniuszko-Jakoniuk 2005b). The decreased osteoblastic activity may also influence osteoclastic activity leading to increased bone resorption. During intense bone growth, effects on osteoblasts result in decreased bone formation; after skeletal maturity, cadmium exposure results in increased bone resorption. Cadmium-induced renal damage can also result in secondary effects on bone (Brzóska and Moniuszko-Jakoniuk 2005a). Cadmium-induced renal damage interferes with the hydroxylation of 25-hydroxy-vitamin D to form 1,25-dihydroxy-vitamin D. Decreased serum concentration of 1,25-dihydroxy-vitamin D, along with impaired kidney resorptive function, result in calcium and phosphate deficiency (via decreased gastrointestinal absorption and increased calcium and phosphate urinary loss). To maintain calcium and phosphate homeostasis, parathyroid hormone is released, which enhances bone resorption.

Thus, an appreciable amount of information relevant to the underlying mechanisms and/or MOAs for various cadmium-induced adverse effects is available. See other sources for additional information on potential modes/mechanisms of action (e.g., Maret and Moulis 2013).

As is often the case for inhalation studies, air concentration was the only dose metric available from the key study for the acute 1-h (and 24-h) ReV. Therefore, air concentration was used as the default dose metric for derivation of the 1-h acute ReV.

3.1.4 Dosimetric Adjustments for Graham et al. (1978)

3.1.4.1 Default Exposure Duration Adjustment

The 2-h duration NOAEL/POD (C1) from Graham et al. (1978) was adjusted to a POD_{ADJ} of 1-h exposure duration (C2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity (TCEQ 2015):

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(110\ \mu g\ Cd/m^3)^3 \times (2\ h/1\ h)]^{1/3}$$
$$= 138.6\ \mu g\ Cd/m^3 = POD_{ADJ}$$

3.1.4.2 Default Dosimetry Adjustment from Animal-to-Human Exposure

The Graham et al. (1978) study was conducted in mice. Therefore, a dosimetric adjustment factor was applied to the POD_{ADJ} from Graham et al. (1978) to convert the laboratory animal POD_{ADJ} to a human equivalent concentration POD_{HEC}. Per TCEQ (2015), the TCEQ used the USEPA RDDR model as suggested in the USEPA RfC Methodology (USEPA 1994), which is the appropriate model for mice. Additionally, the extrarespiratory RDDR was selected as the appropriate output to use to develop a POD_{HEC} because the adverse effect noted in the animal study is immunotoxicity, a systemic effect as opposed to a point of contact effect occurring only in a particular portion of the respiratory system (see Section 4.3.5.2 of USEPA 1994).

In general, the RDDR model allows the adjustment of an animal concentration to a human equivalent concentration for particulate and aerosolized compounds. Parameters necessary for the RDDR model are the MMAD and GSD (σg), along with species-specific information on the mice used in the study. Graham et al. (1978) provided a weight range for the CD-1 mice used (20-25 g), but did not provide the MMAD or σg. In the absence of study-specific information on particle characteristics, USEPA (1994) allows use of particle size information from other studies to estimate the particle characteristics for the exposure in question. Several other cadmium chloride studies were considered as sources of surrogate values for the MMAD and σg (e.g., Greenspan et al. 1988; Greenspan and Morrow 1984; Boudreau et al. 1988), consistent with the recommended default approach in USEPA (1994). Based on an evaluation of sensitivity, smaller MMAD values and lower mouse body weights result in lower (i.e., more conservative) extrarespiratory RDDR values. Consequently, the low end of the mouse body weight range reported for the study (20 g) was used as it results in somewhat more conservative extrarespiratory RDDR values. Additionally, as 0.5 µm is the lowest MMAD value that the RDDR model will accept and the lowest MMAD among these studies was ≈ 0.4 µm with a σg of ≈ 1.5 (Greenspan et al. 1988; Greenspan and Morrow 1984), the calculated RDDR of 4.746 was therefore reduced to 4 (i.e., a 15.7% reduction). This RDDR is conservative considering that, for example, a reduction of 0.1 µm in the MMAD from 0.6 to 0.5 µm reduces the extrarespiratory RDDR only about 8.5%. Thus, a conservative extrarespiratory RDDR value of 4 will be used.

3.1.4.3 Calculation of the POD_{HEC}

To derive a POD_{HEC} for cadmium, the POD_{ADJ} of 138.6 µg Cd/m^3 was multiplied by the RDDR of 4 for the extrarespiratory region:

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 138.6\ \mu g\ Cd/m^3 \times 4$$
$$= 554\ \mu g\ Cd/m^3$$

where: POD_{ADJ} = duration adjusted point of departure (µg/m^3)
RDDR = regional deposited dose ratio
POD_{HEC} = dosimetrically adjusted point of departure (µg/m^3)

3.1.5 Critical Effect and Adjustments of the POD_{HEC}

The POD_{HEC} of 554 µg Cd/m^3 is based on immunotoxicity (i.e., suppression of the primary humoral immune response) as the critical effect. The acute 1-h ReV was derived based on this POD_{HEC}. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate uncertainty factors (UFs) to derive the acute ReV (i.e., assume a threshold MOA) (TCEQ 2015). A total UF of 30 was applied to the POD_{HEC} of 554 µg Cd/m^3 to derive the acute 1-h ReV: a UF_A of 3 for extrapolation from animals to humans, a UF_H of 10 to account for variability within the human population, and a UF_D of 1. The following is more specific concerning the rational for the applicable UFs:

- A UF_A of 3 was used for extrapolation from animals to humans because the RDDR program accounts for toxicokinetic differences and limits uncertainty for mouse-to-human extrapolation but does not account for toxicodynamic differences;
- A UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions); and
- A UF_D of 1 was used because the overall cadmium database is extensive (consistent with ATSDR 2012). More specifically, there are several studies that examined cadmium-induced toxicity due to 0.5-3 h exposure in more than one species (i.e., mice, rats, rabbits, hamsters). Additionally, there are multiple studies that examined reproductive endpoints and developmental toxicity studies in more than one species (i.e., rats, mice), which indicate that the acute 1-h ReV and ESL are expected to be protective of developmental and reproductive effects. Thus, the database quality is considered high for exposure durations relevant to development of the acute1-h ReV.

$$\text{acute 1-h ReV} = POD_{HEC} / (UF_A \times UF_H \times UF_D)$$
$$= 554\ \mu g\ Cd/m^3 / (3 \times 10 \times 1)$$
$$= 18.5\ \mu g\ Cd/m^3$$

3.1.6 Health-Based Acute 1-h ReV and ^{acute}ESL

The acute 1-h ReV for cadmium is 18 µg Cd/m^3 (rounded to two significant figures). The rounded 1-h ReV was then used to calculate the 1-h ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the acute 1-h ^{acute}ESL is 5.4 µg Cd/m^3 (Table 4).

Table 4. Derivation of the Acute 1-h ReV and ^{acute}ESL

Parameter	Summary
Key Study	Graham et al. (1978)
Study Population	6-week old Swiss albino mice (female)
Study Quality Confidence Level	Medium
Exposure Method	Inhalation
Critical Effect	Immunotoxicity (i.e., significant decreases in the number of specific antibody-producing spleen cells)
Exposure Duration	2 h
POD (NOAEL)	110 µg Cd/m^3
Extrapolation to 1-h	Haber's Rule, as modified by ten Berge (1986) with n=3
POD_{ADJ}	138.6 µg Cd/m^3
POD_{HEC}	554 µg Cd/m^3
Total uncertainty factors (UFs)	30
Interspecies UF	*3*
Intraspecies UF	*10*
Incomplete Database UF *Database Quality*	*1* *High*
1-h acute ReV (HQ = 1)	**18 µg Cd/m^3**
1-h ^{acute}ESL (HQ = 0.3)	**5.4 µg Cd/m^3**

3.2 Health-Based Acute 24-h ReV

3.2.1 Key and Supporting Studies for 24-h ReV

When toxicity factors are identified in the scientific literature or elsewhere (e.g., databases, ATSDR toxicological profiles), they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to develop ReVs. If so, the TCEQ considers adoption of the published toxicity factor, with preference given to values that have undergone an external peer review and public involvement process. This is the case for cadmium, for which ATSDR recently reviewed the available scientific literature and derived an acute (i.e., 14-day) inhalation minimal risk level (MRL) (ATSDR 2012). ATSDR toxicological profiles and MRLs undergo internal agency review, a public comment period, and are externally reviewed by a peer review panel. A scientific peer-reviewed literature search (through December 1, 2015) did not

identify a more suitable study than that selected by ATSDR for derivation of the acute (i.e., 14-day) MRL, or for development of a 24-h ReV. Thus, the TCEQ concurs with ATSDR's choice of key study, critical effect, and animal study POD for derivation of the acute MRL, and will use the same study POD (i.e., rat LOAEL) to derive the 24-h ReV. However, as the acute MRL applies to exposures up to 14 days, whereas the exposure duration of interest in this case is only 24 h, the exposure duration adjustment for the 24-h ReV will differ. Most of the text in the section below was taken from Appendix A of ATSDR (2012).

3.2.1.1 Key Study (NTP 1995)

Animal studies indicate that the respiratory tract is a sensitive target of toxicity following inhalation exposure to cadmium (ATSDR 2012). In NTP (1995), groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) for 6.2 h/day, 5 days/week, for 2 weeks. The mean MMAD of the cadmium oxide particles was 1.5 μm with a GSD of 1.6-1.8. The animals were observed twice daily and weighed on days 1 and 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates). Effects noted in the study and corresponding doses include:

- All rats in the 8.8 mg Cd/m^3 group died by day 6; no other deaths occurred.
- A slight decrease in terminal body weights was observed at 2.6 mg Cd/m^3; however, the body weights were within 10% of control weights.
- Significant increases in relative and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/m^3.
- Histological alterations were limited to the respiratory tract and consisted of:
    - alveolar histiocytic infiltrate and focal inflammation in alveolar septa in all rats exposed to ≥ 0.088 mg Cd/m^3;
    - necrosis of the epithelium lining alveolar ducts in all rats exposed to ≥ 0.26 mg Cd/m^3;
    - tracheobronchiolar lymph node inflammation at ≥ 0.88 mg Cd/m^3 (incidences in the 0, 0.088, 0.26, 0.88, 2.6, and 8.8 mg Cd/m^3 groups were 0/3, 0/5, 5/5, 5/5, and 3/4 in males and 0/4, 1/5, 1/5, 3/5, 5/5, and 3/5 in females);
    - degeneration of the nasal olfactory epithelium at 0.88 mg Cd/m^3 (0/5, 0/5, 0/5, 2/5, 5/5, and 5/5 in males and 0/5, 0/5, 0/5, 4/5, 4/5, and 4/4 in females); and
    - inflammation (0/5. 0/5. 0/5, 1/5, 5/5, and 3/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 3/4 in females) and metaplasia (0/5. 0/5. 0/5, 1/5, 0/5, and 5/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 4/4 in females) of the nasal respiratory epithelium at 2.6 mg Cd/m^3.

ATSDR selected the LOAEL of 0.088 mg Cd/m^3 based on alveolar histiocytic infiltrate and focal inflammation in the alveolar septa of all rats, with a dose-dependent increase in severity, as the POD for derivation of the acute (i.e., 14-day) MRL (the data were not amenable to BMD modeling). The TCEQ will utilize this same free-standing LOAEL as the POD for derivation of the 24-h ReV.

3.2.1.2 Other Studies

The following information, much of it taken directly from ATSDR (2012) and used by ATSDR to support their acute (i.e., 14-day) MRL, is also relevant to the 24-h ReV.

The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986) estimated that an 8-h exposure to 1-5 mg/m^3 would be immediately dangerous. Animal studies support the findings in humans that acute exposure to cadmium can result in lung damage. Single exposures to approximately 1-10 mg Cd/m^3 as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m^3 1 h/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). Lower concentrations of 0.4-0.45 mg Cd/m^3 as cadmium oxide for 2-3 h resulted in mild hypercellularity and increases in lung weight in rats (Buckley and Bassett 1987; Grose et al. 1987). Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m^3 as cadmium oxide 6.2 h/day, 5 days/week, for 2 weeks (critical effect for the 24-h ReV based on NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m^3 (NTP 1995). At somewhat higher concentrations (0.19 or 0.88 mg Cd/m^3 as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1-2 hours (2-h LOAEL of 0.19 mg Cd/m^3 in Graham et al. 1978; 1-h LOAEL of 0.88 mg Cd/m^3 in Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m^3 as cadmium carbonate for 2 h (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m^3 as cadmium oxide for 2 h (Rusch et al. 1986).

3.2.1.3 Consideration of Developmental/Reproductive Effects

The potential for cadmium-induced developmental/reproductive effects due to short-term exposure is discussed in Section 3.1.2.3, which indicates that developmental LOAEL values and even the chronic exposure reproductive LOAEL values are higher than the LOAEL (88 μg

Cd/m^3 from NTP 1995) identified based on pulmonary effects for derivation of the 24-h ReV and would result in a higher $LOAEL_{HEC}$. Consequently, the acute 24-h ReV is expected to be protective of developmental and reproductive effects.

3.2.2 MOA Analysis and Dose Metric

See Section 3.1.3 for a discussion of the MOA information available for cadmium. Additionally, cadmium is a direct-acting respiratory irritant (AEGL 2010; USEPA 1999), and exposure of human airway epithelial cells to cadmium has been shown to promote the *in vitro* secretion of IL-6 and IL-8 (two pivotal pro-inflammatory cytokines known to play an important role in pulmonary inflammation) in a dose-dependent manner (Rennolds et al. 2012; Cormet-Boyaka et al. 2012). Furthermore, mice exposed to cadmium intranasally *in vivo* had significant increases in murine IL-8 homologs (MIP-2, KC) in bronchoalveolar lavage (BAL) and lung tissue, a 5-fold increase in the number of neutrophils in BAL (e.g., IL-8 plays a key role in inflammation *in vivo* due to its ability to recruit and activate neutrophils and macrophage), and marked lung inflammation with a high number of inflammatory cell infiltrates. The secretion of IL-8 was reported to be mediated through an NF-κB-independent and Erk1/2-dependent pathway (Cormet-Boyaka et al. 2012).

Air concentration was the only dose metric available from the key study for the acute 24-h ReV. Therefore, air concentration was used as the default dose metric.

3.2.3 Dosimetric Adjustments for NTP (1995)

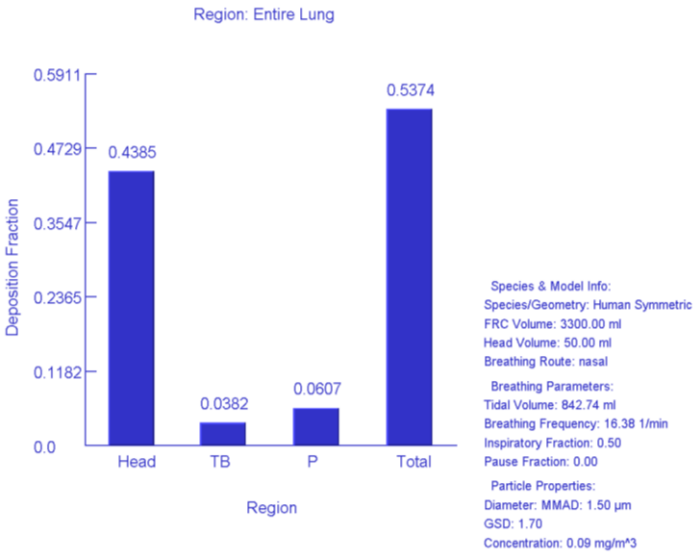
3.2.3.1 Exposure Duration Adjustment

The POD (LOAEL of 0.088 mg Cd/m^3) based on data from NTP (1995) is associated with exposure for 6.2 h/day, 5 days/week, for 2 weeks (62 h total). The acute ReV duration of interest is appreciably (2.6-fold) shorter at 24 h. However, conservatively no duration adjustment will be performed. The POD_{ADJ} is therefore the LOAEL of 0.088 mg Cd/m^3.

3.2.3.2 Default Dosimetry Adjustment from Animal-to-Human Exposure

Since NTP (1995) was conducted in laboratory animals, a dosimetric adjustment factor for particulate matter must be applied to the POD_{ADJ} to convert the animal (i.e., rat) concentration to a POD_{HEC}. The TCEQ uses the Multiple Pass Particle Dosimetry (MPPD) Model, which is an appropriate model for rats (TCEQ 2015). Consistent with Section 3.7.2.5 of TCEQ (2015) and ATSDR (2012), the TCEQ calculated the regional deposited dose ratio (RDDR) for the rat POD (LOAEL of 0.088 mg Cd/m^3) using the reported MMAD of 1.5 μm and the midpoint of the reported range of GSDs (1.7). The RDDR for the pulmonary region (1.87) is the appropriate output to develop a POD_{HEC} because the adverse effect noted in the key animal study is a pulmonary region effect (i.e., alveolar histiocytic infiltrate and focal inflammation in the alveolar septa). The human and rat MPPD modeling results for increase in relative lung weight are presented in Figure 1.

Human Output



Rat Output

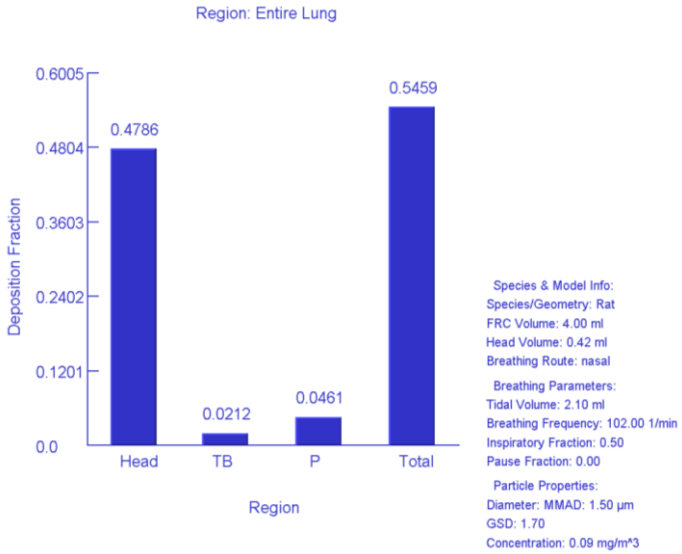


Figure 1. MPPD Model Input and Output for NTP (1995)

The deposition fractions determined from the MPPD program above were then used to calculate the RDDR for the key study:

$$RDDR = \frac{(V_E)_A}{(V_E)_H} \times \frac{DF_A}{DF_H} \times \frac{NF_H}{NF_A}$$

where:
V_E = minute volume
DF = deposition fraction in the target region of the respiratory tract
NF = normalizing factor
A = animal
H = human

$$RDDR = \frac{214.2\ mL/min}{13{,}800\ mL/min} \times \frac{0.0461}{0.0607} \times \frac{54\ m^2}{0.34\ m^2} = 1.87$$

3.2.3.3 Calculation of the POD_{HEC}

To derive a POD_{HEC} for cadmium, the LOAEL of 0.088 mg Cd/m^3 was multiplied by the RDDR of 1.87 for the pulmonary region:

$POD_{HEC} = POD_{ADJ} \times RDDR$
$= 0.088$ mg Cd/m^3 $\times$ 1.87
$= 0.165$ mg Cd/m^3
$= 165$ µg Cd/m^3

where: POD_{ADJ} = duration adjusted point of departure (mg/m^3)
RDDR = regional deposited dose ratio
POD_{HEC} = dosimetrically adjusted point of departure (mg/m^3 or µg/m^3)

3.2.4 Critical Effect and Adjustments of the POD_{HEC}

The POD_{HEC} of 165 µg Cd/m^3 was selected as the POD_{HEC} based on the critical pulmonary effects (i.e., alveolar histiocytic infiltrate and focal inflammation in the alveolar septa in NTP 1995). The acute 24-h ReV was derived based on this POD_{HEC}. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the acute ReV (i.e., assume a threshold MOA) (TCEQ 2015).

A total UF of 300 was applied to the POD_{HEC} of 165 µg Cd/m^3 to derive the acute 24-h ReV: a UF_A of 3 for extrapolation from animals to humans, a UF_H of 10 to account for variability within the human population, a UF_L of 10 for extrapolation from a LOAEL, and a UF_D of 1. These UFs are consistent with those used by ATSDR (2012). The following is more specific concerning the rational for the applicable UFs:

- A UF_A of 3 was used for extrapolation from animals to humans because the MPPD program accounts for toxicokinetic differences and limits uncertainty for rat-to-human extrapolation but does not account for toxicodynamic differences;
- A UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions);
- A UF_L of 10 was used to extrapolate from the LOAEL; and
- A UF_D of 1 was used because the overall cadmium database is extensive (consistent with ATSDR 2012). More specifically, there are several studies that examined cadmium-induced toxicity with multiple-day exposure regimens in more than one species (i.e., mice, rats) that may be used to develop shorter-term (i.e., acute/subacute) health-protective comparison values (e.g., from the 24-h ReV to the 14-day ATSDR inhalation MRL). Additionally, there are multiple studies that examined reproductive endpoints and developmental toxicity studies in more than one species (i.e., rats, mice), which indicate that the acute 24-h ReV and ESL are expected to be protective of potential developmental and reproductive effects. Thus, the database quality is considered high for exposure durations relevant to development of the acute 24-h ReV.

acute 24-h ReV = POD_{HEC} / ($UF_A \times UF_H \times UF_L \times UF_D$)

= 165 μg Cd/m^3 / (3 × 10 × 10 × 1)
= 0.55 μg Cd/m^3

3.2.5 Health-Based Acute 24-h ReV

The acute 24-h ReV for cadmium is 0.55 μg Cd/m^3 (Table 5).

Table 5. Derivation of the Acute 24-h ReV

Parameter	**Summary**
Key Study	NTP (1995)
Study Population	F344 rats
Study Quality Confidence Level	High
Exposure Method	Inhalation
Critical Effect(s)	Pulmonary effects (i.e., alveolar histiocytic infiltrate and focal inflammation in the alveolar septa)
Exposure Duration	6.2 h/day, 5 days/week, for 2 weeks
POD (LOAEL)	0.088 mg Cd/m^3 for 62-h exposure (total)
Extrapolation to 24-h	Conservatively, not performed
POD_{HEC}	165 µg Cd/m^3
Total uncertainty factors (UFs)	300
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*10*
Incomplete Database UF *Database Quality*	*1* *High*
24-h acute ReV (HQ = 1)	**0.55 µg Cd/m^3**

3.2.6 Comparison of Results

While the 24-h ReV is based on the same key study as ATSDR's acute (i.e., 14-day) MRL (0.03 µg Cd/m^3), the values are not directly comparable because of the 14-fold difference in the duration of interest. However, given that the exposure duration for the 24-h ReV is 14 times shorter, this value is approximately 18 times higher than the ATSDR 14-day MRL, which is reasonable.

3.3 Welfare-Based Acute ESLs

3.3.1 Odor Perception

Odor information is available for several cadmium compounds and indicates these compounds are odorless (i.e., a lack of odor potential) (Table 3).

3.3.2 Vegetation Effects

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne cadmium and cadmium compounds.

3.4 Acute Values for Air Permitting and Air Monitoring Evaluations

This acute evaluation resulted in the derivation of the following acute values for cadmium and cadmium compounds:

- 1-h acute ReV = 18 µg Cd/m^3
- 1-h ^{acute}ESL = 5.4 µg Cd/m^3
- 24-h acute ReV = 0.55 µg Cd/m^3

The 1-h ^{acute}ESL for air permit evaluations is 5.4 µg Cd/m^3 (Table 4). The acute 24-h ReV of 0.55 µg Cd/m^3 will be used for the evaluation of 24-h air monitoring data (Table 5), although the 1-h ReV may be used as appropriate in the event air sampling is conducted over a comparable duration (Table 4). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5 Acute and Subacute Inhalation Observed Adverse Effect Levels

Risk assessors and the general public are interested in information on air concentrations where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in Development Support Documents (DSDs) (TCEQ 2015). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies may identify a lower POD for this purpose.

3.5.1 Acute Inhalation Observed Adverse Effect Level

Regarding critical effects due to acute cadmium exposure, the animal study of Graham et al. (1978) provides a 2-h LOAEL of 190 µg Cd/m^3 for decreased humoral immune response (i.e., significant decreases in the number of specific antibody-producing spleen cells). Consistent with guidelines, no duration adjustment was made for the acute (i.e., 2-h) inhalation observed adverse effect level (TCEQ 2015). The corresponding 2-h $LOAEL_{HEC}$ is 760 µg Cd/m^3 (190 µg Cd/m^3 × RDDR of 4 = 760 µg Cd/m^3 as the $LOAEL_{HEC}$). This POD_{HEC} determined from an animal study represents a concentration at which similar effects could occur in some individuals exposed to this level over the same duration as used in the study (2 h) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The estimated acute (i.e., 2-h) inhalation observed adverse effect level of 760 µg Cd/m^3 is provided for informational purposes only (TCEQ 2015). The margin of exposure between the estimated acute (i.e., 2-h) inhalation observed adverse effect level of 760 µg Cd/m^3 and the 1-h acute ReV of 18 µg Cd/m^3 is a factor of approximately 42.

3.5.2 Subacute Inhalation Observed Adverse Effect Level

The key study (NTP 1995) for derivation of the 24-h ReV exposed animals subacutely and will be used to derive a subacute (i.e., not 24-h) inhalation observed adverse effect level. The $LOAEL_{HEC}$ of 165 µg Cd/m^3 corresponds to the laboratory animal LOAEL in NTP (1995) for pulmonary effects (i.e., alveolar histiocytic infiltrate and focal inflammation in the alveolar septa) in rats (see Section 3.2.3.3). This value was used as the subacute inhalation observed adverse effect level. This POD_{HEC} determined from an animal study represents a concentration at which similar effects could occur in some individuals exposed to this level over the same duration as used in the study (6.2 h/day, 5 days/week, for 2 weeks) or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The estimated subacute (i.e., not 24-h) inhalation observed adverse effect level of 165 µg Cd/m^3 is provided for informational purposes only (TCEQ 2015). The margin of exposure between the estimated subacute inhalation observed adverse effect level of 165 µg Cd/m^3 and the 24-h acute ReV of 0.55 µg Cd/m^3 is a factor of 300.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

When chronic toxicity factors are identified in the scientific literature or elsewhere (e.g., databases, ATSDR toxicological profiles), they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to develop chronic ReVs. If so, the TCEQ considers adoption of the published toxicity factor, with preference given to values that have undergone an external peer review and public involvement process. This is the case for cadmium, for which ATSDR derived a chronic inhalation MRL in 2012 (ATSDR 2012). The ATSDR (2012) assessment is more recent than the California EPA assessment (CalEPA 2000) and includes numerous studies not available at that time. ATSDR toxicological profiles and MRLs undergo internal agency review, a public comment period, and are externally reviewed by a peer review panel. Much of the text in the sections below was taken from ATSDR (e.g., Appendix A of ATSDR 2012).

Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations include an increase in residual volume in workers exposed to air concentrations of cadmium fumes ranging from 0.008-1.53 mg Cd/m^3 (mean urinary cadmium level in the workers was 4.3 µg Cd/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034-0.156 mg Cd/m^3

(Davison et al. 1988); and decreased force vital capacity in workers exposed to > 0.2 mg Cd/m^3 (Smith et al. 1976). *While the respiratory tract is a relatively sensitive target organ for Cd-induced toxicity, available data indicate that the kidney is the most sensitive target organ* (ATSDR 2012; USEPA 1999).

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as N-acetyl- β-glucosaminidase (NAG), amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate. *The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight (LMW) proteins* (e.g., particularly β2-microglobulin, RBP, and pHC) in cadmium workers (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Significant alterations in the prevalence of LMW proteinuria among cadmium workers has been observed at urinary cadmium levels of 1.5 μg Cd/g creatinine and higher (Chen et al. 2006a; Elinder et al. 1985; Jakubowski et al. 1987; Järup and Elinder 1994). Similarly, significant associations between urinary cadmium levels and the increased prevalence of abnormal levels of these biomarkers have been found in populations living in areas with cadmium pollution. These abnormal biomarker levels are early signs of cadmium-induced kidney damage (e.g., increased LMW proteins such as β2-microglobulin are indicative of renal dysfunction due to defective renal tubular protein reabsorption) and appear to be the most sensitive indicator of cadmium toxicity with alterations at urinary cadmium levels of 1 μg Cd/g creatinine (pHC, a.k.a. α1-microglobulin proteinuria in Järup et al. 2000) and higher (ATSDR 2012). *Similar to the ATSDR chronic inhalation MRL, the TCEQ will use cadmium-induced LMW proteinuria as the critical kidney effect in derivation of the chronic ReV and ESL.*

As mentioned in Section 3.1, the TCEQ will develop chronic values (in addition to acute values) based on the cadmium content of the compound (i.e., on a Cd equivalent basis). The cadmium equivalent for a given dose of a cadmium compound is based on its cadmium content, that is, the percent of the compound's molecular weight that cadmium comprises (i.e., the compound's concentration in μg/m^3 × (MW of Cd in compound / MW of compound)). From a protection of public health perspective, use of cadmium equivalents assumes that other forms are equally as toxic as the compound(s) in the key study on a μg Cd/m^3 basis. This science policy decision is necessary given the lack of available studies to derive individual values for every cadmium compound and is consistent with the approach of other agencies (e.g., USEPA, ATSDR). However, the derived chronic ReV and ESL values are expected to be sufficiently health-protective regardless of the environmental chemical form (e.g., cadmium oxide, sulfide, or chloride) because they will be based on the cadmium compound(s) that have produced adverse effects at the lowest concentrations (i.e., the most toxic form(s) in the most sensitive species based on a robust database), which is the most conservative (i.e., health-protective) choice.

4.1.1 Key Studies

A meta-analysis of environmental and occupational exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of adverse renal function effects in exposed populations was conducted by ATSDR for the chronic inhalation MRL:

- Environmental studies: Buchet et al. 1990; Järup et al. 2000; Jin et al. 2004; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; and Wu et al. 2001
- Occupational studies: Chen et al. 2006a, 2006b; Järup and Elinder 1994; and Roels et al. 1993

The studies were selected based on the following qualitative criteria: (1) the study measured an urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of LMW proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. The relationship between urinary cadmium and cadmium body burden was established in workers in the 1980s, and although more uncertainty exists when using urinary cadmium as an index of cadmium body burden for the general population, epidemiological studies on cadmium typically use urinary cadmium as a noninvasive measure of cumulative long-term exposure to cadmium (e.g., lifetime accumulation of cadmium in the body, such as in the kidney) (Bernard 2016; Byber et al. 2016). Studies using a cut-off value for β2-microglobulin of ≥ 1,000 μg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000-10,000 μg/g creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in glomerular filtration rate. Additionally, multiple analyses of the same study population were avoided.

See ATSDR (2012) for a discussion of these studies. An updated search of the peer-reviewed scientific literature did not reveal a more appropriate study and/or assessment for derivation of TCEQ's chronic ReV. For example, a 2015 meta-analysis of thirteen environmental studies (Woo et al. 2015) evaluating urinary cadmium and markers of renal dysfunction (e.g., β2-microglobulin, NAG) derived various pooled estimates of BMD/BMDL values that while supportive, do not provide a lower POD than that identified in Section 4.1.2 (Hu et al. 2014 is also supportive).

4.1.1.1 Consideration of Developmental/Reproductive Effects

Based on human data, the potential for cadmium exposure to cause developmental toxicity from pre- or post-natal exposures is not known (ATSDR 2012). In regard to animal inhalation studies, several developmental effects have been reported following subacute-to-chronic exposure to 20-

1,750 μg Cd/m^3 (e.g., altered performance on neurobehavioral tests, decreased fetal body weight and reduced ossification, decreased pup viability). For subacute exposure, decreased fetal body weight in Swiss mice is the effect that occurred at the lowest LOAEL (400 μg Cd/m^3 for 6.3 h/day on gestational days 4-17 in NTP 1995). In regard to developmental studies involving chronic rodent exposure (i.e., > 3-month rodent exposure), impaired performance on certain neurobehavioral tests (e.g., decreased avoidance acquisition, latency in geotaxis test) is the effect that has been identified as occurring at the lowest long-term exposure concentrations (4-5 month LOAEL range of 20-160 μg Cd/m^3 in Baranski 1984, 1985) (ATSDR 2012).

Only limited or conflicting evidence is available to evaluate the potential for cadmium exposure to cause reproductive toxicity in humans. However, adverse reproductive effects in animals have been reported due to subacute-to-chronic inhalation exposure (ATSDR 2012). These effects include increased resorptions per litter in mice exposed to 1,750 μg Cd/m^3 for 6.3 h/day on gestational days 4-17 (NTP 1995 as cited by AEGL 2010), increased duration of the estrous cycle at 880-1,000 μg Cd/m^3 in Fischer 344 and Wistar rats exposed 5-6 h/day, 5 days/week, for 13-20 weeks (Baranski and Sitarek 1987; NTP 1995), and decreased spermatid counts at 880 μg Cd/m^3 in Fischer 344 rats exposed 6 h/day, 5 days/week, for 13 weeks (NTP 1995). The NOAEL for effects on the estrous cycle and spermatid count was 220 μg Cd/m^3 (NTP 1995). As Fischer 344 rats exposed to 1,060 μg Cd/m^3 6 h/day, 5 days/week, for 62 days experienced increased relative testes weight without loss in reproductive success (Kutzman et al. 1986), this is considered a reproductive NOAEL (ATSDR 2012).

The lowest potential POD values referenced above based on developmental/reproductive endpoint data range from 20 to 220 μg Cd/m^3. These values are significantly (i.e., 200-2,200 times) higher than the POD ultimately used to derive the chronic ReV (POD of 0.1 μg Cd/m^3 for a 10% increase in the prevalence of β2-microglobulin proteinuria; ATSDR 2012). Thus, the chronic ReV and ESL are expected to be protective of developmental and reproductive effects.

4.1.2 Evaluation of Potential PODs

The individual dose-response functions from each study examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of adverse renal function effects were used by ATSDR (2012) to estimate the internal dose (urinary cadmium expressed as μg Cd/g creatinine) corresponding to a 10% excess risk of LMW proteinuria (urinary cadmium dose, UCD_{10}). Tubular proteinuria (i.e., increased excretion of LMW proteins) is considered an early adverse effect in the sequence of events leading to cadmium-induced compromised renal function (ATSDR 2012). When available, male and female data were treated separately, resulting in a total of eleven analyses for the seven environmental studies. For studies that did not report the UCD_{10}, the value was estimated by iteration of the reported dose-response relationship for varying values of urinary cadmium, until an excess risk of 10% (i.e., the critical effect size) was achieved. For studies that reported the dose-response relationship graphically but did not report the actual dose-response function, ATSDR derived a function by least squares fitting based on data from a digitization of the graphic. The UCD_{10} and 95% lower confidence limit $UCDL_{10}$ values cited in ATSDR (2012) are provided in Table 6.

Table 6. Estimates of Study UCD_{10}/ $UCDL_{10}$ Values Corresponding to a 10% Excess Risk of β2-Microglobulin Proteinuria from ATSDR (2012)

Study Type	Mean UCD_{10} [a] (µg Cd/g creatinine)	$UCDL_{10}$ (µg Cd/g creatinine)	$UCDU_{10}$ (µg Cd/g creatinine)
Environmental Exposure			
Europe (n=4) [b]	1.34	**0.50**	2.18
Japan (n=4) [c]	5.23	4.24	6.21
China (n=3) [d]	9.55	2.96	16.1
Overall	*4.99*	*1.44*	*6.60*
Occupational Exposure			
European Cohorts [e]	7.50	---	---
Chinese Cohort [f]	4.58	---	---

[a] Estimates of urinary cadmium dose (UCD) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (UCD_{10}).
[b] Dose-response function data from Buchet et al. (1990), Suwazono et al. (2006), and Järup et al. (2000); dose-response data from males and females in the Buchet et al. (1990) study were treated separately.
[c] Dose-response function data from Kobayashi et al. (2006) and Shimizu et al. (2006); dose-response data from males and females were treated separately.
[d] Dose-response function data from Jin et al. (2004) and Wu et al. (2001); dose-response data from males and females in the Jin et al. (2004) study were treated separately.
[e] Dose-response function data from Järup and Elinder (1994) and Roels et al. (1993).
[f] Dose-response function data from Chen et al. (2006a, 2006b).

This meta-analysis was used to establish potential PODs for the urinary cadmium-response relationship. More specifically, analysis of the available environmental and occupational exposure studies resulted in estimates of urinary cadmium levels that would result in a 10% increase in the prevalence of β2-microglobulin proteinuria (i.e., the critical effect). The UCD_{10} values from the occupational exposure studies were 7.50 µg Cd/g creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 µg Cd/g creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). However, the lowest UCD_{10} (1.34 µg Cd/g creatinine) was estimated from environmental exposure studies, the European environmental studies in particular (Buchet et al. 1990; Järup et al. 2000; Suwazono et al. 2006).

Similar to ATSDR (2012), the $UCDL_{10}$ (0.5 µg Cd/g creatinine) corresponding to the lowest UCD_{10} value (1.34 µg Cd/g creatinine from the environmental exposure studies) was used as the

POD for derivation of the chronic ReV. This value appears conservative considering it is approximately 10-fold lower than the mean UCD_{10} value for the seven environmental studies (4.99 μg Cd/g creatinine) and about 3-fold lower than the $UCDL_{10}$ value (1.44 μg Cd/g creatinine) using all seven environmental studies (see Table 6). However, the TCEQ notes that adverse effect levels for skeletal effects are similar to those observed for renal effects (e.g., increased risks of fractures and osteoporosis at ≈ 1 μg Cd/g creatinine and greater), as such effects may be secondary to renal damage (USEPA 1999). Thus, skeletal adverse effect levels support and further justify the POD based on a stronger renal effects database (ATSDR 2012).

4.1.3 MOA Analysis and Dose Metric

Please refer to Section 3.1.3 for a discussion on MOA. Generally, the mechanism of cadmium toxicity in renal cells (and other tissues) probably involves the binding of free cadmium ions (CdII or Cd^{2+}) to key cellular enzymes and proteins (ATSDR 2012; Maret and Moulis 2013). Cadmium down regulates the synthesis of megalin (a multi-ligand endocytic receptor protein in proximal tubule cells that plays an important role for the tubular uptake of filtered proteins) and chloride channel 5 (a renal endosome-associated chloride channel that when lost strongly inhibits the endocytosis of filtered proteins by kidney proximal tubular cells) in a dose-dependent manner, thereby interfering with renal tubular reabsorption, degradation and/or reclamation pathways. Cadmium effects on cubilin (a multi-ligand endocytic receptor protein that is co-expressed with megalin in the renal proximal tubule and also important for the tubular reabsorption of proteins) have also been suggested (Byber et al. 2016; Christensen and Birn 2001; Christensen et al. 2003). With amnionless (a transmembrane protein), these proteins (megalin, cubilin) form a complex that plays an important role in tubular high molecular weight and LMW protein reabsorption as well as endosomal and lysosomal processing, and a disturbance in this process represents a primary tubular proteinuria (Byber et al. 2016). As mentioned above, urinary cadmium (expressed as μg Cd/g creatinine) is used as the internal dose metric for derivation of the chronic ReV.

4.1.4 POD, Critical Effect, and Dosimetric Adjustments

Abnormal biomarker (e.g., LMW proteins such as β2-microglobulin) levels are early signs of cadmium-induced kidney damage and appear to be the most sensitive indicator of chronic cadmium toxicity (ATSDR 2012). Per the discussion above, the POD (i.e., $UCDL_{10}$) of 0.5 μg Cd/g creatinine, corresponding to a 10% excess risk of LMW proteinuria (i.e., the critical kidney effect), was used as the POD for derivation of the chronic ReV. This renal effect POD is supported by somewhat higher PODs for various skeletal effects (e.g., increased risks of fractures and osteoporosis at ≈ 1 μg Cd/g creatinine and greater), which have a less robust database (ATSDR 2012).

Pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) were used by ATSDR (2012) to predict the corresponding cadmium air concentration. More specifically, deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition,

retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow (S); moderate (M); or fast (F)). Cadmium compounds were classified as follows: oxides and hydroxides (S); sulfides, halides, and nitrates (M); and all other (F) (e.g., chloride salts).

Inhalation exposures to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μm (activity median aerodynamic diameter or AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucociliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Kjellström and Nordberg pharmacokinetic model (1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure. An airborne cadmium concentration of 1.8-2.4 μg Cd/m^3 as cadmium oxide or 1.2-1.4 μg Cd/m^3 as cadmium sulfide would result in a urinary cadmium level of 0.5 μg Cd/g creatinine (the urinary cadmium POD), assuming that inhalation was the only source of cadmium. However, the diet is a significant contributor to the cadmium body (e.g., renal) burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in nonsmoking males and females in the United States are 0.35 and 0.30 μg Cd/kg-day, respectively, and for males and females combined the average intake is 0.32 μg Cd/kg-day (Choudhury et al. 2001).

Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (AMAD=1 μm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 μg Cd/m^3 (with a dietary intake of 0.3 μg Cd/kg-day) would result in the urinary cadmium POD of 0.5 μg Cd/g creatinine (ATSDR 2012). Thus, 0.1 μg Cd/m^3 will be used as the conservative air concentration POD for derivation of the chronic ReV and ESL.

4.1.5 Adjustments of the POD

The POD of 0.1 μg Cd/m^3 for the critical kidney effect (i.e., a 10% increase in the prevalence of β2-microglobulin proteinuria) was used to derive the chronic ReV. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the chronic ReV (i.e., assume a threshold MOA) (TCEQ 2015).

Similar to ATSDR (2012), a total UF of 9 was applied to the POD of 0.1 μg Cd/m^3 to derive the chronic ReV: a UF_H of 3 for variability within the human population as well as a UF_D of 3. These UF values are the same as those used by ATSDR (2012) to derive their chronic inhalation MRL. The following is more specific concerning the rational for the applicable UFs:

- A UF_H of 3 was used to account for the possible increased sensitivity of diabetics because although the POD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations, there is concern that individuals with diabetes

may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990). Thus, a UF_H of 3 was used despite using the lowest and most conservative $UCDL_{10}$ among environmental exposure studies (e.g., the POD is about 3-fold lower than the $UCDL_{10}$ for the seven environmental studies) and conservatively taking in to account another exposure pathway (i.e., dietary intake); and

- A UF_D of 3 was used for database uncertainty because while the database for cadmium is extensive, additional chronic human data are needed to better characterize the relative sensitivities of the respiratory tract (a sensitive target organ for cadmium-induced toxicity) and the kidneys, the effects upon which serve as the basis for the chronic ReV. Additionally, information regarding the potential for cadmium-induced developmental/reproductive effects is available (Section 4.1.1.3) and indicates that the chronic ReV and ESL are expected to be protective of potential developmental/ reproductive effects.

chronic ReV = POD / ($UF_H \times UF_D$)

= 0.1 µg Cd/m^3 / (3 × 3)
= 0.1 µg Cd/m^3 / 9
= 0.011 µg Cd/m^3

4.1.6 Health-Based Chronic ReV and ^{chronic}ESL

The chronic ReV for cadmium is 0.011 µg Cd/m^3 (rounded to two significant figures). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target HQ of 0.3, the $^{chronic}ESL_{threshold(nc)}$ for cadmium is 0.0033 µg Cd/m^3 (Table 7).

Table 7. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	**Summary**
Key Study	Meta-analysis of multiple studies (ATSDR 2012)
Study Population	Humans
Study Quality Confidence Level	Medium-High
Exposure	Environmental and occupational
Critical Effect	Kidney/renal effects (i.e., β2-microglobulin proteinuria)
Exposure Duration	Chronic
POD_{HEC} (urine)	0.5 µg Cd/g creatinine ($UCDL_{10}$)
POD_{HEC} (air)	0.1 µg Cd/m^3 (calculated using pharmacokinetic models)
Total uncertainty factors (UFs)	9
Intraspecies UF	*3*
Incomplete Database UF *Database Quality*	*3* *Medium-High*
chronic ReV (HQ = 1)	**0.011 µg Cd/m^3**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.0033 µg Cd/m^3**

4.1.7 Comparison of Results

The TCEQ chronic ReV of 0.011 µg Cd/m^3 would be identical to the ATSDR (2012) chronic inhalation MRL (0.01 µg Cd/m^3) if rounded to one significant figure, although the TCEQ rounds its toxicity factors to two significant figures (TCEQ 2015). CalEPA has evaluated the noncancer inhalation toxicity data for cadmium and derived a chronic inhalation Reference Exposure Level (REL) based on kidney effects (proteinuria) and respiratory effects (reduction in forced vital capacity and reduction in peak expiratory flow rate) in occupationally exposed humans (CalEPA 2000). The CalEPA chronic REL of 0.02 µg Cd/m^3 is about 2-fold higher than the TCEQ's chronic ReV of 0.011 µg Cd/m^3 and 6-fold higher than the TCEQ's $^{chronic}ESL_{threshold(nc)}$ of 0.0033 µg Cd/m^3. USEPA does not currently have a reference concentration (RfC) for cadmium on IRIS. However, at one time the USEPA had evaluated the noncancer inhalation toxicity data and produced a draft assessment (USEPA 1999). The draft RfC (0.65 µg Cd/m^3) derived in that USEPA document is 59-fold higher than TCEQ's chronic ReV.

4.2 Carcinogenic Potential

USEPA (1985) derived a unit risk factor (URF) of 1.8E-03 per µg Cd/m^3 for environmental exposure to cadmium using lung cancer data from a now outdated occupational study (Thun et al. 1985 was first updated in Stayner et al. 1992 and later in Park et al. 2012). Although USEPA conducted a draft assessment in 1999 (USEPA 1999), the URF on USEPA's Integrated Risk Information System (IRIS) has not been updated in three decades (i.e., since 1985). Consequently, the TCEQ performed an updated carcinogenic dose-response assessment.

4.2.1 Weight of Evidence (WOE) and Classifications

The majority of text below was taken from ATSDR (2012) [*emphasis added*].

The relationship between occupational exposure to cadmium and increased risk of cancer has been explored in a number of occupational exposure studies. The results of these studies are conflicting and the carcinogenicity of cadmium has not been unequivocally established. *Overall, the results provide suggestive evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium.* Significant increases in mortality from lung cancer have been reported in workers employed at a U.S. cadmium recovery facility (Stayner et al. 1992; Thun et al. 1985), nickel-cadmium battery facilities in England (Sorahan 1987) and Sweden (Järup et al. 1998), and in a cohort of workers at cadmium processing facilities and/or smelters (Ades and Kazantzis 1988; Kazantzis et al. 1988). However, no clear relationships between level and duration of cadmium exposure and lung cancer risk have been established and many of these studies did not account for confounding exposure to other carcinogenic metals (particularly arsenic and nickel) and cigarette smoking (ATSDR 2012).

The possible association between occupational exposure to cadmium and lung cancer was investigated in several studies of a cohort of workers employed at a U.S. cadmium recovery facility. The cohort was initially examined by Lemen et al. (1976) who found a significant increase in deaths from malignant neoplasms of the respiratory tract among hourly workers employed for at least 2 years between 1940 and 1969. *A re-examination of the cohort (deaths through 1978) also found statistically significant standardized mortality rates (SMRs) for malignant neoplasms in the respiratory tract (Thun et al. 1985).* To adjust for possible arsenic exposure (the facility functioned as an arsenic smelter between 1918 and 1925), workers were divided based on year of hire. Mortality from lung cancer was significantly elevated in workers hired prior to 1926 and among workers hired after 1926 with 2 or more years of employment. *Dividing the workers into three exposure groups based on estimated cumulative exposure resulted in a significant dose-related trend for lung cancer deaths, and a 2- to 8-fold increase in the risk of lung cancer deaths was observed in the highest exposure group (cumulative exposures >8 years-mg Cd/m^3) (Thun et al. 1985).* A subsequent analysis of these data (workers followed through 1985) used comparisons of rates with the cohort rather than the U.S. population (Stayner et al. 1992). *Lung cancer mortality was significantly increased among non-Hispanic whites, among workers with the highest cumulative exposure (> 2,291 days-mg Cd/m^3), and among workers with the longest time since first exposure (> 20 years).* While the nested case-control

analysis of Lamm et al. (1992, 1994) suggest that arsenic exposure and cigarette smoking (not cadmium) were the major determinants of lung cancer risk for this cohort, Stayner et al. (1993) provided additional analyses including the use of the Armitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure. Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from timesheet records, to better resolve the potential confounding effects of arsenic. Poisson regression was used to investigate risks of mortality from lung cancer in relation to four concentrations of accumulative exposure to cadmium (< 400, 400-999, 1,000-1,999, and > 2,000 mg Cd-days/m^3). After adjustment for age attained, year of hire, and Hispanic ethnicity, Sorahan and Lancashire (1997) report a significant positive trend ($p < 0.05$) between cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. The carcinogenicity of cadmium has also been examined in European alloy, battery, smelter, and process workers. However, results were mixed and in several cases where a significant increase in lung cancer deaths was found, there was no relationship between cumulative cadmium exposure and lung cancer deaths (Järup et al. 1998; Ades and Kazantzis 1988) (ATSDR 2012). Appendix C provides additional discussion of the uncertainty (i.e., risk implications) associated with the potential co-exposure of these workers to arsenic (see Section C.4).

Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium. Oldiges et al. (1989) reported a clear dose-response increase in lung tumors in male and female rats from an 18-month continuous exposure to either: cadmium chloride, cadmium oxide dusts, cadmium oxide fume, cadmium sulfate, or cadmium sulfide. A high incidence of nodules and tumors was seen with 30 μg/m^3 exposures to cadmium chloride in both males and females. Increased lung tumors in males and females were also observed with chronic exposures to cadmium oxide dust or fume at 30 μg/m^3, to cadmium sulfate at 90 μg/m^3, and to cadmium sulfide at 90 μg/m^3 (Oldiges et al. 1989). Takenaka et al. (1983) also demonstrated cadmium carcinogenicity in male rats exposed to cadmium chloride aerosols at 0.0134, 0.0257, and 0.0508 mg Cd/m^3 for 18 months. *The exposure produced a dose-related increase in lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas starting at 20 months* (ATSDR 2012).

The available data provide inconclusive evidence on the potential of cadmium to induce lung cancer in humans. The strongest evidence comes from early studies of workers at a U.S. cadmium recovery facility (Stayner et al. 1992; Thun et al. 1985), but later examinations of this cohort did not find conclusive evidence (Lamm et al. 1992, 1994; Sorahan and Lancashire 1997). The inconsistent results may be due to the small number of lung cancer cases and adjustments for possible early exposure to arsenic. Some studies of European cadmium workers have found significant increases in lung cancer (Ades and Kazantzis 1988; Järup et al. 1998; Kazantzis et al. 1988; Sorahan 1987; Sorahan and Waterhouse 1983), but lung cancer deaths were not

significantly associated with cumulative cadmium levels or duration of exposure and the investigators concluded that the effects may not have been related to cadmium exposure (ATSDR 2012).

USEPA (1985) classified cadmium as a *probable human carcinogen* by inhalation (Group B1) based on limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats. IARC (2012) classifies cadmium as *carcinogenic to humans* (Group 1) based on sufficient evidence for carcinogenicity in both human and animal studies. Similarly, the National Toxicology Program (NTP) 13th Report on Carcinogens classifies cadmium and compounds as *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies (NTP 2014).

In summary, ATSDR (2012) indicates:

- The results of studies examining the relationship between occupational exposure to cadmium and increased risk of cancer (e.g., lung) are conflicting and *the carcinogenicity of cadmium has not been unequivocally established*;
- Overall, *human study results provide suggestive evidence of an increased risk of lung cancer* following prolonged inhalation exposure to cadmium; while
- *Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium.*

Considering the information above, although arguments can be made for a *Carcinogenic to Humans* classification, cadmium most clearly (i.e., inarguably) satisfies the criteria of the *Likely to Be Carcinogenic to Humans* via inhalation WOE descriptor in USEPA (2005a) (e.g., data demonstrate carcinogenic potential to humans, at a minimum, with strong support by positive animal study results). For example, this classification, which is more broad than the *Carcinogenic to Humans* WOE descriptor, is consistent with ATSDR's statements that "…the carcinogenicity of cadmium has not been unequivocally established" and that, "Overall, the results provide suggestive evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium." This WOE descriptor is also consistent with the *Probable Human Carcinogen* via inhalation classification in the draft USEPA (1999) assessment, for which the relevant studies cited above were available and considered by USEPA (see citations in USEPA 1999). USEPA indicated [*emphasis added*] that the WOE of human carcinogenicity from cadmium exposure via inhalation consists of: *problematic epidemiological evidence* associating cadmium exposure with lung cancer, the demonstrated induction of lung cancer in two rat inhalation studies, and *equivocal mutagenicity and chromosome aberration induction* in *in vivo* and *in vitro* test systems, coupled with several plausible mechanisms by which mutagenicity might occur other than by direct DNA alkylation. Lastly, the *Likely to Be Carcinogenic to Humans* via inhalation WOE descriptor is more consistent with the overall lack of statistically increased lung cancer in the latest update of the Thun et al. (1985) study (Park et al. 2012) than the *Carcinogenic to Humans* classification. While the difference between these

two classifications is without significance for purposes of this DSD (i.e., TCEQ will perform a carcinogenic dose-response assessment either way), consistent with the above discussion, the TCEQ considers cadmium and cadmium compounds as a group as *Likely to Be Carcinogenic to Humans* via inhalation.

The TCEQ's WOE classification and inhalation URF will be applied to all forms of cadmium. Carcinogenic dose-response assessments are performed for chemicals considered by the TCEQ as *Likely to Be Carcinogenic to Humans* (or *Carcinogenic to Humans*) (TCEQ 2015).

4.2.2 Carcinogenic MOA

IARC (2012) summarizes available information relevant to the carcinogenic MOA for cadmium as follows:

> Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis. Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumor-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth. However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans.

Thus, multiple mechanisms (e.g., aberrant gene expression, inhibition of DNA damage repair, induction of oxidative stress/reactive oxygen species and genomic instability, inhibition of apoptosis) appear to be involved in cadmium-induced carcinogenesis (Joseph 2009; Huff et al. 2007; Luevano and Damodaran 2014). Additionally, the solubilized cadmium ion has been assumed to be responsible for the observed carcinogenicity of cadmium, with the carcinogenic potential of a cadmium compound being related to the cumulative amount of cadmium ion released in proximity to target lung cells over a specific period of time (OSHA 1992). The release of the cadmium ion from the compound is governed by the rate of dissolution, the biological half-life/time in the lung, and the mechanism of clearance from the lung. While the dissolution rate of the cadmium ion is a function of the solubility of the cadmium compound in the physiological environment, biological half-life/time and mechanism of clearance depend upon a number of factors (e.g., nature of the inhaled material, characteristics of the respiratory tract). Particle size determines deposition within the respiratory tract and therefore mechanism of clearance, with clearance by mucociliary escalator being operative in the upper respiratory tract and clearance through direct uptake by macrophage (with subsequent clearance by the mucociliary escalator) and dissolution/diffusion operating in the lower respiratory tract (e.g., alveoli). Biological half-life/time is a function of the efficiency of these clearance processes. In this regard, any cytotoxicity that reduces ciliary movement or overburdens macrophage would increase retention time, allowing more dissolution and cadmium ion formation than may be expected based on solubility alone (OSHA 1992).

Despite the information available on potential mechanisms, the MOA for cadmium-induced carcinogenesis has not been fully elucidated. Additionally, USEPA (1999) points out that:

- While some studies have found cadmium to be genotoxic *in vitro* and *in vivo*, others have not, and that some of the plausible mechanisms for cadmium-induced genotoxicity may operate via thresholds;
- The potential effect of cadmium on DNA repair, the inability of cadmium to directly bind to DNA, and the role of oxidative damage in cadmium-related genotoxicity are suggestive of nonlinearity or indirect mechanisms for carcinogenicity; and
- The suggestion that metallothionein levels play a role in tissue susceptibility could also provide some support for a nonlinear dose-response assessment.

On the other hand, the agency also acknowledges that while several different mechanisms may be operative in the carcinogenic MOA, good dose-response data are not available for the endpoints that may be related to nonlinear mechanisms of carcinogenicity.

As stated more recently by Maret and Moulis (2013), the epidemiological studies linking health effects and cadmium exposure suffer from a relative lack of consensus knowledge about the MOA(s) of cadmium. The various molecular mechanisms involved in cadmium-induced carcinogenesis are poorly understood and are only now beginning to be elucidated (Luevano and Damodaran 2014). Thus, as a clear picture of the MOA for cadmium-induced lung carcinogenesis is yet to be elucidated, no MOA has been widely accepted by the scientific community as definitive.

4.2.3 Carcinogenic Dose-Response Assessment

The TCEQ (2015) guidelines for carcinogenic assessments employ the four-step risk assessment process formalized by the National Research Council (NRC 1983, 1994) and the procedures recommended in the most recent USEPA cancer guidelines (USEPA 2005a, 2005b) and scientific literature. Under TCEQ guidelines, the TCEQ evaluates and adopts low-dose extrapolation approaches (e.g., nonthreshold/linear, threshold) on a chemical-by-chemical basis in the context of the relevant data available. When data on the carcinogenic MOA support a nonthreshold, linear dose-response extrapolation or sufficiently informative data on the carcinogenic MOA are lacking, a linear extrapolation is performed to estimate excess lifetime risk at lower, environmentally-relevant doses. More specifically, the calculation of a health-protective air concentration based on carcinogenic effects due to inhalation is accomplished through the use of linear low-dose extrapolation to derive a URF. Despite that the draft USEPA assessment (USEPA 1999) recommended a less conservative nonlinear dose-response assessment in addition to a linear extrapolation, data appear inadequate to sufficiently justify and perform a nonlinear assessment for cadmium-induced carcinogenicity via inhalation (e.g., USEPA indicated that good dose-response data are not available for the endpoints related to nonlinear mechanisms of carcinogenicity). Therefore, only the default linear low-dose extrapolation (i.e., URF) approach will be utilized in the following sections.

4.2.3.1 Default Linear Low-Dose Extrapolation Approach

The following sections discuss key steps in deriving a URF for cadmium using default linear low-dose extrapolation and an air concentration associated with a 1 in 100,000 excess risk, the TCEQ policy-based target risk used to calculate the cancer-based chronic ESL (i.e., $^{chronic}ESL_{nonthreshold(c)}$) (TCEQ 2015). Application of the URF to all cadmium compounds inherently treats all cadmium compounds as toxicologically equivalent based on cadmium content, consistent with the TCEQ considering cadmium compounds as a group to be *Likely to Be Carcinogenic to Humans* via inhalation.

4.2.3.1.1 Key Study and Cancer Endpoint

The TCEQ prefers human data to animal data for deriving toxicity factors (TCEQ 2015). Consequently, while both human and animal data are available for cadmium, human epidemiological study data were utilized by the TCEQ for an updated assessment of the carcinogenic potential of cadmium and the development of a URF. Whereas USEPA (1985) derived a URF based on the epidemiological study of Thun et al. (1985), the TCEQ will use Park et al. (2012), an update of the Thun et al. cohort with follow-up through 2002 (Stayner et al. 1992 was the previous update with follow-up only through 1984).

The Park et al. (2012) study:

- Conducted the highest quality epidemiology study of lung cancer risk in humans exposed to cadmium;
- Used an adequate-sized cohort (n = 601, with 444 deaths representing 74%) with 99% ascertainment of vital status;
- Characterized exposure on an individual basis using duration worked in a given job category and the average exposure level for that category;
- Observed an exposure-response relationship between lung cancer mortality and cumulative cadmium exposure; and
- Performed analyses to examine potential confounding by concurrent exposure to arsenic.

More specifically, Park et al. (2012) re-analyzed the cadmium smelter worker population (near Denver, CO) from Thun et al. (1985) exhibiting excess lung cancer using more detailed work history information, a revised cadmium exposure matrix, a detailed retrospective exposure assessment for arsenic, and updated mortality data (1940-2002). The earlier cadmium exposure assessment was revised following further analysis of personal protective equipment (PPE) with PPE protection factors developed using parallel air sampling and urinary cadmium concentration data. The resulting exposure matrix consisted of estimated cadmium air concentrations for 32 job activities in six time periods: <1950, 1950-1954, 1955-1959, 1960-1964, 1965-1979, and 1980-2002. For the arsenic exposure assessment, there were 165 determinations for airborne arsenic from 44 area and 121 personal samples in the period 1944-1983. The authors assumed that the

same PPE protection factors applied to both cadmium and arsenic exposures. The arsenic exposure matrix was based on models predicting air concentrations of arsenic from: (1) total dust measurements; (2) feedstock arsenic levels recorded since 1939; and (3) urinary arsenic measurements. The resulting arsenic exposure matrix specified yearly levels from 1939-1983 in each of four groups of job activity titles observed to have similar levels. Arsenic exposure levels prior to 1939 (when feedstock data were not available) were assumed to be the same as those estimated for 1939 (only 12.5% of the study population was hired prior to 1939), and those after 1983 were assumed to be the same as those in 1983. From work histories and the exposure matrices, an exposure history was compiled for each worker consisting of his average cadmium and arsenic air concentration in each 10-day period since January 1, 1920. Cumulative exposures were calculated for use in the SMR analyses.

Study results from Park et al. (2012) demonstrate: (1) a statistically significant effect of cadmium independent of arsenic (SMR of 3.2 for 10 mg Cd/m^3-yr, $p = 0.012$); (2) a substantial healthy worker effect for lung cancer (SMR of 0.69 for unexposed workers); and (3) a large deficit in lung cancer mortality among Hispanic workers (SMR of 0.27, $p = 0.009$), who are known to have low lung cancer rates. These findings support an arsenic-independent effect for cadmium in risk of lung cancer mortality (i.e., occupational airborne cadmium is a lung carcinogen independent of arsenic). See the Park et al. (2012) study for additional information and findings.

The TCEQ concurs with USEPA (1985, 1999) that this cohort of cadmium smelter production area workers represents the best human data upon which to perform a carcinogenic dose-response assessment for URF derivation. A scientific peer-reviewed literature search (through December 1, 2015) did not identify a more suitable epidemiological study for derivation of an inhalation URF for cadmium. Thus, Park et al. (2012), the latest update of the Thun et al. (1985) study, was selected as the key study.

Lung cancer mortality was considered the cancer endpoint of interest for the dose-response assessment consistent with the WOE (Section 4.2.1). Additionally, lung cancer mortality is the same endpoint used in the USEPA analyses (1985, 1999) and other cancer risk analyses (e.g., OSHA 1992).

4.2.3.1.2 Dose Metric and Dose-Response Data

The key occupational study (Park et al. 2012) used for URF development evaluated lung cancer mortality in white male workers by the mean cumulative exposure level for each of six exposure groups. As is often the case, cumulative exposure was lagged 5 years as the most recent exposures may be etiologically irrelevant to cancer risk because of an apparent minimum delay between exposure and the effect of that exposure on cancer risk. A previous update of this cohort (Stayner et al. 1992) reported that lagging exposure 5 years increased the magnitude of the cadmium exposure parameter (β) in Poisson regression analysis while longer exposure lags decreased both this parameter and the likelihood of the model. Moreover, Park et al. consider a 5-yr exposure lag appropriate. SMRs were provided both unadjusted and adjusted for arsenic exposure and Hispanic ethnicity, since Hispanics have been reported to have lower lung cancer

rates than non-Hispanics. The dose-response data from Park et al. (2012) are provided in Table 8 below.

Table 8. Lung Cancer Dose-Response Data for Park et al. (2012) [a]

Cumulative Exposure (mg Cd/m^3-yr)	Mean Exposure [b] (µg Cd/m^3-yr)	Expected Lung Cancer Deaths (E) [c]	Observed Lung Cancer Deaths (O)	Lung Cancer SMR (O/E)
Adjusted for Arsenic Exposure and Ethnicity				
0-0.72	230	9.091	7	0.77
0.73-2.42	1,470	8.511	8	0.94
2.43-7.81	4,460	8.889	8	0.90
7.82-16.63	11,130	3.571	8	2.24
16.76-24.98	19,960	1.007	3	2.98
25.15-39.94	33,080	0.224	2	8.93
Total	3,000	32.143	36	1.12
Unadjusted for Arsenic Exposure and Ethnicity				
0-0.72	230	8.861	7	0.79
0.73-2.42	1,470	10.127	8	0.79
2.43-7.81	4,460	9.877	8	0.81
7.82-16.63	11,130	3.653	8	2.19[†]
16.76-24.98	19,960	1.186	3	2.53
25.15-39.94	33,080	0.226	2	8.85[*]
Total	3,000	33.962	36	1.06

[a] Based on Table 1 of Park et al. (2012).

[b] Mean 5-yr lagged cumulative exposure (mg/m^3-yr) from Table 1 of Park et al. (2012) multiplied by 1,000 µg/mg.

[c] Calculated as E = O / SMR.

[†] 95% confidence interval 1.00, 4.07; [*] Statistically significant with $p < 0.05$

As can be seen from examination of Table 8, the total number of lung cancers in the updated cohort was close to expected (SMRs of 1.12 and 1.06), and lung cancer mortality was statistically increased only for the highest exposure group (mean cumulative exposure of 33,080 µg Cd/m^3-yr) with the SMR of 8.85 unadjusted for arsenic exposure and ethnicity (95% confidence interval = 1.47, 27.3). However, the 95% confidence interval (1.00, 4.07) for the SMR of 2.19 (unadjusted analysis) at a mean cumulative exposure of 11,130 µg Cd/m^3-yr just barely included 1, and although increased lung cancer did not achieve statistical significance for any other exposure group or overall (SMRs of 1.12 and 1.06), there is an apparent monotonic dose-response for increased lung cancer risk beginning at a mean cumulative exposure of 11,130 µg Cd/m^3-yr, and the study did report a statistically significant SMR of 3.2 ($p = 0.012$) for a cumulative cadmium exposure of 10,000 µg Cd/m^3-yr (independent of arsenic; see Table 3 of Park et al. 2012). While statistical significance as a measure of strength of the association can be

a consideration in the evaluation of the suitability of epidemiologic study data for dose-response modeling, Stayner et al. (1999) note that dose-response modeling of weak associations may be informative in providing potential upper bound or best estimates of risk. Additionally, lack of statistical significance is not proof of lack of effect in carcinogenicity risk assessments, there is a need in this case for the TCEQ to characterize cancer risk due to cadmium exposure in the interest of public health, and there is regulatory agency precedent for use of such studies for risk characterization (e.g., TCEQ 2011; USEPA 1986).

4.2.3.1.3 Poisson Regression Modeling

Poisson regression modeling was used to calculate the maximum likelihood estimate (MLE) of the slope parameter β for lung cancer mortality (Appendix A). Maximum likelihood estimation with Poisson regression is preferred when the number of responses (i.e., observed and expected cases) is known (Section 8.3.3.2.1.1 of USEPA 1986; Crump and Allen 1985; Appendix A), as in this case. Two multiplicative relative risk models were used to calculate β values. The preferred model included the term "α", while the other model did not. The "α" term is used in the preferred model to account for differences in lung cancer mortality background rates between the study population and the reference population used to determine the number of expected lung cancer mortalities. The use of this term may account for potential issues such as the healthy worker effect and any differences between internally- and externally-derived background rates. As discussed in Appendix A, incorporation of the "α" term into the relative risk model equation from USEPA (1986; p. 8-201) yields:

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

where:

$E(O_j)$ = expected number of lung cancer mortality cases for exposure group j
α = accounts for differences in lung cancer mortality background rates between the study population and the reference population
E_{oj} = expected number of background lung cancer mortality cases for exposure group j
β = multiplicative factor by which background risk increases with cumulative exposure
d_j = cumulative exposure for exposure group j

The linear multiplicative relative risk model, as opposed to an additive risk model, was used to calculate β estimates. The multiplicative relative risk model is preferred over the additive risk model for lung cancer because of more plausible assumptions concerning the increase in risk with age. For lung cancer, risk increases rapidly with age, which is better captured by the multiplicative relative risk model where risk increases over background rates multiplicatively. By contrast, the additive risk model assumes that cumulative exposure causes the same absolute increase in risk regardless of the age at which the risk is calculated, which is less plausible relative to actual observed age-related increases in lung cancer incidence and mortality.

For both SMR analyses in Table 8, the mean 5-yr lagged cumulative exposure for each exposure group in units of µg Cd/m^3-yr was used to estimate β values. Additionally, a modeling run was conducted with the "α" term set to 0.8, as Park et al. state that an intercept of 0.8 is a reasonable choice for the healthy worker effect in this cohort (e.g., the SMRs for the lowest exposure groups in Table 8 are 0.77-0.79). Table 9 presents these β estimates for Park et al. (2012) evaluated in units of increase of relative risk per µg Cd/m^3-yr.

Table 9. β Values and Standard Error (SE) Based on Lung Cancer Mortality

Park et al. (2012) Analysis	Lag	α	SE	β (95% LCL) [a, b]	β (MLE) [a]	β (95% UCL) [a, c]
Adjusted for Arsenic Exposure and Ethnicity	5-yr	0.67	1.22E-04	-1.41E-05	**1.87E-04**	3.88E-04
		0.80	4.69E-05	5.87E-05	1.36E-04	2.13E-04
		-	4.16E-05	1.91E-05	8.76E-05	1.56E-04
Unadjusted for Arsenic Exposure and Ethnicity	5-yr	0.62	1.22E-04	-1.78E-05	1.82E-04	3.82E-04
		0.80	4.29E-05	4.43E-05	1.15E-04	1.86E-04
		-	3.81E-05	9.26E-06	7.20E-05	1.35E-04

[a] Estimates are excess relative risk per µg Cd/m^3-yr.
[b] 95%LCL = β - (1.645 × SE).
[c] 95%UCL = β + (1.645 × SE).

Consistent with USEPA (2005a) and TCEQ (2015) guidelines, in addition to the β (MLE), the standard error (SE), 95% lower confidence limit on the β (95%LCL β), and 95% upper confidence limit on the β (95%UCL β) were also calculated and are presented. The 95%LCL values are negative for the preferred and most conservative model (which includes the modeled "α" term), suggesting the possibility of zero excess lung cancer risk with cadmium exposure.

4.2.3.1.4 Dosimetric Adjustments

Consistent with TCEQ (2015), occupational concentrations ($Concentration_{OC}$) were converted to environmental concentrations for the general population ($Concentration_{HEC}$) using the following equation:

$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (ds\ per\ week_{oc}/ds\ per\ week_{res})$$

where:

$Concentration_{HEC}$ = human equivalent concentration for the general public (µg/m^3)
$Concentration_{OC}$ = occupational exposure concentration (µg/m^3)
VE_{ho} =occupational ventilation rate for an 8-h d (10 m^3/d)
VE_h = non-occupational/environmental ventilation rate for a 24-h d (20 m^3/d)
$ds\ per\ week_{oc}$ = occupational weekly exposure frequency (5 days per week)
$ds\ per\ week_{res}$ = residential weekly exposure frequency (7 days per week)

4.2.3.1.5 URFs and Air Concentrations at 1 in 100,000 Excess Lung Cancer Risk

URFs express cancer potency in units of excess risk per air concentration (e.g., excess risk per µg/m^3) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is mutagenic, unknown, or sufficient information to justify an alternative extrapolation approach is not available (TCEQ 2015). As mentioned previously, since the MOA for cadmium-induced lung carcinogenesis is yet to be fully elucidated, default linear low-dose extrapolation is utilized to derive the URF estimates herein.

When a dose-response curve is modeled for tumor data (see Figure 2 below), the URF is the slope of a straight line from the POD to the origin, with the POD being the lowest tumor response level supported by the study data.

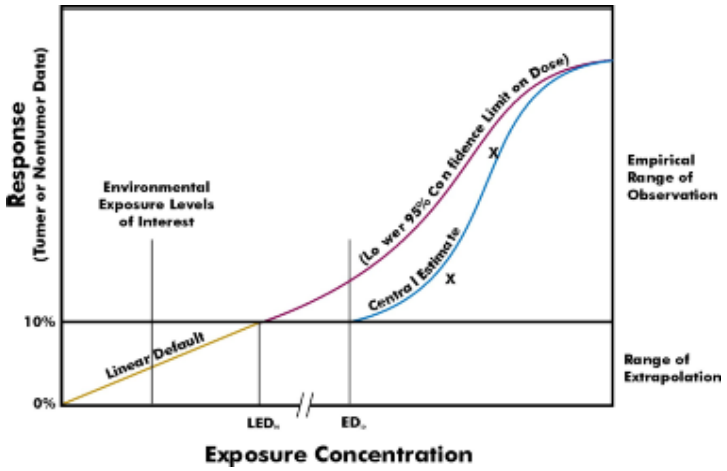


Figure 2. Example of Linear Approach for Low-Dose Extrapolation

Frequently in animal-based risk estimates, the lower statistical bounds on the concentration producing a 10% excess tumor response (LEC_{10}) is used as the POD for linear low-dose extrapolation and calculation of the URF since the limit of detection of tumor studies is often around 10%, and the resulting equation is:

$$URF = \text{risk per } \mu g/m^3 = 0.10 / LEC_{10} \text{ (where } LEC_{10} \text{ is expressed in } \mu g/m^3)$$

However, for this cancer assessment, the response data are based on humans and have already been fit to a linear equation (linear multiplicative relative risk model) for use with the BEIR IV methodology (NRC 1988). Therefore, consistent with TCEQ (2015) guidelines (e.g., discussion of lung cancer mortality versus incidence in the next section), a URF is calculated using a central estimate of a POD within the range of the epidemiological data (i.e., URF = $1/EC_{001}$) for this risk assessment.

Table 10 shows URFs estimated at an excess risk of 1 in 1,000 and extrapolated air concentrations corresponding to an excess cancer risk of 1 in 100,000 based on β (MLE), β (95% LCLs), and β (95% UCLs) values from Table 9, which were calculated based on Park et al. (2012) using maximum likelihood estimation with Poisson regression. Air concentrations are based on extra risk (as opposed to added risk) and a lifetime exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2015), and were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). The following lung cancer mortality rates and survival probabilities were used in the primary (Texas rates) and supplementary (US rates) analyses:

- Texas-specific lung cancer mortality rates for 2008-2012 and Texas-specific survival rates for 2013 are the latest available (Appendix B);
- US lung cancer mortality rates for 2008-2012 are the latest available (Surveillance, Epidemiology, and End Results database) (Appendix B); and
- US survival rates for 2011 are the latest available (Appendix B).

For comparison to results obtained with Texas rates, the similar results using US rates are also provided in Table 10 below.

Table 10. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Mortality

Park et al. (2012) Analysis	Background Rates	Exposure Lag (α Value)	URF (95% LCL) [a] Air Concentration @ 1 in 100,000 Excess Risk	URF (MLE) [a] Air Concentration @ 1 in 100,000 Excess Risk	URF (95% UCL) [a] Air Concentration @ 1 in 100,000 Excess Risk
Adjusted for Arsenic Exposure and Ethnicity	TX	5-yr (0.67)	NA	**4.87E-04 per µg/m³ 2.05E-02 µg/m³**	1.01E-03 per µg/m³ 9.89E-03 µg/m³
		5-yr (0.80)	1.53E-04 per µg/m³ 6.54E-02 µg/m³	3.54E-04 per µg/m³ 2.82E-02 µg/m³	5.55E-04 per µg/m³ 1.80E-02 µg/m³
		5-yr (NA)	4.98E-05 per µg/m³ 2.01E-01 µg/m³	2.28E-04 per µg/m³ 4.38E-02 µg/m³	4.07E-04 per µg/m³ 2.46E-02 µg/m³
	US	5-yr (0.67)	NA	5.47E-04 per µg/m³ 1.83E-02 µg/m³	1.14E-03 per µg/m³ 8.80E-03 µg/m³
		5-yr (0.80)	1.72E-04 per µg/m³ 5.82E-02 µg/m³	3.98E-04 per µg/m³ 2.51E-02 µg/m³	6.24E-04 per µg/m³ 1.60E-02 µg/m³
		5-yr (NA)	5.59E-05 per µg/m³ 1.79E-01 µg/m³	2.56E-04 per µg/m³ 3.90E-02 µg/m³	4.57E-04 per µg/m³ 2.19E-02 µg/m³
Unadjusted for Arsenic Exposure and Ethnicity	TX	5-yr (0.62)	NA	4.74E-04 per µg/m³ 2.11E-02 µg/m³	9.96E-04 per µg/m³ 1.00E-02 µg/m³
		5-yr (0.80)	1.15E-04 per µg/m³ 8.66E-02 µg/m³	3.00E-04 per µg/m³ 3.34E-02 µg/m³	4.85E-04 per µg/m³ 2.06E-02 µg/m³
		5-yr (NA)	2.41E-05 per µg/m³ 4.14E-01 µg/m³	1.88E-04 per µg/m³ 5.33E-02 µg/m³	3.52E-04 per µg/m³ 2.84E-02 µg/m³
	US	5-yr (0.62)	NA	5.33E-04 per µg/m³ 1.88E-02 µg/m³	1.12E-03 per µg/m³ 8.94E-03 µg/m³
		5-yr (0.80)	1.30E-04 per µg/m³ 7.71E-02 µg/m³	3.37E-04 per µg/m³ 2.97E-02 µg/m³	5.44E-04 per µg/m³ 1.84E-02 µg/m³
		5-yr (NA)	2.71E-05 per µg/m³ 3.69E-01 µg/m³	2.11E-04 per µg/m³ 4.74E-02 µg/m³	3.95E-04 per µg/m³ 2.53E-02 µg/m³

[a] Calculated air concentrations at 1 in 100,000 excess risk using the unrounded URF shown (i.e., 0.00001 / URF).
NA = not applicable (i.e., an "α" term was not included in the model or the 95%LCL β value was negative, suggesting zero excess risk is possible, so calculation of an air concentration at 1 in 100,000 excess risk was not possible.

This table provides several candidate URFs to consider. In selecting a URF, it is noted that lung cancer mortality is reasonably predictive of lung cancer incidence (i.e., 5-yr survival is only about 17% (American Cancer Society 2015)) (Figure 3). Therefore, if incidence data were available, the lung cancer potency estimates would be expected to be very similar to those derived based on lung cancer mortality.

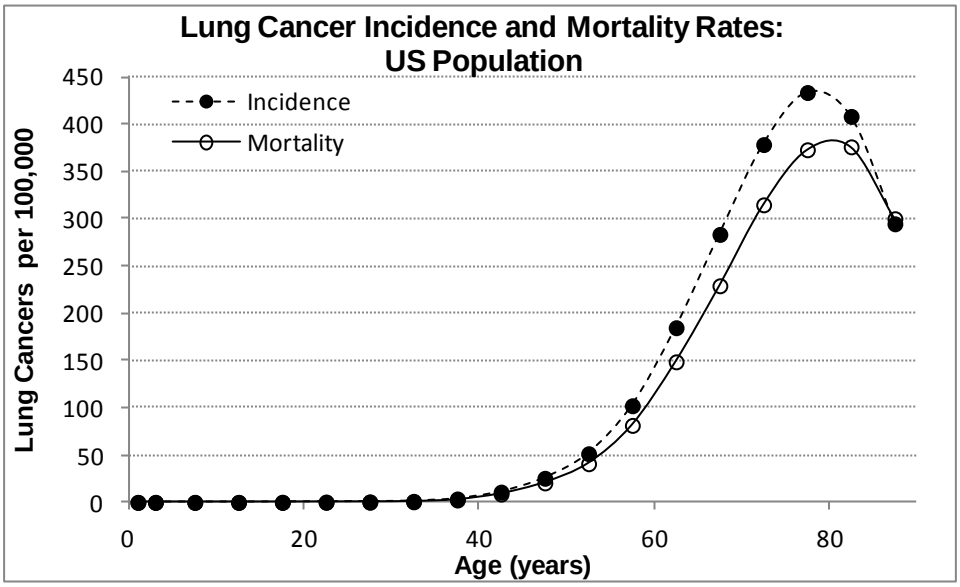


Figure 3. Lung Cancer Incidence versus Mortality

In such instances, the TCEQ selects a URF (MLE) as the best estimate of cancer potency (e.g., TCEQ 2011, 2012, 2014). USEPA also selected the URF (MLE) as the best estimate for their URF since the 95%UCL represented "an unnecessary added level of conservatism." Additionally, Texas background lung cancer mortality rates and survival probabilities are preferred by the TCEQ. Lastly, the Park et al. (2012) analysis that adjusted for arsenic exposure and ethnicity is preferred since, for example, study authors report that previous associations between cadmium exposure and lung cancer were confounded by arsenic. This analysis also happens to result in a slightly higher final URF (MLE), as does the analysis where the "α" term value (0.67) was modeled (compared to results from the model where the "α" term value was set to 0.8 or the model without this term). Therefore, based on the preferred analysis and model, the TCEQ selects the final URF of 4.9E-04 per μg Cd/m^3 (rounded to two significant figures).

4.2.3.1.6 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005b) provides default age-dependent adjustment factors (ADAFs) to account for potential increased susceptibility in children due to early-life exposure when a chemical has been identified as acting through a mutagenic MOA for carcinogenesis. While the mechanism for cadmium-induced lung carcinogenesis is likely multi-factorial (e.g., mimicry of essential nutrient metals, induction of reactive oxygen species and aberrant gene expression and signaling, inhibition of DNA repair, effects on apoptosis), the genotoxicity of cadmium is weak (Huff et al.

2007). As mentioned in Section 4.2.2, IARC (2012) indicates that among the mechanisms identified that potentially contribute to cadmium-induced carcinogenesis, direct binding to DNA appears to be of minor importance, and characterizes mutagenic responses as weak. As the MOA for cadmium-induced carcinogenesis is yet to be fully elucidated, cadmium has not been demonstrated to have a mutagenic MOA for lung carcinogenicity (e.g., cadmium does not directly induce mutagenesis; Luevano and Damodaran 2014). Therefore, ADAFs will not be applied at this time, consistent with both TCEQ and USEPA guidelines (USEPA 2005b; TCEQ 2015). This determination may be revisited in the future if and when significant new carcinogenic MOA data become available for cadmium.

4.2.3.2 Final URF and $^{chronic}ESL_{nonthreshold(c)}$

The final URF is 4.9E-04 per µg Cd/m^3. As the TCEQ considers cadmium and cadmium compounds as a group to be *Likely to Be Carcinogenic to Humans* via inhalation, the TCEQ's inhalation URF will be applied to all forms of cadmium. This URF represents an important update to the 1985 assessment by USEPA (USEPA 1985), which was based on a study that had only followed vital status in the cadmium worker cohort through 1978 (Thun et al. 1985). The TCEQ URF is based on the latest update of this cohort (Park et al. 2012) with an additional 24 years of follow-up (through 2002) to more completely and accurately ascertain the lung cancer mortality experience of these cadmium production workers. Based on the final URF, the air concentration corresponding to the no significant excess risk level of 1 in 100,000 is 0.020 µg Cd/m^3 when rounded to two significant figures (i.e., 0.00001 / 4.9E-04 per µg Cd/m^3). Therefore, the $^{chronic}ESL_{nonthreshold(c)}$ is 0.020 µg Cd/m^3.

4.3 Welfare-Based Chronic ESL

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne cadmium.

4.4 Chronic Values for Air Permitting and Air Monitoring Evaluations

The chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 0.011 µg Cd/m^3
- $^{chronic}ESL_{threshold(nc)}$ = 0.0033 µg Cd/m^3
- $^{chronic}ESL_{nonthreshold(c)}$ = 0.020 µg Cd/m^3

The chronic ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 0.0033 µg Cd/m^3 as it is lower than the $^{chronic}ESL_{nonthreshold(c)}$ of 0.020 µg Cd/m^3 (Table 2). For evaluation of long-term ambient air monitoring data, the chronic ReV of 0.011 µg Cd/m^3 is lower than the $^{chronic}ESL_{nonthreshold(c)}$ of 0.020 µg Cd/m^3 (Tables 1 and 2). However, the $^{chronic}ESL_{nonthreshold(c)}$ value may also be used for the evaluation of long-term air data, in addition to the chronic ReV. The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) value is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Levels

4.5.1 Chronic Noncarcinogenic Inhalation Observed Adverse Effect Level

ATSDR (2012) indicates that as early signs of cadmium-induced kidney damage, abnormal biomarker levels (e.g., increased LMW proteins such as β2-microglobulin) are the most sensitive indicator of cadmium toxicity with alterations at urinary cadmium levels of 1 µg Cd/g creatinine and higher. This urinary level is similar to the lowest UCD_{10} (1.34 µg Cd/g creatinine) for a 10% increase in the prevalence of β2-microglobulin proteinuria (i.e., the critical effect) estimated from environmental exposure studies in ATSDR's meta-analysis of the urinary cadmium-response relationship. For noncarcinogenic effects with a threshold MOA, if BMD modeling is conducted, the central estimate BMD_{HEC} corresponding to the critical effect size (e.g., $BMD_{10\text{-}HEC}$ for decreased body weight) which does not require significant extrapolation below the range of the data is used as the lowest level where effects in the human population could be expected to occur (TCEQ 2015). Thus, the UCD_{10} of 1.34 µg Cd/g creatinine will be used as the POD to derive a chronic inhalation observed adverse effect level for tubular proteinuria (i.e., increased urinary excretion of β2-microglobulin) as an early adverse effect in the sequence of events leading to cadmium-induced compromised renal function (ATSDR 2012). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies may identify a lower POD for this purpose. Exposure to an airborne cadmium concentration of approximately 0.3 µg Cd/m^3 (with a dietary intake of 0.3 µg Cd/kg-day) would result in a urinary cadmium level of 1.34 µg Cd/g creatinine. This value represents a chronic (e.g., lifetime) concentration at which it is probable that similar effects could occur in some individuals exposed chronically to this level. Importantly, adverse effects are not a certainty due to potential intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 0.3 µg Cd/m^3 is provided for informational purposes only (TCEQ 2015).

The margin of exposure between the chronic inhalation observed adverse effect level of 0.3 µg Cd/m^3 and the chronic ReV of 0.011 µg Cd/m^3 is a factor of approximately 27.

4.5.2 Chronic Carcinogenic Inhalation Observed Adverse Effect Level

A chronic (e.g., lifetime) carcinogenic effect level may be estimated based on an evaluation of the dose-response data. More specifically, the lowest air concentration/exposure corresponding to excess risk observed in the key epidemiological study can be considered the lowest level for which cancer effects in some individuals in the human population would be expected with reasonable certainty if exposed over a similar (or longer) exposure duration than those in the epidemiological study. In this regard, lung cancer mortality was statistically increased only for the highest exposure group (mean cumulative exposure of 33,080 µg Cd/m^3-yr) with the SMR of 8.85 unadjusted for arsenic exposure and ethnicity (95% confidence interval = 1.47, 27.3). However, the 95% confidence interval (1.00, 4.07) for the SMR of 2.19 (unadjusted analysis) at a mean cumulative exposure of 11,130 µg Cd/m^3-yr just barely included 1 (see Table 8 above or Table 1 of Park et al. 2012), and the study reported a statistically significant SMR of 3.2 ($p = 0.012$) for a cumulative cadmium exposure of 10,000 µg Cd/m^3-yr (independent of arsenic; see

Table 3 of Park et al. 2012). The cumulative exposure of 10,000 µg Cd/m^3-yr corresponds to an estimated average occupational air concentration of approximately 1,560 µg Cd/m^3 (i.e., 10,000 µg Cd/m^3-yr / mean exposure duration of 6.4 years per Park et al. = 1,562.5 µg Cd/m^3). This chronic (e.g., lifetime) carcinogenic effect level of 1,560 µg Cd/m^3 is 78,000 times greater than the $^{chronic}ESL_{nonthreshold(c)}$ of 0.020 µg Cd/m^3. An important caveat for a chronic observed adverse effect level is that it may only be appropriately compared to a long-term average air concentration for an exposure duration that is greater than or equal to the duration for which the observed adverse effect level was derived. Additionally, adverse effects are not a certainty due to potential intraspecies differences in sensitivity, depending upon the sensitivity of the study population relative to that of those exposed environmentally. The chronic carcinogenic inhalation observed adverse effect level of 1,560 µg Cd/m^3 is provided for informational purposes only (TCEQ 2015).

Chapter 5 References

Acute Exposure Guideline Levels (AEGL). 2010. Interim Acute Exposure Guideline Levels (AEGLs) for Cadmium (CAS Reg. No. 7440-43-9), Interim. Available at http://www2.epa.gov/sites/production/files/2014-9/documents/cadmium_interim_sept_2010.pdf

Ades A, Kazantzis G. 1988. Lung cancer in a non-ferrous smelter: The role of cadmium. Br J Ind Med 45:435-442.

Åkesson A, Lundh T, Vahter M, et al. 2005. Tubular and glomerular kidney effects in Swedish women with low environmental cadmium exposure. Environ Health Perspect 113(11):1627-1631.

American Cancer Society. 2015. Cancer facts and figures. Available at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf

ATSDR. 2008. Draft Toxicological Profile for Cadmium. Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR. 2012. Toxicological profile for cadmium. Agency for Toxic Substances and Disease Registry (ATSDR). Available at http://www.atsdr.cdc.gov/toxprofiles/tp5.pdf

Baranski B. 1984. Behavioral alterations in offspring of female rats repeatedly exposed to cadmium oxide by inhalation. Toxicol Lett 22:53-61.

Baranski B. 1985. Effect of exposure of pregnant rats to cadmium on prenatal and postnatal development of the young. J Hyg Epidemiol Microbiol Immunol 29:253-262.

Baranski B, Sitarek K. 1987. Effect of oral and inhalation exposure to cadmium on the oestrous cycle in rats. Toxicol Lett 36:267-273.

Bernard A. 2016. Confusion about cadmium risks: the unrecognized limitations of an extrapolated paradigm. Environ Health Perspect 124:1-5.

Bernard A, Roels H, Cardenas A, et al. 1990. Assessment of urinary protein 1 and transferrin as early markers of cadmium nephrotoxicity. Br J Ind Med 47:559-565.

Bernard A, Stolte H, DeBroe M, et al. 1997. Urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. IV. Current information on interpreting the health implications of tests. Renal Fail 19(4):553-566.

Boudreau J, Vincent R, Nadeau D, et al. 1988. Toxicity of inhaled cadmium chloride: early responses of the antioxidant and surfactant systems in rat lungs. J Toxicol Environ Health 23(2):241-256.

Boudreau J, Vincent R, Nadeau D, et al. 1989. The response of the pulmonary surfactant-associated alkaline phosphatase following acute cadmium chloride inhalation. Am Ind Hyg Assoc J 50:331-335.

Brzóska M, Moniuszko-Jakoniuk J. 2005a. Effect of low-level lifetime exposure to cadmium on calciotropic hormones in aged female rats. Arch Toxicol 79(11):636-646.

Brzóska MM, Moniuszko-Jakoniuk J. 2005b. Disorders in bone metabolism of female rats chronically exposed to cadmium. Toxicol Appl Pharmacol 202(1):68-83.

Buchet J, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Buckley B, Bassett D. 1987. Pulmonary cadmium oxide toxicity in the rat. J Toxicol Environ Health 22:233-250.

Bus J, Vinegar A, Brooks S. 1978. Biochemical and physiologic changes in lungs of rats exposed to a cadmium chloride aerosol. Am Rev Respir Dis 118:573-580.

Byber K, Lison D, Verougstraete V, et al. 2016. Cadmium or cadmium compounds and chronic kidney disease in workers and the general population: a systematic review. Crit Rev Toxicol 46(3):191-240.

CalEPA. 2000. Determination of noncancer chronic reference exposure levels: chronic toxicity summary for cadmium and cadmium compounds, December 2000. California Environmental Protection Agency (CalEPA). Available at http://oehha.ca.gov/air/hot_spots/2008/AppendixD3_final.pdf#page=59

Cardenas A, Bernard A, Lauwerys R. 1992. Incorporation of [^{35}S]sulfate into glomerular membranes of rats chronically exposed to cadmium and its relation with urinary glycosaminoglycans and proteinuria. Toxicology 76:219-231.

Chan O, Poh S, Lee H, et al. 1988. Respiratory function in cadmium battery workers: A follow-up study. Ann Acad Med Singapore 17:283-287.

Chen L, Jin T, Huang B, et al. 2006a. Plasma metallothionein antibody and cadmium-induced renal dysfunction in an occupation population in China. Toxicol Sci 91(1):104-112.

Chen L, Jin T, Huang B, et al. 2006b. Critical exposure level of cadmium for elevated urinary metallothionein: An occupational population study in China. Toxicol Appl Pharmacol 215(1):93-99.

Cherian M, Shaikh Z. 1975. Metabolism of intravenously injected cadmium-binding protein. Biochem Biophys Res Commun 65:863-869.

Chia K, Tan A, Chia S, et al. 1992. Renal tubular function of cadmium exposed workers. Ann Acad Med Singapore 21(6):756-759.

Choudhury H, Harvey T, Thayer W, et al. 2001. Urinary cadmium elimination as a biomarker of exposure for evaluating a cadmium dietary exposure-biokinetics model. J Toxicol Environ Health A 63:321-350.

Christensen E, Birn H. 2001. Megalin and cubilin: synergistic endocytic receptors in renal proximal tubule. Am J Physiol Renal Physiol 280:F562–F573.

Christensen E, Devuyst O, Dom G, et al. 2003. Loss of chloride channel ClC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules. In: Proceedings of the National Academy of Sciences of the United States of America, Vol. 100, No. 14:8472-8477.

Cormet-Boyaka E, Jolivette K, Bonnegarde-Bernard A, et al. 2012. An NF-jB–independent and Erk1/2-dependent mechanism controls CXCL8/IL-8 responses of airway epithelial cells to cadmium. Toxicol Sci 125(2):418-429.

Cortona G, Apostoli P, Toffoletto F, et al. 1992. Occupational exposure to cadmium and lung function. In: Nordberg GF, Herber RFM, Alessio L, eds. Cadmium in the human environment: Toxicity and carcinogenicity. IARC Scientific Publications No. 118. Lyon, France: International Agency for Research on Cancer, 205-210.

Crump K, Allen B. 1985. Methods for quantitative risk assessment using occupational studies. Journal of the American Statistical Association 39(4):442-450.

Davison A, Fayers P, Taylor A, et al. 1988. Cadmium fume inhalation and emphysema. Lancet 1(8587):663-667.

Dorian C, Gattone V, Klaasen C. 1992a. Renal cadmium deposition and injury as a result of accumulation of cadmium-metallothionein (CdMT) by the proximal convoluted tubules: A light microscopic autoradiography study with ^{109}CdMT. Toxicol Appl Pharmacol 114:173-181.

Dorian C, Gattone V, Klaasen C. 1992b. Accumulation and degradation of the protein moiety of cadmium-metallothionein (CdMT) in the mouse kidney. Toxicol Appl Pharmacol 117:242-248.

Dorian C, Gattone V, Klaasen C. 1995. Discrepancy between the nephrotoxic potencies of cadmium-metallothionein and cadmium chloride and the renal concentration of cadmium in the proximal convoluted tubules. Toxicol Appl Pharmacol 130:161-168.

Dorian C, Klaassen C. 1995. Protection by zinc-metallothionein (znmt) against cadmium-metallothionein-induced nephrotoxicity. Fundam Appl Toxicol 26(1):99-106.

Dudley R, Gammal L, Klaassen C. 1985. Cadmium-induced hepatic and renal injury in chronically exposed rats: Likely role of hepatic cadmium-metallothionein in nephrotoxicity. Toxicol Appl Pharmacol 77:414-426.

Edling C, Elinder C, Randma E. 1986. Lung function in workers using cadmium-containing solders. Br J Ind Med 43:657-662.

Elinder C. 1985. Cadmium: Uses, occurrence and intake. In: Friberg L, Elinder CG, Kjellström T, et al., eds. Cadmium and health: A toxicological and epidemiological appraisal. Vol. I. Exposure, dose, and metabolism. Effects and response. Boca Raton, FL: CRC Press, 23-64.

Elinder C. 1986. Respiratory effects. In: Friberg L, Elinder CG, Kjellström T, et al., eds. Cadmium and health: A toxicological and epidemiological appraisal. Vol. II. Effects and response. Boca Raton, FL: CRC Press, 1-20.

Ellis K, Yuen K, Yasumura S, et al. 1984. Dose-response analysis of cadmium in man: Body burden vs kidney dysfunction. Environ Res 33:216-226.

Ellis K, Cohn S, Smith T. 1985. Cadmium inhalation exposure estimates: Their significance with respect to kidney and liver cadmium burden. J Tox Environ Health 15:173-187.

European Chemicals Bureau. 2007. European union risk assessment report. Cadmium metal and cadmium oxide. Luxembourg: European Chemicals Bureau, Institute for Health and Consumer Protection. Available at: http://echa.europa.eu/documents/10162/4ea8883d-bd43-45fb-86a3-14fa6fa9e6f3

Falck F, Fine L, Smith R, et al. 1983. Occupational cadmium exposure and renal status. Am J Ind Med 4:541-549.

Foulkes E. 1978. Renal tubular transport of cadmium-metallothionein. Toxicol Appl Pharmacol 45:505-512.

Gill K, Pal R, Sandhir R, et al. 1989. Effect of chronic cadmium exposure on lipid composition and peroxidation in liver and kidneys in rats. Med Sci Res 17:921-924.

Glaser U, Kloppel H, Hochrainer D. 1986. Bioavailability indicators of inhaled cadmium compounds. Ecotoxicol Environ Saf 11:261-271.

Goyer R, Miller C, Zhu S, et al. 1989. Non-metallothionein-bound cadmium in the pathogenesis of cadmium nephrotoxicity in the rat. Toxicol Appl Pharmacol 101:232-244.

Graham J, Miller F, Daniels M, et al. 1978. Influence of cadmium, nickel, and chromium on primary immunity in mice. Environ Res 16:77-87.

Greenspan B, Morrow P. 1984. The effects of in vitro and aerosol exposures to cadmium on phagocytosis by rat pulmonary macrophages. Fundam Appl Toxicol 4(1):48-57.

Greenspan B, Morrow P, Ferin J. 1988. Effects of aerosol exposures to cadmium chloride on the clearance of titanium dioxide from the lungs of rats. Exp Lung Res 14:491-500.

Grose E, Richards J, Jaskot R, et al. 1987. A comparative study of the effects of inhaled cadmium chloride and cadmium oxide: Pulmonary response. J Toxicol Environ Health 21:219-232.

Hart B. 1986. Cellular and biochemical response of the rat lung to repeated inhalation of cadmium. Toxicol Appl Pharmacol 82:281-291.

Henderson R, Rebar A, Pickrell J, et al. 1979. Early damage indicators in the lung. III. Biochemical and cytological response of the lung to inhaled metal salts. Toxicol Appl Pharmacol 50:123-136.

Herron N. 2001. Cadmium Compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology, 5th ed., Vol. 4. New York: John Wiley & Sons, pp. 507-523.

Hu J, Han T, Chen J, et al. 2014. Benchmark dose estimation for cadmium-induced renal tubular damage among environmental cadmium-exposed women aged 35-54 years in two counties of China. PLoS ONE 9(12):e115794.doi:10.1371/journal.pone.0115794. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4275258/pdf/pone.0115794.pdf

Huff J, Ruth M, Waalkes M, et al. 2007. Cadmium-induced cancers in animals and humans. Int J Environ Health 13(2):202-212.

IARC. 2012. Cadmium and cadmium compounds. In: IARC monographs on the evaluation of carcinogenic risks to humans. Arsenic, metals, fibres, and dusts. IARC monographs, Vol.

100 C. Lyon, France: International Agency for Research on Cancer (IARC). Available at http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C.pdf

ICRP. 1980. Metabolic data for cadmium. Limits for intakes of radionuclides by workers. Protection Pergamon Press, NY: International Commission on Radiological, 42-44. ICRP Publication No. 30, Part 2.

ICRP. 1994. Human respiratory tract model for radiological protection. Pergamon Press, Oxford: International Commission on Radiological Protection. ICRP publication 66.

International Cadmium Association. 2011. Available at http://www.cadmium.org

Jakubowski M, Trojanowska B, Kowalska G, et al. 1987. Occupational exposure to cadmium and kidney dysfunction. Int Arch Occup Environ Health 59:567-577.

Jakubowski M, Razniewska G, Halatek T, et al. 1992. Integrated index of occupational exposure to cadmium as a predictor of kidney dysfunction. Cadmium in the human environment: Toxicity and carcinogenicity. IARC Sci Publ 118:319-324.

Jamall I, Naik M, Sprowls J, et al. 1989. A comparison of the effects of dietary cadmium on heart and kidney oxidant enzymes: Evidence for the greater vulnerability of the heart to cadmium toxicity. J Appl Toxicol 9:339-345.

Jamall I, Smith J. 1985a. Effects of cadmium on glutathione peroxidose, superoxide dismutase and lipid peroxidation in the rat heart: A possible mechanism of cadmium cardiotoxicity. Toxicol Appl Pharmacol 80:33-42.

Jamall I, Smith J. 1985b. The effects of dietary selenium on cadmium binding in rat kidney and liver. Arch Toxicol 56:252-255.

Järup L, Elinder C, Spang G. 1988. Cumulative blood-cadmium and tubular proteinuria: A dose-response relationship. Int Arch Occup Environ Health 60:223-229.

Järup L, Elinder C. 1994. Dose-response relations between urinary cadmium and tubular proteinuria in cadmium-exposed workers. Am J Ind Med 26(6):759-769.

Järup L, Bellander T, Hogstedt C, et al. 1998. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occup Environ Med 55(11):755-759.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Jin T, Nordberg G, Ye T, et al. 2004. Osteoporosis and renal dysfunction in a general population exposed to cadmium in China. Environ Res 96(3):353-359.

Joseph P. 2009. Mechanisms of cadmium carcinogenesis. Toxicol Appl Pharmacol 238(3):272-279.

Kazantzis G, Lam T, Sullivan K. 1988. Mortality of cadmium-exposed workers. A five-year update. Scand J Work Environ Health 14:220-223.

Kjellström T, Nordberg G. 1978. A kinetic model of cadmium metabolism in the human being. Environ Res 16:248-269.

Klimisch H. 1993. Lung deposition, lung clearance and renal accumulation of inhaled cadmium chloride and cadmium sulphide in rats. Toxicology 84:103-124.

Kobayashi E, Suwazono Y, Uetani M, et al. 2006. Estimation of benchmark dose as the threshold levels of urinary cadmium, based on excretion of total protein, β2-microglobulin and N-acetyl-β-Dglucosaminidase in cadmium nonpolluted regions in Japan. Environ Res 101(3):401-406.

Kotsonis F, Klaassen C. 1978. The relationship of metallothionein to the toxicity of cadmium after prolonged administration to rats. Toxicol Appl Phamacol 46:39-54.

Krzystyniak K, Fournier M, Trottier B, et al. 1987. Immunosuppression in mice after inhalation of cadmium aerosol. Toxicol Lett 38:1-12.

Kutzman R, Drew R, Shiotsuka R, et al. 1986. Pulmonary changes resulting from subchronic exposure to cadmium chloride aerosol. J Toxicol Environ Health 17:175-189.

Lamm S, Parkinson M, Anderson M, et al. 1992. Determinants of lung cancer risk among cadmium exposed workers. Ann Epidemiol 2:195-211.

Lamm S, Hall T, Kutcher J. 1994. Particulate exposure among cadmium workers: Is the risk due to cigarette, cadmium or arsenic particulates? Ann Occup Hyg 38:873-878.

Lemen R, Lee J, Wagoner J, et al. 1976. Cancer mortality among cadmium production workers. Ann N Y Acad Sci 271:273-279.

Liu J, Liu Y, Habecbu S, et al. 1998. Susceptibility of MT-null mice to chronic $CdCl_2$-induced nephrotoxicity indicates that renal injury is not mediated by the CdMT complex. Toxicol Sci 46(1):197-203.

Luevano J, Damodaran C. 2014. A review of molecular events of cadmium-induced carcinogenesis. J Environ Pathol Toxicol Oncol 33(3):183-194.

Maret W, Moulis J. 2013. The bioinorganic chemistry of cadmium in the context of its toxicity. Metal Ions Life Sci 11:1-29.

Morrow H. 2001. Cadmium and Cadmium Alloys. In: Kirk-Othmer Encyclopedia of Chemical Technology, 5th ed., Vol. 4. New York: John Wiley & Sons, pp. 471-507.

National Resources Canada. 2007. Canadian Minerals Yearbook.

NRC. 1983. Risk Assessment in Federal Government. National Academy Press, Washington, DC.

NRC. 1988. Health risks of radon and other internally deposited alpha-emitters: BEIR IV. Washington, DC: National Academy Press.

NRC. 1994. Science and Judgment in Risk Assessment. National Academy Press, Washington, DC.

NTP. 1995. NTP technical report on toxicity studies of cadmium oxide (CAS No. 1306-19-0) administered by inhalation to F344/N rats and B6C3F mice. Research Triangle Park, NC: National Toxicology Program. Toxicity report series number 39. Available at https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox039.pdf

NTP. 2014. Report on carcinogens. Thirteenth Edition. US Department of Health and Human Services, Public Health Service, National Toxicology Program (NTP). Available at http://ntp.niehs.nih.gov/ntp/roc/content/profiles/cadmium.pdf

Oldiges H, Hochrainer D, Glaser U. 1989. Long-term inhalation study with Wistar rats and four cadmium compounds. Toxicol Environ Chem 19:217-222.

OSHA. 1992. Occupational Exposure to Cadmium, Final Rule. Occupational Safety and Health Administration (OSHA). Federal Register 57:42102 (September 14, 1992).

Palmer K, Mari F, Malian M. 1986. Cadmium-induced acute lung injury: Compromised repair response following thyroidectomy. Environ Res 41:568-584.

Park R, Stayner L, Petersen M, et al. 2012. Cadmium and lung mortality accounting for simultaneous arsenic exposure. Occup Envir Med 69:303-309.

Petering H, Choudhury H, Stemmer K. 1979. Some effects of oral ingestion of cadmium on zinc, copper and iron metabolism. Environ Health Perspect 28:97-106.

Prigge E. 1978. Inhalative cadmium effects in pregnant and fetal rats. Toxicology 10:297-309.

Rennolds J, Smith M, Fatemat H, et al. 2012. Curcumin regulates airway epithelial cell cytokine responses to the pollutant cadmium. Biochem Biophys Res Commun 417(1):256-261.

Roels H, Bernard A, Cardenas A, et al. 1993. Markers of early renal changes induced by industrial pollutants. III. Application to workers exposed to cadmium. Brit J Ind Med 50:37-48.

Rusch G, O'Grodnick J, Rinehart W. 1986. Acute inhalation study in rat of comparative uptake, distribution and excretion of different cadmium containing materials. Am Ind Hyg Assoc 47:754-763.

Sendelbach L, Klaassen C. 1988. Kidney synthesizes less metallothionein than liver in response to cadmium chloride and cadmium-metallothionein. Toxicol Appl Pharmacol 92:95-102.

Shaikh Z, Tohyama C, Noland C. 1987. Occupational exposure to cadmium: Effect on metallothionein and other biological indices of exposure and renal function. Arch Toxicol 59:360-364.

Shimizu A, Kobayashi E, Suwazono Y, et al. 2006. Estimation of benchmark doses for urinary cadmium based on β2 -microglobulin excretion in cadmium-polluted regions of the Kakehashi River basin, Japan. Int J Environ Health Res 16(5):329-337.

Smith T, Petty T, Reading J, et al. 1976. Pulmonary effects of chronic exposure to airborne cadmium. Am Rev Resp Dis 114:161-169.

Snider G, Hayes J, Korthy A, et al. 1973. Centrilobular emphysema experimentally induced by cadmium chloride aerosol. Am Rev Resp Dis 108:40-48.

Sorahan T. 1987. Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946- 1984. Br J Ind Med 44:803-809.

Sorahan T, Lancashire R. 1994. Lung cancer findings from the NIOSH study of United States cadmium recovery workers: A cautionary note. Occup Environ Med 51(2):139-140.

Sorahan T, Lancashire R. 1997. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: An analysis with detailed job histories. Occup Environ Med 54(3):194-201.

Sorahan T, Waterhouse J. 1983. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br J Ind Med 40:293-300.

Squibb K, Pritchard J, Fowler B. 1984. Cadmium-metallothionein nephropathy: Relationships between ultrastructural/biochemical alterations and intracellular cadmium binding. J Pharmacol Exp Ther 229:311-321.

Stayner L, Smith R, Thun M, et al. 1992. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. Ann Epidemiol 2(3):177-194.

Stayner L, Smith R, Schorr T, et al. 1993. Letter to the editor. Ann Epidemiol 3(1):114-116.

Stayner L, Bailer A, Smith R, et al. 1999. Sources of uncertainty in dose-response modeling of epidemiological data for cancer risk assessment. Ann NY Acad Sci 895:212-222.

Stowe H, Wilson M, Goyer R. 1972. Clinical and morphological effects of oral cadmium toxicity in rabbits. Arch Pathol 94:389-405.

Suwazono Y, Saloman S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Suzuki C, Cherian M. 1987. Renal toxicity of cadmium-metallothionein and enzymuria in rats. J Pharmacol Exp Ther 240:314-319.

Takenaka S, Oldiges H, Konig H, et al. 1983. Carcinogenicity of cadmium chloride aerosols in Wistar rats. J Natl Cancer Inst 70:367-373.

Takenaka S, Karg E, Kreyling W, et al. 2004. Fate and toxic effects of inhaled ultrafine cadmium oxide particles in the rat lung. Inhal Toxicol 16:83-92.

ten Berge W, Zwart A, Appelman L. 1986. Concentration-time mortality response relationship of irritant and systemically acting apours and gases. J Hazard Mater 13(3):301-309.

TCEQ. 2011. Development support document for nickel and inorganic nickel compounds. Texas Commission on Environmental Quality (TCEQ).

TCEQ. 2012. Development support document for arsenic and inorganic arsenic compounds. Texas Commission on Environmental Quality (TCEQ).

TCEQ. 2014. Development support document for hexavalent chromium. Texas Commission on Environmental Quality (TCEQ).

TCEQ. 2015. Guidelines to develop toxicity factors. RG-442: Texas Commission on Environmental Quality (TCEQ).

Thun M, Schnorr T, Smith A, et al. 1985. Mortality among a cohort of U.S. cadmium production workers-an update. J Natl Cancer Inst 74:325-333.

Toffoletto F, Apostoli P, Ghezzi I, et al. 1992. Ten-year follow-up of biological monitoring of cadmium exposed workers. In: Nordgerg GF, Herber RFM, Alessio L, eds. Cadmium in the human environment: Toxicity and carcinogenicity. Geneva: International Agency for Research on Cancer, 107-111.

UNEP. 2008. Interim Review of Scientific Information on Cadmium. Geneva: United Nations Environment Program (UNEP).

UNEP. 2010. Review of Scientific Information on Cadmium. Geneva: United Nations Environment Program (UNEP). Available at http://www.unep.org/chemicalsandwaste/Portals/9/Lead_Cadmium/docs/Interim_reviews/UNEP_GC26_INF_11_Add_2_Final_UNEP_Cadmium_review_and_apppendix_Dec_2010.pdf

USGS. 2008. Mineral Commodity Summaries, Cadmium. pp. 42-43. Available at http://minerals.usgs.gov/minerals/pubs/mcs/2008/mcs2008.pdf

USEPA. 1985. Updated mutagenicity and carcinogenicity assessment of cadmium (addendum to the health assessment document for cadmium of May 1981). EPA-600/8-83-025F. U.S. Environmental Protection Agency (USEPA), Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC.

USEPA. 1986. Health assessment document for nickel and nickel compounds: final report. EPA/600/8-83/012F. U.S. Environmental Protection Agency (USEPA), Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

USEPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Research Triangle Park, NC: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency (USEPA).

USEPA. 1999. Toxicological review of cadmium and compounds in support of summary information on the integrated risk information system (IRIS), external review draft. U.S. Environmental Protection Agency (USEPA), Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

USEPA. 2005a. Guidelines for carcinogen risk assessment. EPA/630/P-03/001B. U.S. Environmental Protection Agency (USEPA), Risk Assessment Forum, Washington, DC.

USEPA. 2005b. Supplemental guidance for assessing susceptiblility from early-life exposure to carcinogens. EPA/630/R-03/003F. U.S. Environmental Protection Agency (USEPA), Risk Assessment Forum, Washington, DC.

Verschoor M, Herber R, van Hemmen, et al. 1987. Renal function of workers with low-level cadmium exposure. Scand J Work Environ Health 13:232-238.

Vestergaard P, Shaikh Z. 1994. The nephrotoxicity of intravenously administered cadmiummetallothionein: Effect of dose, mode of administration, and preexisting renal cadmium burden. Toxicol Appl Pharmacol 126:240-247.

Wittman R, Hu H. 2002. Cadmium exposure and nephropathy in a 28-year old female metals worker. Environ Health Perspect 110:1261-1266.

WHO. 2000. Air Quality Guidelines, 2nd ed. World Health Organization (WHO). Available at http://www.euro.who.int/__data/assets/pdf_file/0016/123073/AQG2ndEd_6_3Cadmium.PDF

Woo H, Chiu W, Jo S, et al. 2015. Benchmark dose for urinary cadmium based on a marker of renal dysfunction: a meta-analysis. PLoS ONE 10(5):e0126680. doi:10.1371/journal.pone.0126680. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430293/pdf/pone.0126680.pdf

Wu X, Jin T, Wang Z, et al. 2001. Urinary calcium as a biomarker of renal dysfunction in a general population exposed to cadmium. J Occup Environ Med 43(10):898-904.

Xu C, Holscher M, Jones M, et al. 1995. Effect of monoisoamyl meso-2,3-dimercaptosuccinate on the pathology of acute cadmium intoxication. J Toxicol Environ Health 45:261-277.

Appendix A. Linear Multiplicative Relative Risk Model (Crump and Allen 1985)

Robert L. Sielken Jr., Ph.D.
Ciriaco Valdez-Flores, Ph.D., P.E.
Sielken & Associates Consulting Inc.
3833 Texas Avenue, Suite, 230, Bryan, TX 77802
Tel: 979-846-5175; Fax: 979-846-2671; Email: SielkenAssoc@aol.com
TCEQ, Austin, TX

December 17, 2007

This appendix provides a general overview of the multiplicative Poisson relative risk model. The multiplicative relative risk Poisson regression models are well-known models frequently used in the analyses of epidemiological data. This appendix is not a comprehensive study of multiplicative relative risk models or Poisson regression models. Rather, this appendix is meant as a simple exposition identifying the specific model applied to the nickel risk characterization in this DSD. For more Poisson regression modeling, Feldman and Valdez-Flores (2010) provide a basic introduction to Poisson regression models and include simple examples applied to engineering. Crump and Allen (1995) provide a more in-depth development of additive and multiplicative Poisson regression models applied to health risk assessment. This later reference also discusses calculations of excess risks once a model has been fitted to data and a target population, with its corresponding background hazard rates and risks from competing causes, has been defined.

A.1 Adjustments for Possible Differences Between the Population Background Cancer Rate and the Cohort's Cancer Rate in the Relative Risk Model

The USEPA (1986) uses a relative risk model in their risk assessment for nickel to fit the observed number of cancer deaths in a cohort study. Section 8.3.3.2.1.1 in USEPA (1986) describes the equations used to find the slope and the variance of the slope in the relative risk model. The model presented by EPA can be easily solved analytically because it estimates only one parameter (i.e., the slope). This simple model, however, does not adjust for possible discrepancies between the cohort's cancer rate and the reference population background cancer rate. A model that uses reference population background cancer rates to fit the cohort's observed cancer rates should adjust for the possibility of discrepancies between the background cancer rates in the reference population and the cohort.

Crump and Allen (1985) discuss the relative risk model with an extra factor that accounts for the possibility of different background rates in an epidemiological cohort and its reference population. This extra factor may adjust for issues like the healthy worker effect, the difference between internally and externally derived background cancer rates, covariate effects not explicitly incorporated in the summary epidemiological data, etc. For example, EPA's model

with modified notation for the nickel carcinogenic assessment (USEPA 1986), the multiplicative or relative risk model can be extended from

$$E(O_j) = E_{oj} \times (1 + \beta \times d_j)$$

to

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

where the α term adjusts for any possible difference between the population's background cancer rates and the cohort's observed cancer rates.

In the equations above the variables are:

$E(O_j)$ = expected number of lung cancer deaths for exposure group j predicted by the model;

E_{oj} = expected number of background lung cancer deaths for exposure group j based on the reference population background cancer rates;

β = multiplicative factor by which background risk increases with cumulative exposure;

d_j = cumulative exposure for exposure group j;

α = multiplicative factor that accounts for differences in cancer mortality background rates between the study cohort and the reference population.

A.2 Estimating the Slope Parameter, β, in the Relative Risk Model Adjusting for Differences in Background Rates

Poisson regression is a standard modeling technique in epidemiological studies. Poisson regression relies on the assumption that the number of cancer deaths in a dose group follows a Poisson distribution with mean equal to the expected number of cancer deaths and uses the maximum likelihood estimation procedure for the estimation for the parameters α and β in the model.

The Poisson distribution that describes probabilistically the number of cancers observed in a group is given by:

$$P(x) = \lambda^x \times e^{-\lambda} / x!,$$

where P(x) is the probability of observing x cancers, x is the number of cancer deaths actually observed, x! = x (x-1) (x-2) … 1, and λ is the expected number of cancers in the group. Thus, for dose group j, $x_j=O_j$ and $\lambda_j= E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$. That is, for each group j of person-years with average dose d_j, the observed number of cancer deaths in the dose interval (O_j) follows a Poisson distribution with parameter $\lambda_j= E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$ and the likelihood of this is given by,

$$P(O_j) = \lambda_j^{Oj} \times e^{-\lambda j} / O_j!$$

The likelihood (L) is given by the product of the likelihoods of observing the number of cancer deaths in each dose group. That is,

$$L = P(O_1) \times P(O_2) \times \ldots.$$

or, equivalently,

$$L = (\lambda_1^{O1} \times e^{-\lambda 1} / O_1!) \times (\lambda_2^{O2} \times e^{-\lambda 2} / O_2!) \times \ldots.$$

where O_j is the number of cancer cases observed for the person-years with cumulative exposures equal to d_i. Substituting the value of λ_j by $\alpha \times E_{oj} \times (1 + \beta \times d_j)$ in the equation above, the likelihood is expressed as follows:

$$L = \prod [\alpha \times E_{oj} \times (1 + \beta \times d_j)]^{Oj} \times \exp\{-[\alpha \times E_{oj} \times (1 + \beta \times d_j)]\} / O_j!$$

where the symbol $\prod$ indicates that it is the product over all dose groups j=1,2,… and exp{.} is the base of the natural logarithm (e) raised to the power in the braces.

The maximum likelihood estimates of α and β can then be obtained by selecting the values of α and β that maximize the value of L. Finding the values of α and β that maximize the value of the likelihood L cannot be determined using a close-form solution as that offered by USEPA (1986), because here there are two variables, as opposed to only one being estimated by USEPA. However, any routine that can maximize non-linear functions of more than one variable can be used to calculate the maximum likelihood estimates of α and β.

The parameters α and β that maximize the likelihood function given above also maximize the logarithm of the likelihood because the logarithm is a monotone function. The logarithm of the likelihood (LL) of the function given above is,

$$LL = \sum \{ O_j \times \ln[\alpha \times E_{oj} \times (1 + \beta \times d_j)] - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] - \ln(O_j!) \}$$

where the symbol $\sum$ indicates that it is the sum over all dose groups j=1,2,… and ln(x) is the natural logarithm of x. The LL function can also be written as,

$$LL = \sum \{ O_j \times \ln(\alpha) + O_j \times \ln(E_{oj}) + O_j \times \ln(1 + \beta \times d_j) - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] - \ln(O_j!) \}.$$

Note that the terms $O_j \times \ln(E_{oj})$ and $\ln(O_j!)$ do not depend on the values of α and β, and hence, the values of α and β that maximize the LL also maximize the following simplified LL function:

$$LL = \sum \{ O_j \times \ln(\alpha) + O_j \times \ln(1 + \beta \times d_j) - [\alpha \times E_{oj} \times (1 + \beta \times d_j)] \}.$$

Finally, the maximum likelihood estimates of α and β can also be obtained by solving for α and β in the following system of equations:

$$(\partial LL) / (\partial \alpha) = \sum \{ O_j/\alpha - E_{oj} \times (1 + \beta \times d_j) \} = 0$$

$$(\partial LL) / (\partial \beta) = \sum \{ (O_j \times d_j) / (1 + \beta \times d_j) - \alpha \times E_{oj} \times d_j \} = 0$$

where $\partial LL/\partial\alpha$ and $\partial LL/\partial\beta$ are the partial derivatives of the logarithm of the likelihood with respect to α and β, respectively.

A.3 Estimating the Asymptotic Variance for the Slope Parameter in the Relative Risk Model

The system of equations of the partial derivatives of the logarithm of the likelihood given in the previous section can be used to estimate the asymptotic variance of the maximum likelihood estimates of α and β. The variance-covariance matrix of the parameters α and β is approximated by

$$\text{Cov}(\alpha,\beta) = - \begin{pmatrix} \partial^2 LL/\partial\alpha^2 & \partial^2 LL/\partial\alpha\partial\beta \\ \partial^2 LL/\partial\alpha\partial\beta & \partial^2 LL/\partial\beta^2 \end{pmatrix} -1$$

where $[.]^{-1}$ is the inverse of the matrix, $\partial^2 LL/\partial\alpha^2$ is the second partial derivative of the logarithm of the likelihood with respect to α, $\partial^2 LL/\partial\beta^2$ is the second partial derivative of the logarithm of the likelihood with respect to β, and $\partial^2 LL/\partial\alpha\partial\beta$ is the partial derivative of the logarithm of the likelihood with respect to α and β. The approximation of the covariance is then given by

$$\text{Cov}(\alpha,\beta) = - \begin{pmatrix} \partial^2 LL/\partial\beta^2 & -\partial^2 LL/\partial\alpha\partial\beta \\ -\partial^2 LL/\partial\alpha\partial\beta & \partial^2 LL/\partial\alpha^2 \end{pmatrix} / \text{Determinant}$$

where

$$\text{Determinant} = 1 / [\ \partial^2 LL/\partial\alpha^2 \times \partial^2 LL/\partial\beta^2 - (\partial^2 LL/\partial\alpha\partial\beta)^2\ ]$$

The second-order derivatives used for the estimation of the variance-covariance matrix are:

$$(\partial^2 LL) / (\partial\alpha^2) = \sum -O_j/\alpha^2$$

$$(\partial^2 LL) / (\partial\beta^2) = \sum -(O_j \times d_j^2) / (1 + \beta \times d_j)^2$$

$$(\partial^2 LL) / (\partial\alpha\partial\beta) = \sum -E_{oj} \times d_j$$

A better asymptotic variance calls for substituting the variance-covariance matrix of α and β by the expected value of the above matrix. That is, by replacing the observed number of cancer deaths in a dose group j (O_j) by its expected value (i.e., $E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$). After

substituting O_i by $\alpha \times E_{oj} \times (1 + \beta \times d_j)$ in the second-order derivatives and the variance-covariance matrix given above and some simplification, the better approximation of Cov(α,β) is given by:

$$\text{Cov}(\alpha,\beta) = \begin{pmatrix} \sum E_{oj} \times (1 + \beta \times d_j)/\alpha & \sum E_{oj} \times d_j \\ \sum E_{oj} \times d_j & \alpha \times \sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j) \end{pmatrix}^{-1}$$

The determinant for the matrix is

$$\text{Determinant} = [\sum E_{oj} \times (1 + \beta \times d_j)] \times [\sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j)] - (\sum E_{oj} \times d_j)^2$$

and the variance of the maximum likelihood estimate of α is

$$\text{var}(\alpha) = [\alpha \times \sum (E_{oj} \times d_j^2) / (1 + \beta \times d_j)] \ / \text{Determinant},$$

while the variance of the maximum likelihood estimate of β is

$$\text{var}(\beta) = [\sum E_{oj} \times (1 + \beta \times d_j)/\alpha] / \text{Determinant},$$

and the standard errors (SE) of the estimated parameters are the square root of their respective variances.

A.4 References

Crump, KS and BC Allen. 1985. Methods of Quantitative Risk Assessment Using Occupational Studies. *The Am* Stat 39: 442-450.

Feldman, R. M and C. Valdez-Flores, Applied Probability and Stochastic Processes, Second Edition, Springer-Verlag Berlin Heidelberg, 2010.

United States Environmental Protection Agency (USEPA). 1986 Health Assessment Document for Nickel and Nickel Compounds. EPA/600/8-83/012FF.

Appendix B. Lung Cancer Mortality Rates and Survival Probabilities

Years	US Total Population 2008-2012 Total Lung Cancer Mortality Rates per 100,000 [1]	Texas Statewide Population 2008-2012 Total Lung Cancer Mortality Rates per 100,000 [2]
00	0	0.1
01-04	0	0
05-09	0	0
10-14	0	0
15-19	0	0.1
20-24	0.1	0.1
25-29	0.2	0.2
30-34	0.5	0.5
35-39	1.5	1.1
40-44	5.1	3.5
45-49	16.6	12
50-54	36.9	31.2
55-59	64.4	56.8
60-64	109.9	97.9
65-69	186.8	172.2
70-74	266.2	247.5
75-79	336.6	317.3
80-84	375.5	348.4
85+	327.6	323.2

[1] Table 15.10, Surveillance, Epidemiology, and End Results, Cancer Statistics Review 1975-2012. Available at http://seer.cancer.gov/csr/1975_2012/results_merged/sect_15_lung_bronchus.pdf

[2] Texas age-specific lung and bronchus 2008-2012 cancer rates, Texas Department of State Health Services. Available at http://www.dshs.state.tx.us/tcr/data.shtm

2011 US All Life Tables [1]		2013 Total Texas Population Life Tables [2]	
Age	**Survival**	**Age**	**Survival**
0	1	0	1
1	0.99394	1	0.99418
5	0.99289	5	0.99307
10	0.99230	10	0.99244
15	0.99159	15	0.99176
20	0.98917	20	0.98948
25	0.98493	25	0.98536
30	0.98017	30	0.98075
35	0.97465	35	0.97545
40	0.96784	40	0.96899
45	0.95816	45	0.95971
50	0.94281	50	0.94482
55	0.91975	55	0.92151
60	0.88746	60	0.88732
65	0.84368	65	0.84132
70	0.78184	70	0.77921
75	0.69513	75+	0.69288
80	0.57493		
85	0.41733		

[1] Arias E. 2015. United States Life Tables, 2011. National Vital Statistics Reports 64(11):1-62, Table VI. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_11.pdf

[2] Table 24, Life Tables, Texas 2013. Texas Department of State Health Services. Available at http://www.dshs.state.tx.us/chs/vstat/vs13/t24.aspx

Appendix C. Uncertainty Analysis

This appendix presents an uncertainty analysis concerning the derivation of the inhalation URF and the $^{chronic}ESL_{nonthreshold(c)}$. Many of the areas discussed are common to risk assessments utilizing epidemiological studies.

C.1 Dose-Response Modeling

The $^{chronic}ESL_{nonthreshold(c)}$ of 0.020 µg Cd/m^3 is based on the best estimate of the slope β parameter from the Poisson regression model fit to the most appropriate available epidemiological data of workers exposed to cadmium (Park et al. 2012), which represent updated data for the same cohort used by USEPA for URF derivation (Thun et al. 1985). Maximum likelihood estimation with Poisson regression was used by the TCEQ and is preferred when the number of responses (i.e., observed and expected cases) is known, as in this case. The preferred multiplicative relative risk model used to calculate the β value included a term (α) to account for differences in lung cancer mortality background rates between the study population and the reference population used to determine the number of expected lung cancer mortalities. The use of this term may account for potential issues such as the healthy worker effect and any differences between internally- and externally-derived background rates. This represents the best TCEQ statistical analysis for the given epidemiological data so as not to increase the uncertainty and variability already present in the epidemiological data. In regard to the remaining variability and uncertainty, the final $^{chronic}ESL_{nonthreshold(c)}$ reflects some degree of variability and uncertainty inherent in all epidemiological studies that cannot be eliminated or further reduced with the available data. The excess risk of lung cancer mortality for the final $^{chronic}ESL_{nonthreshold(c)}$ could be as high as 2.0 in 100,000 if the highest URF (95% UCL) value based on Texas background rates were used for the final URF instead of the maximum likelihood estimate (MLE), and could be as low as zero if the β (95% LCL) value were predictive.

Conservatively, 5-yr lagged cumulative exposure was used as the dose metric, which increases the magnitude of the cadmium exposure parameter (β) in Poisson regression analysis compared to non-lagged exposure, was considered appropriate by Park et al. (2012), and is common since the most recent exposures may be etiologically irrelevant to cancer risk because of an apparent minimum delay between exposure and the effect of that exposure on cancer risk. Application of the URF derived using cumulative exposure to cadmium as the dose metric inherently treats all cadmium compounds as toxicologically equivalent based on cadmium content. This practice is consistent with the TCEQ considering cadmium compounds as a group to be *Likely to Be Carcinogenic to Humans* via inhalation.

URFs calculated with slope β parameter estimates corresponding to the MLE and 95% UCL were reported for the preferred model (which includes the modeled "α" term) and analysis (incorporating adjustments for arsenic exposure and ethnicity) in order to provide information on the uncertainty in excess risk. The ratio of the URF (95% UCL) to the preferred best estimate URF (MLE) of 4.9E-04 per µg/m^3 was approximately 2.1 (Table 10), indicative of the precision of the estimates. Additionally, this final URF (MLE) is the most conservative (i.e., highest)

among the six URF (MLE) values calculated using Texas rates. For example, the final URF is 2.1-fold higher (i.e., more conservative) than that based on the same analysis (with adjustments for arsenic exposure and ethnicity) using the multiplicative relative risk model without the "α" term (Table 10). It is important to also note that lung cancer was only statistically increased for one exposure group and was not statistically elevated overall (see SMRs of 1.06 and1.12 in Table 8), and that the negative β (95% LCL) value in Table 9 using the preferred multiplicative relative risk model (which includes the modeled "α" term) and analysis (incorporating adjustments for arsenic exposure and ethnicity) suggests that risk could be as low as zero.

C.2 Estimating Risks for the General Population from Occupational Workers

Human studies are preferred over animal studies to develop toxicity factors for chemicals to avoid uncertainty due to interspecies differences. However, as in the current case, human carcinogenic studies are usually epidemiological occupational studies, which themselves are subject to the following inherent uncertainties:

- The relationship between lung cancer mortality and exposure to cadmium was evaluated based on presumably healthy male workers employed in a cadmium smelter. The model may underestimate excess risks for subpopulations that are particularly more sensitive to cadmium exposures than cadmium smelter workers. Although workers are often healthier than the general population, the approach used by the TCEQ estimates how the risk of lung cancer changes with exposure to cadmium while adjusting for the differences between the worker and the general population background lung cancer rates (i.e., Texas general population lung cancer mortality background rates were used as opposed to those for the workers). The estimates of excess risk based on the derived models apply to the target population (e.g., Texas all sexes and all races) whose background lung cancer rates and survival probabilities are used in the estimation of the extra risks. The assumption being made in the calculation of the URFs is that the increase in the relative risk per unit increase in the dose metric (cumulative exposure) is the same for the workers and for the target population. Any populations with higher background lung cancer mortality rates would have higher estimated URFs, while any populations having lower background lung cancer rates would have lower estimated URFs.
- The general population does not have the same exposure levels as occupational workers, who are generally exposed to significantly higher concentrations. For example, workers were typically exposed to hundreds of µg Cd/m^3 (see Table 1 of Thun et al. 1985), while the approximate statewide mean is only 0.0008 µg Cd/m^3 (2005-2014).

C.3 Uncertainty Due to Potential Exposure Estimation Error

Results from epidemiology studies have uncertainties because of potential exposure estimation error or insufficient characterization of exposure data (e.g., range, peak, mean exposure levels). For example, while daily measurements from personal air samples for each cohort member would be ideal, epidemiologists must estimate exposure based on professional judgment and whatever exposure data are available (e.g., area and personal exposure air measurement data,

urinary cadmium and arsenic data, information on PPE, total dust and feedstock data). As is frequently the case, this was the case for the key study used for carcinogenic dose-response assessment (Park et al. 2012). See Section 4.2.3.1.1 and Park et al. (2012) for additional information on the detailed exposure assessment. In regard to uncertainty, if historical exposures were of lessor magnitude than concentration estimates used to derive the URF, cadmium risk would tend to be underestimated. Conversely, if historical exposures were of greater magnitude than concentration estimates used to derive the URF for this study, excess risk due to cadmium exposure would tend to be overestimated. Additionally, co-exposure to other carcinogens (e.g., arsenic) not adequately accounted for in the dose-response modeling would also tend to result in the overestimation of cadmium risk, and this possibility is discussed below.

C.4 Uncertainty Due to Co-Exposures to other Compounds

Excess lung cancer risk estimates can be confounded by smoking, which is common in epidemiological studies (i.e., many of the workers in such studies were smokers). However, both the prior update of this cohort (Stayner et al. 1992) and OSHA (1992) have previously examined this potential issue. Smoking habits would have to vary appreciably between the exposure categories to confound the relationship between cadmium and lung cancer, which was considered unlikely by Stayner et al. (1992). Additionally, Stayner et al. (1992) included a parameter for Hispanic ethnicity in their regression models as a surrogate for lower cigarette smoking (based on smoking statistics), which had little effect on cadmium exposure coefficients suggesting that smoking was not a strong confounder. OSHA (1992) also addressed the potential for confounding by smoking in this cohort and indicated that smoking information was available for 43% of the workers, and that these data do not suggest that differences in smoking habits (i.e., excess smoking in the cohort) could have accounted for the excess lung cancers observed. Thus, it appears unlikely that confounding by cigarette smoking was significant.

In regard to other co-exposures, the facility had been an arsenic smelter from 1918-1925, and a previous nested case-control analysis concluded that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk for this cohort (Lamm et al. 1992, 1994). As some arsenic is evolved during the cadmium recovery process (Stayner et al. 1992; Thun et al. 1985), it is possible that the URF could reflect some contribution of arsenic exposure in addition to that of cadmium. For example, the geometric mean of arsenic in facility feed material was estimated to be 2-3% during 1926-1940 (reaching 5-7% four years within this period), dropping to 1% afterwards (Stayner et al. 1992), and Thun et al. (1985) estimated an inhaled average of 14 μg arsenic/m^3 based on urinary arsenic levels for workers in the high-arsenic work areas (i.e., near the roasting and calcine furnaces). However, OSHA (1992) previously evaluated this potential issue and: (1) identified several issues with the work of Lamm et al. (e.g., estimates of arsenic exposure and arsenic content of the fines used as feedstock before/after 1940); (2) highlighted results of analyses conducted by Stayner et al. and Thun et al. that are inconsistent with the hypothesis that arsenic exposure was largely responsible for the increased lung cancer mortality observed for the cohort (e.g., the estimated β for cadmium exposure increased rather than deceased when year of hire was used by Stayner et al. as a proxy for arsenic exposure); (3) estimated that out of the 24 lung cancer deaths observed for the cohort as of 1984, no more than

1 was likely related to arsenic exposure (i.e., 0.97 based on the highest OSHA estimate of average arsenic exposure, and 0.52 based on the preferred estimate); and (4) concluded that the excess lung cancer mortality for this cohort is unlikely to be due to arsenic exposure or cigarette smoking and is more likely due to cadmium exposure.

More recently, in order to differentiate the effects of cadmium and arsenic on lung cancer risk, the Park et al. (2012) update of this cohort conducted a detailed retrospective exposure assessment for arsenic as had previously been performed for cadmium (e.g., mean exposure for cadmium was over ten times that for arsenic). Then, using prior estimates for the exposure-response for arsenic and lung cancer, the independent effect of cadmium was estimated. More specifically, in order to separate the independent contributions of the correlated exposures for cadmium and arsenic, models were fit in which the arsenic-associated lung cancer risk was imposed using exposure-response estimates from previous studies (this is a form of indirect adjustment for a confounder). Attributable lung cancer cases were calculated by applying the final constrained lung cancer rate model to the observation time of the study population alternately setting cadmium, arsenic, or neither metric to zero and then computing the predicted number of lung cancer deaths. Following this procedure in strata of cumulative cadmium exposure and then taking differences yielded estimated attributable lung cancer cases. Fourteen of the 36 total lung cancer deaths observed for the cohort (followed through 2002) were predicted to be attributable to cadmium exposure, while only five were predicted to be attributable to arsenic exposure. Most of the arsenic-attributed deaths occurred in the four lower strata of cadmium cumulative exposure. Moreover, for the three exposure groups with an SMR > 1, approximately 5-12 times more cases were predicted to be attributable to cadmium compared to arsenic (see Table 1 of Park et al. 2012). Park et al. concluded that dose-response analyses with the arsenic effect imposed using prior arsenic exposure-response estimates should largely remove mutual confounding between cadmium and arsenic exposures, and the TCEQ relied on such an analysis (adjusted for arsenic exposure) for derivation of the URF (see Tables 8-10). Thus, the TCEQ URF for cadmium is considered unlikely to be significantly affected by worker co-exposure to arsenic.