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Nickel and

Inorganic Nickel Compounds

CAS Registry Numbers:

Nickel: 7440-02-0

Nickel Sulfate: 7786-81-4

Nickel Subsulfide: 12035-72-2

Nickel Oxide: 1313-99-1

Nickel Chloride: 7718-54-9

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
AMCV	Air monitoring comparison values
BAL	bronchoalveolar lavage
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
$BMCL_{10}$	benchmark concentration lower corresponding to the 10% response level
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	benchmark dose software
BMR	benchmark response
C	concentration
Cal EPA	California Environmental Protection Agency
CI	confidence interval
CIIT	Chemical Industry Institute of Toxicology
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
D	exposure duration, hour per day
d	day
DF	deposition fraction in the target region of the respiratory tract
DAF	dosimetric adjustment factor
DNA	deoxyribonucleic acid
DSD	development support document
E	exposure level or concentration
EC	effective concentration
ET	extrathoracic
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{linear(c)}$	chronic health-based Effects Screening Level for linear dose response cancer effect

Acronyms and Abbreviations	Definition
$^{chronic}ESL_{linear(nc)}$	chronic health-based Effects Screening Level for linear dose response noncancer effects
$^{chronic}ESL_{nonlinear(c)}$	chronic health-based Effects Screening Level for nonlinear dose response cancer effects
$^{chronic}ESL_{nonlinear(nc)}$	chronic health-based Effects Screening Level for nonlinear dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
F	exposure frequency, days per week
FEV_1	Forced Expiratory Volume in one second
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HIF-1	hypoxia-inducible transcription factor-1
HQ	hazard quotient
IARC	International Agency for Research on Cancer
Ig	Immunoglobulins (Antibodies)
IgE	immunoglobulin E
IgM	immunoglobulin M
IRIS	Integrated Risk Information System
LCL	lower confidence limit
LDH	lactate dehydrogenase
LEC	lowest effective concentration
LOAEL	lowest-observed-adverse-effect-level
MF	modifying factor
MLE	maximum likelihood estimate
MW	molecular weight
µg	microgram
µm	micrometer
Mm	millimeter
min	minute
MMAD	mass median aerodynamic diameter
MPPD	multiple pass particle dosimetry
MOA	mode of action
MRL	Minimal Risk Level
NAAQS	National Ambient Air Quality Standards
NAC	National Advisory Committee
Ni	Nickel

Acronyms and Abbreviations	Definition
$NiCl_2$	Nickel Chloride
NiS_2	Nickel Disulfide
NiO	Nickel Oxide
Ni_3S_2	Nickel Subsulfide
$NiSO_4 \cdot 6H_2O$	Nickel Sulfate Hexahydrate
NiS	Nickel Sulfide
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NTP	National Toxicology Program
PBPK	physiologically-based pharmacokinetic model
PC	provocation concentration
PC_{20}	Provocation concentration producing a 20% decrease in Forced Expiratory Volume in one second
PM	particulate matter
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
POE	portal of entry
PU	pulmonary
ppbv	parts per billion by volume
ppm	parts per million
RDDR	regional deposited dose ratio
ReV	Reference Value
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
RPF	relative potency factor
RR	Rate Ratio
RTECS	Registry of Toxic Effects of Chemical Substances
SE	Standard Error
SIR	standardized incidence ratio
SMR	standardized mortality ratio
σ_g	geometric variance
T	time or exposure duration
TB	trachiobronchial
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TH	thoracic

Acronyms and Abbreviations	Definition
TLV	Threshold Limit Value
TRI	Toxics Release Inventory
TWA	Time-Weighted Average
TWA-TLV	Time-Weighted Average Threshold Limit Value
UCL	upper confidence limit
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
VE	minute ventilation
VE_{ho}	default occupational ventilation rate for an eight-hour day
VE_h	default non-occupational ventilation rate for a 24-h day

Chapter 1 Summary Table

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 respirable (particle size less than 10 micrometers (< 10 µm)) nickel and inorganic nickel compounds . Please refer to the Air Monitoring Comparison Value (AMCV) Document and Fact Sheet available at *AMCVs at TCEQ* for an explanation of the values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on nickel and nickel compound's physical/chemical data.

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

Short-Term Values	**Concentration**	**Notes**
Acute ReV (HQ = 1.0)	1.1 µg/m^3 **Short-Term Health**	**Critical Effect(s):** Bronchial constriction in human volunteers with occupational asthma
$^{acute}ESL_{odor}$	- - - **Odor**	No data found
$^{acute}ESL_{veg}$	- - - **Short-Term Vegetation**	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	0.23 µg/m^3	**Critical Effect(s):** Chronic active lung inflammation and associated lesions in rats
$^{chronic}ESL_{linear(c)}$	0.059 µg/m^3 [a] **Long-Term Health**	**Critical Effect(s):** Lung cancer in industrial workers
$^{chronic}ESL_{veg}$	- - - **Long-Term Vegetation**	No data found

[a] Based on an inhalation unit risk factor (URF) of 1.7×10^{-4} per µg/m^3.

Abbreviations used in Tables 1 and 2: **ppb**, parts per billion; **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$_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effects; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL.

Table 2. Air Permitting Effects Screening Levels (ESLs)

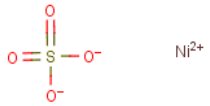
Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	0.33 µg/m^3 [a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Bronchial constriction in human volunteers with occupational asthma
$^{acute}ESL_{odor}$	- - - **Odor**	No data found
$^{acute}ESL_{veg}$	- - - **Short-Term Vegetation**	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	0.07 µg/m^3 [b]	**Critical Effect(s):** Chronic active lung inflammation and associated lesions in rats
$^{chronic}ESL_{linear(c)}$	0.059 µg/m^3 [c] **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Lung cancer in industrial workers
$^{chronic}ESL_{veg}$	- - - **Long-Term Vegetation**	No data found

[a] Based on the acute ReV of 1.1 µg/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

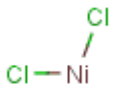
[b] Based on the chronic ReV of 0.23 µg/m^3 multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[c] Based on an inhalation unit risk factor (URF) of 1.7×10^{-4} per µg/m^3 and a no significant risk level of 1 in 100,000 excess cancer risk

Table 3. Chemical and Physical Properties

Parameter	Value	Value	Value	Reference
Name of Chemical	Nickel	Nickel Sulfate [a]	Nickel Subsulfide	ATSDR 2005
Molecular Formula	Ni	$NiSO_4$	Ni_3S_2	ChemIDplus Lite
Chemical Structure			Not Available	ChemIDplus Lite
Molecular Weight	58.69	154.75	240.12	ATSDR 2005
Physical State at 25°C	Solid	Solid	Solid	ATSDR 2005
Color	Silvery	Greenish-yellow	Pale yellowish	ATSDR 2005
Odor	Odorless	Odorless	No-data	ATSDR 2005
CAS Registry Number	7440-02-0	7786-81-4	12035-72-2	ATSDR 2005
Synonyms	CI 77775; Nickel 200; Nickel 201; Nickel 205; Nickel 207; Alnico; NP 2	Nickel monosulfate; nickelous sulfate; nickel (II) sulfate; sulfuric acid nickel salt	Trinickel disulfide; nickel sulfide; Heazlewoodite; nickel sesquisulfide; khislevudite; nickel tritadisulfide	ATSDR 2005
Solubility in water (mg/L)	1.13 at 37°C	293,000 at 0°C	517 at 37°C	ATSDR 2005
Log K_{ow}	No data	No data	No data	ATSDR 2005
Vapor Pressure (mm Hg)	1 at 1,810°C	No data	No data	ATSDR 2005
Relative Density (g/cm^3)	8.91	4.01	5.87	ATSDR 2005
Melting Point	1,455°C	840°C	787°C	ATSDR 2005
Boiling Point	2,730°C	Decomposes at 840°C	No data	ATSDR 2005

[a] Nickel sulfate is the parent compound for nickel sulfate hexahydrate (CAS # 10101-97-0).

Table 3. Chemical and Physical Properties (Continued)			
Parameter	Value	Value	Reference
Name of Chemical	Nickel Chloride	Nickel Oxide	ATSDR 2005
Molecular Formula	$NiCl_2$	NiO	ChemIDplus Lite
Chemical Structure			ChemIDplus Lite
Molecular Weight	129.6	74.69	ATSDR 2005
Physical State at 25°C	Solid	Solid	ATSDR 2005
Color	Golden yellow	Green or Black	ATSDR 2005
Odor	Odorless	No Data	ATSDR 2005
CAS Registry Number	7718-54-9	1313-99-1	ATSDR 2005
Synonyms	Nickel (II) chloride; nickel dichloride; nickelous chloride	Bunsenite;CI 77777; green nickel oxide; mononickel oxide; nickel(II) oxide; nickelous oxide; nickel monoxide; nickel oxide sinter 75; nickel protoxide; mononickel	ATSDR 2005
Solubility in water (mg/L)	642,000 at 20°C	1.1 at 20°C	ATSDR 2005
Log K_{ow}	No data	No data	ATSDR 2005
Vapor Pressure (mm Hg)	1 at 671°C	No data	ATSDR 2005
Relative Density (g/cm^3)	3.55	6.72	ATSDR 2005
Melting Point	1,001°C	1,955°C	ATSDR 2005
Boiling Point	Sublimes at 973°C	No data	ATSDR 2005

Chapter 2 Major Uses or Sources

Nickel and nickel compounds are valuable mineral commodities because of nickel's resistance to corrosion and its siderophilic (iron loving) nature, which facilitates the formation of nickel-iron alloys. The principal fixed sources that emit nickel into ambient air are:

- production sources (nickel ore mining/smelting and nickel matte refining);
- combustion and incineration sources (coal and oil burning units in utility, industrial, commercial and residential use sectors and municipal and sewage sludge incinerators);
- high temperature metallurgical sources (steel manufacturing, nickel alloy manufacturing, secondary nickel smelting, secondary nonferrous metal smelting, and iron and steel foundries);
- chemical and catalyst sources (nickel chemical manufacturing, electroplating, nickel cadmium battery manufacturing and catalyst production, use and reclamation); and
- miscellaneous sources (co-product recovery, cement manufacturing, coke ovens, asbestos mining/milling and cooling towers) (USEPA 1986).

Mobile sources that emit nickel are considered smaller contributors and derive primarily from engine wear and impurities in engine oil and fuel additives. Marine vessels are also significant mobile sources of nickel in areas near harbors (Galbreath *et al.* 2003). Nickel and nickel compounds in ambient and workplace air have been characterized based on their estimated emissions from historical and current sources, process knowledge, and sampling results (ICNCM 1990, Andersen *et al.* 1996, Grimsrud *et al.* 2000, Vincent *et al.* 2001, Seilkop *et al.* 2003, Sivulka and Seilkop 2009). Thus, determining the speciation of nickel in ambient air is very important for assessing the respiratory health risk associated with nickel (Galbreath *et al.* 2003). Nickel species are usually divided into four main categories:

- *metallic* (nickel CAS# 7440-02-0),
- *insoluble* (oxidic nickel CAS # 1313-99-1),
- *soluble* (including nickel sulfate CAS # 7786-81-4, nickel sulfate hexahydrate CAS # 10101-97-0, and nickel chloride CAS # 7718-54-9), and
- *sulfidic* (nickel subsulfide CAS# 12035-72-2).

Nickel compounds in these four categories can be separated by sequentially extracting increasingly less soluble forms of nickel using increasingly stronger leaching solutions (e.g., the Zatka method). Soluble nickel refers to compounds with water solubility between 0.001 and 0.5 mol/L. Insoluble nickel refers to compounds with water solubility less than 0.0001 mol/L. Slightly soluble is the term that applies to nickel compounds with water solubility between 0.0001 and 0.001 mol/L. Sulfidic nickel generally consists of nickel disulfide (NiS_2), nickel sulfide (NiS), and nickel subsulfide (Ni_3S_2). Metallic nickel consists of elemental nickel and its alloys (e.g., nickel-containing steels) (Goodman *et al.* 2009).

In regard to refinery nickel compounds, soluble nickel usually refers to highly water-soluble nickel salts such as nickel sulfate hexahydrate and nickel chloride hexahydrate, and may also include other nickel compounds depending upon the extraction method (e.g., hydrated nickel sulfate or carbonate). Insoluble nickel includes metallic, sulfidic (e.g., nickel subsulfide, nickel sulfide), and oxidic nickel (nickel oxides) (Goodman *et al.* 2009). Nickel subsulfide emissions are mainly associated with nickel refining and mining operations. According to ATSDR (2005), there are no nickel refining or mining operations in the United States. Based on 2005 Toxics Release Inventory (TRI) data (USEPA 2005), the top three sources of nickel and nickel compounds emissions in Texas were railroad equipment facilities, electric utilities, and petroleum refineries. These sources represented close to 90% of the nickel emissions in Texas in 2005. More recent 2008 TRI data reported the top three source of nickel and nickel compounds were all other basic inorganic chemical manufacturing, petroleum refineries, and fossil fuel electric power generation. The 2005 and 2008 estimated emissions of nickel and nickel compounds from these sources include varying percentages (35–65%) of metallic nickel, nickel sulfate, or nickel oxide (personal communication with Dr. Adrianna Oller, Nickel Institute 2008, 2010). Refer to Section 4.2.4 *Nickel Emissions from Texas Facilities*.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

This section is mainly based on a review of the toxicological literature provided in ATSDR (2005) and AEGL (2006). Acute animal toxicity studies have shown that the soluble forms of nickel (e.g., nickel sulfate, nickel chloride) are more toxic than the insoluble forms (e.g., nickel subsulfide, nickel oxide, metallic nickel) (Benson et al. 1986; Dunnick et al. 1988), probably due to the ability of soluble nickel compounds to cross the cell membrane (Snow and Costa 1992, Hansen and Stern 1984). Briefly, the NTP (1996a, 1996b, and 1996c) studies allowed for a comparison of the toxicity of various forms of nickel (i.e., nickel sulfate, nickel subsulfide, nickel oxide, soluble, water insoluble/less soluble, insoluble) in rats and mice. Following acute (and intermediate) exposure, the toxicity of the different nickel compounds were related to their solubility, with soluble nickel sulfate being the most toxic and nickel oxide being the least. In the key study selected by the Toxicology Division (TD) (Cirla et al. 1985), humans were exposed to a soluble and more toxic form of nickel, nickel sulfate. As a science policy decision, the TD will develop an acute reference value (acute ReV) and effects screening level (acuteESL) based on nickel sulfate and use its nickel equivalents as a surrogate for all inorganic forms of nickel (i.e., metallic, soluble, insoluble, and sulfidic). However, the acute ReV and acuteESL will not apply to organic forms of nickel (e.g., nickel carbonyl), which have different toxicity and chemical/physical properties than inorganic nickel compounds (ACGIH 2001, AEGL 2006).

Regarding nickel equivalents, the nickel equivalent for a given dose of a nickel compound is based on its nickel content, that is, the percent of the compound's molecular weight that nickel represents (e.g., the nickel equivalent for a nickel sulfate hexahydrate ($NiSO4·6H2O$) concentration of 300 µg/m3 = 300 µg/m3 × (MW of nickel in compound / MW of compound) = 300 µg/m3 × (58.71 / 262.89) = 67 µg/m3 of nickel). From a protection of public health

perspective, use of nickel equivalents based on nickel sulfate for the acute evaluation of other inorganic forms of nickel assumes that other forms are no more toxic than nickel sulfate on a nickel equivalent basis. Although this assumption is a function of a science policy decision to use acute ReV and acuteESL values based on nickel sulfate, it is likely a sufficiently conservative assumption as data from acute inhalation studies have indicated that nickel sulfate is the most toxic of the inorganic forms tested. In other words, the science policy decision was an informed one which considered available data from acute inhalation studies which indicate that other forms are unlikely to be more toxic than nickel sulfate. For example, the most conservative lowest-observed-adverse-effect-level (LOAEL) identified by ATSDR (2005) for short-term animal studies considered acute by TD (< 24 hours) is for nickel chloride with a nickel equivalent LOAEL of 250 µg Ni/m3 in mice (from Graham et al. 1978 discussed below). After adjustment to a human equivalent concentration, that LOAEL (563 µg Ni/m3) would be significantly higher than that based on nickel sulfate from the key Cirla et al. (1985) human study. As another example, the 16-day NTP studies (1996a,b,c) identified 700 µg Ni/m3 as a serious LOAEL for respiratory effects in nickel sulfate exposed rats, while 3,650 µg Ni/m3 was the serious LOAEL for respiratory effects in nickel subsulfide exposed rats, and even the less serious LOAEL for respiratory effects in nickel oxide exposed rats (7,900 µg Ni/m3) was significantly higher than the serious LOAEL for nickel sulfate. Based on the less serious LOAELs for respiratory effects in mice, these NTP studies showed the same general order of toxicity as discussed above for rats (i.e., nickel sulfate > nickel subsulfide > nickel oxide). Additionally, Adkins et al. (1979) showed that inhalation exposure to nickel sulfate impaired murine respiratory immunological function at a nickel equivalent concentration (LOAEL of 455 µg Ni/m3) lower than but similar to that for nickel chloride (LOAEL of 499 µg Ni/m3). These are some of the data which support the science policy decision (and the inherent underlying assumption) to use nickel sulfate for the derivation of acute ReV and acuteESL values as the most conservative (i.e., health protective) choice.

3.1.1 Chemical/Physical Properties and Key Studies

3.1.1.1 Chemical/Physical Properties

The main chemical and physical properties of nickel, nickel sulfate, nickel subsulfide, nickel chloride, and nickel oxide are summarized in Table 3. Bulk metallic nickel is a hard, lustrous, silvery white metal which, at ordinary temperatures in bulk form, is resistant to air and water assault. Nickel has typical metallic properties; it can be readily rolled, drawn into wire, forged, and polished. It is also ferromagnetic and a good conductor of both heat and electricity. Nickel forms useful alloys with many metals and is added to metals to increase their hardness, strength, and corrosion resistance. Powdered nickel is reactive in air and may spontaneously ignite (ATSDR 2005).

While nickel can exist in various oxidation states (-1, 0, +2, +3, +4), its only important oxidation state is divalent nickel (+2) under normal environmental conditions (ATSDR 2005). Divalent nickel exists either in particulate form or as a coordination/metal complex (i.e., a compound containing a metal ion and coordinate covalent bonds). The coordination/metal complex form is

believed to be the oxidation state that is readily absorbed by animals and humans, and has been shown to be more acutely toxic (Coogan *et al.* 1989)**.** Nickel sulfate, a divalent nickel compound, is being used for development of the acute ReV and ^{acute}ESL.

3.1.1.2 Key and Supporting Studies

3.1.1.2.1 Human Studies

Human studies are available and preferred over animal studies for calculation of the acute ReV and ^{acute}ESL (TCEQ 2006). No well-conducted human inhalation reproductive/developmental studies were identified. Nickel-specific hypersensitization (i.e., occupational asthma, dermatitis) and bronchoconstriction in occupational asthmatics are the most sensitive effects identified in human studies, and may result from susceptible individuals being exposed to nickel via inhalation (and dermal contact) (Dolovich *et al.* 1984, Davies *et al.* 1986, Nicklin *et al*. 1992). Acute-duration animal studies confirm that the respiratory tract is the most sensitive target following inhalation exposures, and provide strong evidence that nickel sulfate is more toxic to the lungs than nickel subsulfide or nickel oxide (ATSDR 2005, NTP 1996a, 1996b, 1996c). Nickel sulfate has frequently been associated with bronchial asthma in humans (Davies *et al.* 1986, Nieboer *et al.* 1992, Brera *et al.* 2005), and the selected key study (Cirla *et al.* 1985) provides evidence that soluble forms of nickel compounds are the primary cause of occupational asthmatic symptoms in the electroplating industry and related professions. Specifically, for the key study, the TD evaluated significant bronchoconstriction in nickel workers, a significant portion of whom were occupational asthmatics, following exposure to aerosolized nickel sulfate. The Cirla *et al.* (1985) study was selected as the basis for the acute assessment since it is human study of relevant exposure duration (1/2 hour) that evaluated a sensitive effect for likely the most sensitive target (respiratory system), reliable air exposure concentrations were available from the study, and the study group included a sensitive human subpopulation (asthmatics), thereby reducing the uncertainty and concern associated with intrahuman variability (i.e., the greater sensitivity of some individuals). No other study had all of these attributes, which are desirable in performing human health hazard assessments and deriving health-protective criteria. See ATSDR (2005) for a detailed discussion of other short-term studies, which is beyond the scope of this document. The key study is supported by Fernandez-Nieto *et al.* (2006), which demonstrated that specific inhalation challenges with nickel salts induced significant changes in bronchial hyperresponsiveness to methacholine.

3.1.1.2.1.1 Key Study – Cirla et al. (1985)

Human data indicate that acute nickel sulfate exposure can elicit significant bronchoconstriction in occupational asthmatics. Occupational asthmatics exhibit variable airflow limitation and/or airway hyperresponsiveness due to exposure to a specific agent (or conditions) in a work environment and not to stimuli encountered outside the workplace (Lombardo and Balmes 2000). Cirla et al. (1985) performed bronchial provocation tests in an exposure chamber on 12 workers (eight men, four women) from a nickel plating operation with recurring respiratory distress (e.g., coughing, wheezing, difficulty breathing) associated with work days. In one case, respiratory troubles were unfounded and only dermatitis was present, which was also present in

three other workers. There were seven asthmatics (clinically-confirmed) in this group, which the TD considers a sensitive subpopulation. The volunteers were exposed to an aerosol of nickel sulfate hexahydrate at a concentration of 300 µg/m3 for 30 minutes (min), for which 67 µg/m3 is the divalent nickel equivalent. Air concentrations for this study are discussed in the remainder of the document in terms of concentrations of nickel equivalents, as opposed to nickel sulfate hexahydrate. In addition, some subjects were challenged with copper, chromium, or iron salt aerosols as controls. All metallic salt solutions were nebulized to obtain the challenge airborne concentrations. Forced expiratory volume in one second (FEV1) was determined before and after the exposure during 24-hours (h). A greater than 15% decrease in FEV1, which is often a result of significant bronchoconstriction, was considered a positive response. Nickel inhalation in this study induced significant bronchoconstriction in six of the asthmatic subjects, although the specific magnitudes of the FEV1 decreases in these individuals were not given. Three of these subjects also experienced dermatitis, and some other subjects experienced rhinitis and chest tightness and/or dermatitis. Exposure to the control metal salts did not induce bronchial reactivity.

Cirla *et al.* (1985) also provided details of an inconclusive companion skin-test panel of 15 common allergens that was carried out by an intradermal technique in order to evaluate atopic status. Patch tests were applied for nickel sulfate, nickel chloride, potassium dichromate, copper sulfate, and cobalt sulfate, with evaluations after 20 min and 48 h. Immunoglobulin classes and total serum IgE were determined using an immunodiffusion test and radioimmunosorbent assay, respectively. Nickel-specific IgE antibodies were detected in three of the six asthmatics. The activation of IgE is commonly associated with immediate-type hypersensitivity (Nicklin 1992), and the three asthmatics with nickel-specific IgE antibodies experienced both an immediate and late reaction to inhalation exposure.

The TD considers the lowest-observed-adverse-effect-level (LOAEL) to be 67 µg Ni/m^3 based on positive bronchial provocation tests (greater than a 15% decrease in FEV_1) in six of seven asthmatics.

3.1.1.2.1.2 Fernandez-Nieto et al. (2006)

Even though reliable airborne concentrations were not made available, Fernandez-Nieto *et al.* (2006) provided a qualitative confirmation that the soluble forms of nickel are agents that can cause occupational asthma and an immune response. In the study, four male workers were exposed to potassium dichromate and nickel sulfate solutions. The subjects had a latency period of 12–36 months between first occupational exposure and the onset of asthma symptoms. All were ex-smokers or nonsmokers suspected of having occupational asthma. Two of the subjects worked in factories where potassium dichromate and nickel sulfate were used for electroplating, another subject worked in a cement factory (exposed to potassium dichromate), and one was a metal-arc welder (exposed to different metal fumes, including nickel and chromium). The potassium dichromate and nickel sulfate solutions were given separately at 0.001, 0.01, 0.1, 1.0, and 10.0 mg/ml in both the skin-prick test and specific inhalation challenge. The skin result was read 15 min after puncture, and results were expressed as the mean wheal/welt diameter. A

wheal diameter equal or greater than 3 millimeter (mm), accompanied by erythema, compared with the saline control, was considered a positive response.

The inhalation challenges were conducted with metallic solutions that increased dosages in 10-fold increments at intervals of 24 h. The nickel sulfate solutions were nebulized and delivered straight into a face mask and inhaled through the mouth, the nose being closed by a clip, by quiet tidal breathing for 2 min. FEV_1 and forced vital capacity were measured every 10 min during the first hour after inhalation exposure of each concentration and then hourly for 12 h. Control challenges with normal saline were conducted before provocation with metallic solutions. The inhalation challenge testing was discontinued when there was a fall in FEV_1 of 20% or more from the lowest post-saline value or when the highest concentration had been given. A fall in FEV_1 of 20% or more from the lowest post-saline value was considered a positive asthmatic reaction. To assess metallic salt-induced changes in bronchial hyperresponsiveness, methacholine inhalation tests were conducted the day before and 24 h after metallic salt challenge. A two-fold or greater reduction in the methacholine provocative concentration (PC) producing a 20% decrease in FEV_1 (post-metallic salt challenge PC_{20}) as compared to the pre-metallic salt challenge PC_{20} was considered significant.

Two subjects showed a decrease in FEV_1 of at least 20% in response to inhalation challenge with nickel sulfate, one with both early and late (dual) asthmatic reactions and one with a late asthmatic reaction. They also had a wheal diameter of 3-4 mm in response to the nickel skin prick test, although the role of skin testing in the diagnosis of metal-induced asthma is unclear. One subject was positive for nickel-specific IgE antibodies. The concentrations of nickel sulfate that elicited the dual asthmatic reaction and late asthmatic reactions were 10 and 0.1 mg/ml, respectively. At these concentrations, the study authors considered it highly unlikely that the asthmatic reactions that occurred were due to an irritant mechanism. A significant decrease in PC_{20} occurred in one of these subjects following inhalation exposure to nickel sulfate, indicating a nickel-induced change in bronchial hyperresponsiveness. The study authors indicate that nickel sulfate should be considered a true causative agent (inducer) of occupational asthma. The TD considers Fernandez-Nieto *et al.* (2006) informative as a supporting study because their results of nickel-induced asthmatic reactions and bronchial hyperresponsiveness support the positive bronchial provocation tests observed in the key study. However, a supporting acute ReV was not developed from this study primarily because reliable airborne concentrations of nickel were not available.

3.1.1.2.2 Animal Studies

Human data are available and used for derivation of the acute ReV and ^{acute}ESL based on bronchial hyperreactivity in occupational asthmatics, which may be immunologically (i.e. IgE) mediated at least in some cases. The National Toxicology Program (NTP) conducted subacute studies (NTP 1996a, 1996b, 1996c) with various forms of nickel (nickel sulfate, nickel subsulfide, nickel oxide), but the Graham *et al.* (1978) acute study is more appropriate in supporting the acute ReV. Animal data have also demonstrated effects involving the immune system. Graham *et al.* (1975, 1978) demonstrated that acute exposure to a number of trace

metals, including soluble nickel chloride, can cause immunosuppression in mice by negatively impacting the number of antibody-producing spleen cells. Graham *et al.* (1978) is used as a supporting study because it: (1) is an acute study; (2) utilizes another water soluble nickel compound (nickel chloride) and water soluble compounds are considered more acutely toxic as the acute toxicity of the different nickel compounds is primarily thought to be related to solubility; and (3) demonstrates an effect on the immune system, which may also play a role in the nickel-induced occupational asthma observed in human studies.

3.1.1.2.2.1 Supporting Study – Graham et al. (1978)

Swiss albino female mice, strain CD-1, were exposed to aerosolized nickel chloride for 2 h. As discussed in ATSDR (2005), the two lower nickel equivalent doses were 100 and 250 µg Ni/m^3, and the two higher exposure concentrations were approximately 380 and 490 µg Ni/m^3 (as read from the dose-response curve provided in Fig. 3 of Graham *et al.* 1978). Ninety-nine percent of the particles were less than 3 µm in diameter. Immediately 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. A linear regression analysis on the number of plaques per 10^6 cells of nickel chloride exposed mice showed a negative dose response at all concentrations greater than or equal to 250 µg Ni/m^3, which is considered the LOAEL. No significant difference was reported between the control group's number of plaques per 10^6 cells versus the mice exposed to 100 µg/m^3 nickel. Therefore, the TD considers this concentration (100 µg Ni/m^3) as the no-observed-adverse-effect-level (NOAEL).

3.1.1.2.2.2 Developmental Effects

Reproductive/developmental effects have been investigated in animals and occur at higher concentrations than concentrations causing respiratory effects. For example, a decrease in fetal body weight was observed in the offspring of rats exposed to 1,600 µg Ni/m^3 as nickel oxide 23.6 hours/day on gestation days 1–21 (Weischer *et al.* 1980 as cited in ATSDR 2005). No effect on fetal body weight was observed at 800 µg Ni/m^3, although decreased maternal body weight gain was observed at this concentration. No effects on the number of fetuses or on the weight of placenta were observed (ATSDR 2005).

3.1.2 Mode-of-Action Analysis and Dose Metric

The underlying mechanism involved in nickel asthma/bronchoconstriction studies has not yet been fully elucidated (Fernandez-Nieto *et al.* 2006), so as a default, a threshold, nonlinear dose-response relationship is used. The mode-of-action (MOA) for the acute critical effect, a greater than 15% decrease in FEV_1 along with asthmatic symptoms, is not fully known to inform the choice of the most appropriate dose metric. Therefore, the exposure concentration of nickel from the key and supporting studies was used as the default dose metric. Regardless, data on other dose metrics which may be more closely related to the critical effect are not available.

3.1.3 Point of Departure (POD) for the Key Study

A LOAEL of 67 µg Ni/m^3 from the Cirla *et al.* (1985) study was associated with significant bronchoconstriction (> 15% decrease in FEV_1). The TD chose to use this value as the POD_{HEC} to derive the acute ReV because it is a LOAEL based on a human exposure study that involved a sensitive population, occupational asthmatics.

In the acute animal study by Graham *et al.* (1978), mice were exposed to nickel chloride aerosol for 2 h. Mice exposed to 100 µg Ni/m^3 did not show evidence of a significant negative effect on the number of antibody-producing spleen cells (plaques per 10^6 cells). Therefore, 100 µg Ni/m^3 was considered a NOAEL and the relevant supporting POD.

3.1.4 Dosimetric Adjustments

3.1.4.1 Default Exposure Duration Adjustment

Human Study: An adjustment of the LOAEL of 67 µg Ni/m^3 (Cirla *et al.* 1985) from a 30-min exposure to a POD_{ADJ} of 1-h exposure duration (C_2) was conducted 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 = 1. This is the default procedure used when MOA information is lacking regarding whether both concentration and duration play a role in the effect observed in the key study and is generally considered to be conservative as it results in a relatively rapid decrease in concentration (TCEQ 2006):

$$C_2 = [(C_1) \times (T_1 / T_2)] = [(67\ \mu g\ Ni/m^3) \times (30\ min/60\ min)] = 33.5\ \mu g\ Ni/m^3 = POD_{ADJ}$$

Animal Study: No adjustment was conducted to convert the 2-h NOAEL of 100 µg Ni/m^3 (Graham *et al.* 1978) to a 1-h exposure duration since MOA information is lacking regarding whether both concentration and duration play a role in the effect observed in the supporting study. It is conservative to assume the 1-h NOAEL is equal to the 2-h NOAEL. This conservative procedure is consistent with TCEQ (2006):

$$C_2 = C_1 = 100\ \mu g\ Ni/m^3 = POD_{ADJ}$$

3.1.4.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

The POD_{ADJ} based on Cirla *et al.* (1985) is equal to the human equivalent concentration (POD_{HEC}) since this study was conducted in humans. However, the supporting Graham *et al.* (1978) study was conducted in mice. Therefore, a dosimetric adjustment factor for particulate matter (PM) was applied to the POD_{ADJ} from Graham *et al.* (1978) to convert the POD_{ADJ} to a POD_{HEC}. Per TCEQ (2006), the TD used the USEPA regional deposited dose ratio (RDDR) model version (v) 2.3 as suggested in the USEPA RfC Methodology (USEPA 1994), which is the appropriate model for mice. In general, the RDDR model allows the adjustment of an animal concentration to a human equivalent concentration for PM and aerosolized compounds. Parameters necessary for the RDDR model are the mass median aerodynamic diameter (MMAD) and geometric particle size distribution (σ_g), 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 σ_g. However, as Graham *et al.* (1978) is not the key study, study-specific information on MMAD and σ_g is not considered particularly critical. Additionally, 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. Estimated values for the MMAD and σ_g of 3.1 and 2.9, respectively, are available from subacute studies (NTP 1996a, 1996b, 1996c) for use as surrogates which represented the high-end of the ranges available and yielded the smallest (i.e., most conservative) RDDR values for the respiratory tract region of interest. This is consistent with the recommended default approach in USEPA (1994). Therefore, the TD used input terms from several studies (Graham *et al.* 1978; NTP 1996; Serita 1999; Ishihara *et al.* 2002) for the RDDR model run for the supporting study. Other than a study-specific mouse body weight (20 g) and the estimated values for the MMAD and σ_g, default model values were used for calculation of the RDDR. The TD used the low end of the mouse body weight range reported for the study (20 g) as it resulted in a somewhat more conservative extrarespiratory RDDR value. The input and output terms are presented in Figure 1.

```
MMAD     =  3.10
Sigma g =  2.90

           Body                Extrathoracic    Tracheobronchial
Pulmonary
SPECIES WEIGHT(G) VE(ML)   SA(CM^2)  DEP  SA(CM^2)  DEP   SA(M^2)   DEP
-------------------------------------------------------------------------
  mouse       20      22.8     3.000   0.428     3.500   0.065     0.050
0.062
  human    70000   13800.0   200.000   0.466  3200.000   0.086    54.000
0.175
-------------------------------------------------------------------------
 RATIO     0.000     0.002     0.015   0.919     0.001   0.757     0.001
0.355

 RDDR                              0.101             1.145            0.633

                              Thoracic         Total RT
Extrarespiratory
                              SA(M^2)   DEP  SA(M^2)   DEP    BW(G)    DEP
-------------------------------------------------------------------------
  mouse                        0.050   0.127     0.051   0.555        20
0.555
  human                       54.320   0.125    54.340   0.727     70000
0.727
-------------------------------------------------------------------------
 RATIO                         0.001   1.013     0.001   0.764     0.000
0.764

 RDDR                              0.870             1.356            4.423
                                                                        V.
2.3
```

Figure 1. RDDR Model Run Output for Nickel Chloride Data

Per USEPA (1994), 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). To derive the POD_{HEC}, the extrarespiratory RDDR was multiplied by the POD_{ADJ} from the Graham *et al.* (1978) study:

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 100\ \mu g\ Ni\ /m^3 \times 4.423$$
$$= 442.3\ \mu g\ Ni\ /m^3$$

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

3.1.5 Adjustments of the POD_{HEC} and Critical Effect

3.1.5.1 Uncertainty Factors (UFs)

The MOA by which soluble forms of nickel may produce toxicity is not fully elucidated (see Section 3.1.2). 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/nonlinear MOA).

3.1.5.1.1 Cirla *et al.* (1985) Human Study

The following UFs were applied to the POD_{HEC} derived from the key study of Cirla *et al.* (1985):

- the UF for extrapolation from animals to humans (UF_A) is not applicable because the key study was in humans, so it is not included in the equation below;
- 1 for interindividual variability (UF_H) because the study population included a significant percentage of occupational asthmatics, which are considered a sensitive subpopulation;
- 10 for extrapolation from a LOAEL to a NOAEL (UF_L) because: (1) the severity of effects (mild or severe) could not be determined based on the FEV_1 information presented in the study and Table E-3 of TCEQ (2006); (2) the potential magnitude of the difference between the NOAEL for these respiratory effects and the single arbitrary concentration selected for use and later identified as the study LOAEL is unknown, which is concerning especially when considering the relatively high adverse response rate of 50%; and (3) short-term inhalation data from other studies are lacking for bounding a threshold concentration for the critical effect identified (e.g., the 16-day NTP studies (1996a,b,c) did not include a similar sensitive subpopulation or sufficiently low dose groups for nickel sulfate and nickel subsulfide to allow bounding of a short-term threshold for respiratory effects in mice and rats below the LOAEL reported for Cirla *et al.* 1985 to inform the selection of a UF_L value); and
- 3 for incomplete database uncertainty (UF_D) due to deficiencies in the acute study database (e.g., few acute (< 24 h) inhalation studies; acute human inhalation study data are limited and insufficient alone without animal data for identifying the lung as the most sensitive target of nickel toxicity (ATSDR 2005); lack of acute inhalation studies utilizing low soluble nickel concentrations, for example, even in the key study a NOAEL or lower LOAEL may have been identified had lower exposure concentrations been evaluated).

Regarding a more detailed discussion of the third bullet above, although the 16-day NTP studies (1996a,b,c) do not provide data which can be used to bound a short-term threshold concentration for the critical effect identified in the key study (Cirla *et al.* 1985), which in addition to the considerations listed above would help inform the selection of a UF_L value, information from the 2-year study with nickel sulfate suggests that the UF_L selected (10) for Cirla *et al.* (1985) is not unreasonably conservative. More specifically, the chronic NOAEL for the respiratory effects of nickel sulfate in Fisher 344 rats from NTP (1996c) is 30 μg Ni/m^3, which dosimetrically adjusted to a human equivalent NOAEL is approximately 1.6 μg Ni/m^3 (see CalEPA 1995). However, this NOAEL does not account for intrahuman variability as does the calculated study "NOAEL" for

Cirla *et al.* (1985) using a UF_L of 10. Dividing this human equivalent NOAEL from NTP (1996c) by a UF_H of 3-10 would yield a human equivalent chronic NOAEL (adjusted for intrahuman variability) of 0.16-0.53 μg Ni/m^3. These chronic human NOAELs based on NTP (1996c) may be used to help put into perspective the calculated acute study "NOAEL" from Cirla *et al.* (1985) using a UF_L of 10 (i.e., the LOAEL-based POD_{HEC} of 33.5 μg Ni/m^3 divided by a UF_L of 10 to yield a study "NOAEL" of 3.35 μg Ni/m^3). The calculated human equivalent NOAELs (adjusted for intrahuman variability) based on NTP (1996c) are approximately 6-21 times lower than the calculated NOAEL (includes intrahuman variability) based on Cirla *et al.* (1985) using a UF_L of 10. In addition to the considerations listed above supporting the selection of a UF_L of 10, the direction and magnitude of the difference (6-21 fold) between the calculated human NOAELs (including intrahuman variability) based on the chronic NTP (1996c) study and the acute Cirla *et al.* (1985) study suggests that application of a UF_L of 10 does not result in an unreasonably low calculated acute study NOAEL for Cirla *et al.* (1985). The same conclusion would result if using the human equivalent NOAELs calculated by ATSDR (2005) for the 2-year chronic or 13-week intermediate exposure NTP (1996c) studies.

A total UF of 30 was applied to the POD_{HEC} to derive the acute ReV:

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 33.5\ \mu g\ Ni/m^3 / (1 \times 10 \times 3)$$
$$= 1.12\ \mu g\ Ni/m^3$$

3.1.5.1.2 Graham *et al.* (1978) Mouse Study

A similar calculation applying the following UFs to the POD_{HEC} derived from the acute animal study (Graham *et al.* 1978) was used to derive the supporting acute ReV: 3 for UF_A, 10 for UF_H, and 3 for UF_D. A UF_L was not applicable as the POD was a NOAEL and is not shown in the equation below. A UF_A of 3 was used because default dosimetric adjustments using the RDDR were conducted to account for toxicokinetic differences but not toxicodynamic differences. A UF_H of 10 was used to account for potentially sensitive human subpopulations. A UF_D of 3 was applied due to deficiencies in the acute study database, as discussed above for the Cirla *et al.* (1985) study. A total UF of 100 was applied to the POD_{HEC}:

$$\text{supporting acute ReV} = POD_{HEC} / (UF_A \times UF_H \times UF_D)$$
$$= 442.3\ \mu g\ Ni/m^3 / (3 \times 10 \times 3)$$
$$= 4.91\ \mu g\ Ni/m^3$$

3.1.5.2 Critical Effect

The acute ReV based on the human study (Cirla et al 1985) is slightly lower than the supporting acute ReV based on the animal study (Graham *et al.* 1978). As indicated in Section 3.1.1.2, data suggest that respiratory effects are the most sensitive endpoint for short-term human exposure to soluble forms of nickel compounds. The specific critical effect of nickel sulfate that occurs at the LOAEL in the key study (Cirla *et al.* 1985) is significant bronchial constriction (> 15% decrease in FEV_1) in persons with occupational asthma exposed to 300 μg/m^3 nickel sulfate hexahydrate

(67 µg Ni/m^3) for 30-min. The supporting animal study of Graham *et al.* (1978) provides evidence of immunotoxic effects (decreased IgM-antibody production in spleen cells) potentially occurring at higher human equivalent concentrations.

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

The acute ReV of 1.12 µg Ni/m^3 was rounded to two significant figures at the end of all calculations which yields an acute ReV of 1.1 µg Ni/m^3. The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 0.33 µg Ni/m^3 (Table 4).

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

Parameter	**Summary**
Study	Cirla *et al.* (1985)
Study population	12 metal plating factory workers (4 women and 8 men) with occupational asthma
Key Study Confidence Level	High
Data Quality	High
Exposure Method	Inhalation chamber, exposure to an aerosol of 300 µg/m^3 nickel sulfate (67 µg Ni/m^3)
Critical Effects	Respiratory effects: significant bronchial constriction (> 15% decrease in FEV_1)
POD_{HEC} (original study)	67 µg Ni/m^3 (LOAEL)
Exposure Duration	30 min
Extrapolation to 1 h	Haber's Rule, as modified by ten Berge (1986) with n=1
$POD_{HEC\ ADJ}$	33.5 µg Ni/m^3
Total uncertainty factors (UFs)	30
Interspecies UF	*Not applicable*
Intraspecies UF	*1*
LOAEL UF	*10*
Incomplete Database UF *Database Quality*	*3* *Medium*
Acute ReV (HQ = 1)	**1.1 µg/m3**
acuteESL (HQ = 0.3)	**0.33 µg/m3**

3.1.7 Comparison of Results

California Environmental Protection Agency (CalEPA) published an acute Reference Exposure Level (REL) for nickel and nickel compounds of 6 μg/m^3 in 1999 based on a LOAEL of 33.5 μg/m^3 nickel for significant (>15%) decrease in FEV_1 (Cirla *et al.* 1985). The TD used the same study in the development of the acute ReV for the same critical effect. However, the TD used a full UF_L of 10 (as opposed to CalEPA using 6) since study data were not available to determine the severity of the effect (mild or severe) and there are no acute low concentration inhalation studies with soluble nickel to provide information regarding what acute exposure concentrations may represent a NOAEL for respiratory effects. In other words, the potential magnitude of the difference between the NOAEL for respiratory effects and the single arbitrary concentration selected for use in the human study and later identified as the study LOAEL is unknown. Additionally, while CalEPA does not use a UF_D, the TD included a UF_D of 3 for acute database deficiencies.

ATSDR (2005) indicates that the acute database (up to 14 days exposure) is not sufficient for derivation of an acute inhalation minimal risk level (MRL) despite ATSDR's definition of acute exposure (up to 14 days) making the acute database significantly more robust for potential derivation of a short-term, health-protective inhalation concentration for nickel compared to TCEQ's definition (< 24 h). ATSDR's evaluation of the sufficiency of the acute database, or lack thereof, supports TD's decision to incorporate a UF_D.

For comparison, the TD also derived a supporting acute ReV of 4.9 μg Ni/m^3 based on the Graham *et al.* (1978) animal study. The supporting animal-based acute ReV is fairly similar to the acute ReV of 1.1 μg/m^3 nickel based on the human key study (Cirla *et al.* 1985). The TD expects the acute ReV of 1.1 μg Ni/m^3 based on the human key study by Cirla *et al.* 1985 to be health-protective for other inorganic forms of nickel compounds (but will not apply to organic forms).

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Data are not available.

3.2.2 Vegetation Effects

Data are not available.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

This acute evaluation resulted in the derivation of the following acute values:

- acute ReV = 1.1 μg/m^3
- ^{acute}ESL = 0.33 μg/m^3

The short-term ESL for air permit evaluations is 0.33 μg/m^3 (Table 2). For evaluation of air monitoring data, the acute ReV of 1.1 μg/m^3 will be used (Table 1). In general, to protect against sensitization, exceedances of the short-term or long-term ESL during the air permit review should be discouraged for any chemicals identified as respiratory sensitizers (Schled *et al.* 2003, TCEQ 2006, and Ishii *et al.* 2009).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

This section is mainly based on reviews of the human and animal toxicological literature provided in ATSDR (2005) and Haber *et al.* (2000). The human database is very limited for evaluating the respiratory effects of the more toxic soluble forms of nickel both in the number of studies and the associated uncertainties and deficiencies (ATSDR 2005), the discussion of which is beyond the scope of this document. Both ATSDR (2005) and Haber *et al.* (2000) identify the NTP animal study (1996c) as having the most appropriate data for derivation of a chronic noncarcinogenic inhalation value. The critical effect identified in these references was chronic active inflammation (and associated lesions such as fibrosis) observed in rats due to soluble nickel (nickel sulfate) exposure.

The TD agrees that NTP (1996c) is the most appropriate study for development of a chronic noncarcinogenic value because:

- chronic (and acute) animal toxicity studies have shown that soluble forms of nickel such as that used in the selected study (nickel sulfate) are more toxic than insoluble forms (ATSDR 2005; Snow and Costa 1992; Hansen and Stern 1984);
- the lung is the most sensitive target of nickel toxicity in animals and humans (ATSDR 2005); and
- the human database evaluating the respiratory effects of soluble nickel is very limited both by study number (e.g., Muir *et al.* 1993, Berge and Skyberg 2003) and uncertainties (e.g., exposure estimates, lack of controls, mixed nickel species, adjusted odds ratio confidence intervals which include the value one) (ATSDR 2005, Haber *et al.* 2000).

Therefore, based on NTP (1996c) and similar to the acute assessment, the TD will develop the chronic noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$ based on nickel sulfate. As a science policy decision, the TD will use this form as a surrogate for all inorganic forms of nickel (i.e., metallic, soluble, insoluble, and sulfidic). *However, these chronic toxicity values will not apply to organic forms of nickel (i.e. nickel carbonyl), which have different toxicity and chemical/physical properties than inorganic nickel compounds (ACGIH 2001, AEGL 2005).*

As with the acute assessment, nickel equivalents based on the nickel sulfate doses used in the key study will be used for the chronic assessment and derivation of noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values. From a protection of public health perspective, use of nickel

equivalents based on nickel sulfate for the chronic noncarcinogenic evaluation of other inorganic forms of nickel assumes that other forms are no more toxic than nickel sulfate on a nickel equivalent basis. This is likely a sufficiently conservative assumption based on available data from chronic inhalation studies. For example, in the NTP studies (1996a,b,c), the nickel equivalent LOAEL for respiratory effects (e.g., chronic inflammation) in Fisher 344 rats due to chronic exposure is much lower for nickel sulfate (60 µg Ni/m^3) than for nickel subsulfide (730 µg Ni/m^3) or nickel oxide (500 µg Ni/m^3). The same is true for B6C3F1 mice in these studies, with nickel sulfate, nickel subsulfide, and nickel oxide having respiratory LOAELs of 60, 440, and 1,000 µg Ni/m^3, respectively (ATSDR 2005). While a detailed review of the studies which comprise the chronic noncarcinogenic database is beyond the scope of this document, these are some of the data which support the science policy decision (and the inherent underlying assumption) to use nickel sulfate for the derivation of chronic ReV and ^{chronic}ESL values as the most conservative (i.e., health protective) choice.

4.1.1 Physical/Chemical Properties and Key Studies

4.1.1.1 Physical/Chemical Properties

Physical/chemical properties of nickel and select inorganic compounds have been previously discussed in Chapter 3, Section 3.1.1.1. Also, the main chemical and physical properties of nickel, nickel sulfate, nickel subsulfide, nickel chloride, and nickel oxide are summarized in Table 3.

4.1.1.2 Key and Supporting Studies

4.1.1.2.1 Human Studies

The human database is very limited for evaluating the respiratory effects of the more toxic soluble forms of nickel both in the number of studies and the associated uncertainties and deficiencies. Therefore, the TD selected a chronic animal study as the key study for derivation of the chronic noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$. See ATSDR (2005) for a discussion of available chronic human studies.

4.1.1.2.2 Animal Studies

4.1.1.2.2.1 NTP Studies

The 2-year chronic portion of the comprehensive 16-day, 13-week, or 2-year NTP studies (1996a, 1996b, 1996c) evaluates the potential for noncarcinogenic and carcinogenic effects of inhalation exposure to nickel sulfate, nickel subsulfide, and nickel oxide. Although exposure-related increases were observed in male and female rats in the incidences of alveolar/bronchiolar adenoma and/or carcinoma in 2-year inhalation studies involving nickel sulfate, nickel subsulfide, and nickel oxide, these increases were not seen in the companion mice studies. Relevant to this noncarcinogenic assessment, non-neoplastic lung lesions were observed in male and female rats in the 2-year studies, including: fibrosis; chronic active inflammation; focal

alveolar epithelial hyperplasia; macrophage hyperplasia; proteinosis; bronchial lymphoid; and interstitial inflammation. Overall, the 2-year chronic studies were consistent with the acute and subchronic studies that also demonstrated that the soluble nickel compound, nickel sulfate hexahydrate, was more toxic for noncarcinogenic effects than other forms (Haber *et al.* 2000). Haber *et al.* (1998, 2000) concluded that a nickel reference concentration (RfC) could be derived based on the most sensitive noncarcinogenic critical effect in the 1996 NTP studies, lung fibrosis in male rats following chronic inhalation exposure to nickel sulfate. Haber *et al.* (2000) also indicates that an additional reason that nickel sulfate may be more appropriate than nickel subsulfide as the basis for a nickel RfC is that nickel sulfate is a more environmentally-relevant compound. Similarly, ATSDR (2005) based the chronic MRL on lung fibrosis and chronic active inflammation observed in rats due to nickel sulfate exposure. The TD will use the same study (NTP 1996c) and endpoints for derivation of the chronic noncarcinogenic ReV and ${}^{chronic}ESL_{nonlinear(nc)}$.

4.1.1.2.2.2 NTP (1996c)

Groups of 63 to 65 male and 63 to 64 female F344/N rats were exposed to nickel sulfate hexahydrate atomized with a Retec nebulizer for inhalation at concentrations of 0, 0.12, 0.25, and 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, 0.11 mg Ni/m^3). Similarly, groups of 80 male and 80 female B6C3F1 mice were exposed to atomized nickel sulfate hexahydrate at concentrations of 0, 0.25, 0.5, and 1 mg/m^3 (equivalent to 0, 0.06, 0.11, or 0.22 mg Ni/m^3). Both rats and mice were exposed for six hours five days per week for 104 weeks. Five male and five female rats and mice from each group were evaluated at seven months for histopathology; as many as seven males and seven females from each group were evaluated at seven months for nickel tissue burden in the lung; and five males and five females from each group were evaluated at 15 months for alterations in hematology, nickel tissue burden in the lung, and histopathology.

In mice, treatment-related lung lesions were diagnosed as inflammation, hyperplasia proteinosis, and cellular infiltration. These mouse lung lesions were observed primarily in the 0.5 and 1 mg/m^3 concentration groups. Respiratory toxicity in the lungs of rats exposed to nickel sulfate hexahydrate occurred primarily in the 0.25 and 0.5 mg/m^3 nickel sulfate hexahydrate concentration groups and was characterized by fibrosis, hyperplasia, and alvelolar proteinosis. These lesions were considered to be various components of chronic active inflammation, which was highly statistically significantly elevated ($p \leq 0.01$) following chronic exposure in both sexes of F344/N rats at the LOAEL of 0.25 mg/m^3 nickel sulfate hexahydrate (nickel equivalent of 0.06 mg Ni/m^3). Similarly, Oller *et al.* (2008) reported that lung lesions of alveolar proteinoiss, alveolar histiocytosis, and chronic or chronic-active inflammation were clearly chronic exposure-related in both sexes of Wistar rats at the LOAEL of 0.1 mg/m^3 nickel metal powder (nickel equivalent of 0.1 mg Ni/m^3). Mice were less sensitive according to the NTP 1996a, 1996b, & 1996c studies, with only female mice achieving statistical significance ($p \leq 0.05$) for chronic active inflammation at this concentration (0.25 mg/m^3 nickel sulfate hexahydrate or the nickel equivalent of 0.06 mg Ni/m^3). In all three NTP nickel studies (NTP 1996a, 1996b, 1996c), as well as the Oller *et al.* (2008) study, rats appear to be more sensitive than mice to nickel-induced lung effects for all durations and nickel compounds tested (ATSDR 2005). In rats, the most

sensitive species tested in NTP (1996c), 0.12 mg/m^3 nickel sulfate hexahydrate is considered the NOAEL, for which 0.03 mg Ni/m^3 is the nickel equivalent. *Unless otherwise specified, the following sections discuss the study NOAEL in terms of the nickel equivalent of 0.03 mg Ni/m^3, as opposed to nickel sulfate hexahydrate.* The TD selected the rat NOAEL of 0.03 mg Ni/m^3 for chronic active pulmonary inflammation (and its associated lesions such as fibrosis) as the basis for derivation of the chronic noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$.

4.1.2 MOA Analysis

The MOA for the adverse respiratory effects of nickel have not been fully elucidated. Therefore, as a default, a threshold, nonlinear dose-response relationship is used. However, available studies indicate that a variety of mechanisms may be involved in nickel toxicity, such as accumulation of macrophages and granular material (primarily phospholipids) in the alveoli, increases in the volume density of alveolar type II cells with large amounts of lamellar bodies, and perhaps decreased alveolar macrophage function. See Section 3.5.2 of ATSDR (2005) for a more detailed discussion of the limited information available.

4.1.3 Dose Metric

The MOA for the chronic noncarcinogenic critical effect (chronic inflammation) is not fully known to inform the choice of the most appropriate dose metric. Regardless, data on other dose metrics which may be more closely related to the critical effect are not available for NTP (1996c). Therefore, the exposure concentration of nickel from the key study was used as the default dose metric. More specifically, the pulmonary regional deposited dose was the ultimate dose metric and was derived using the duration-adjusted exposure concentration and the RDDR for the pulmonary region (see Section 4.1.5 below).

4.1.4 POD

Based on available data, the lung is the most sensitive target of nickel toxicity in animals and humans (ATSDR 2005). Chronic active lung inflammation (and its components) is the critical effect identified in NTP (1996c) as it associated with the lowest LOAEL, and in the absence of sufficient data to the contrary are assumed to be relevant to humans. A NOAEL of 0.03 mg Ni/m^3 from the NTP (1996c) study for chronic active lung inflammation in rats was selected by the TD for use as the POD as the data for chronic inflammation were not amenable to standard benchmark concentration (BMC) modeling (i.e., adequate model fits could not be obtained based on goodness-of-fit p-values, scaled residuals, and visual inspection). However, some adequate model fits were obtained by BMC modeling for two lesions considered components of chronic inflammation by NTP (1996c) (i.e., alveolar proteinosis and macrophage hyperplasia), and the similarity of these BMCs to the NOAEL support use of the NOAEL for chronic active lung inflammation as the POD (Appendix G).

4.1.5 Dosimetric Adjustments

4.1.5.1 Duration Adjustments

Using the NOAEL from the key study, the animal POD based on nickel was adjusted to a continuous exposure regimen:

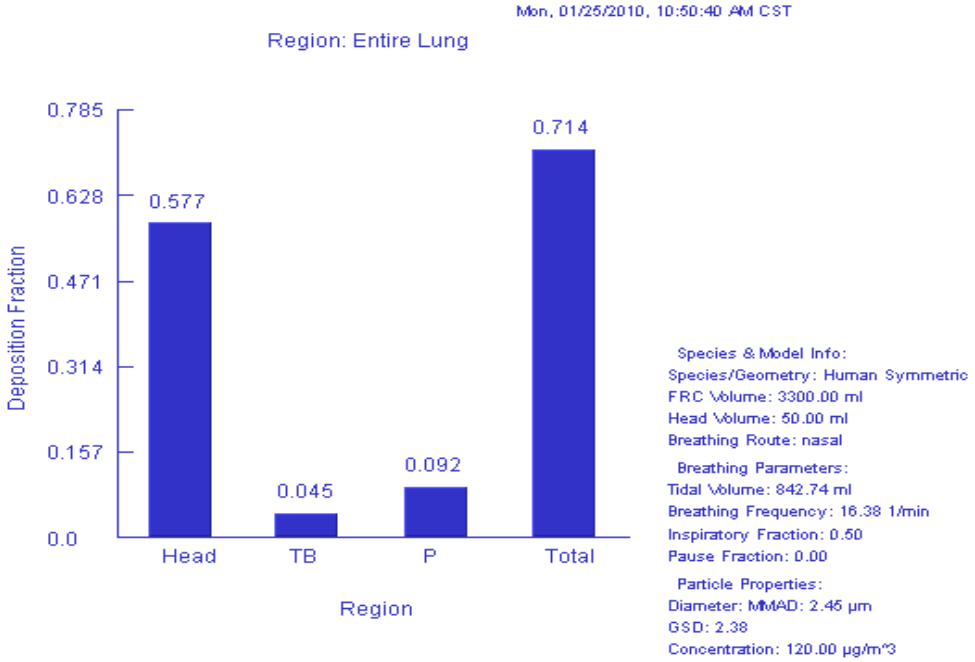
$$POD_{ADJ} = POD \times D/24 \times F/7$$
$$POD_{ADJ} = 0.03 \text{ mg Ni/m}^3 \times 6 \text{ h/24 h} \times 5 \text{ d/7 d}$$
$$POD_{ADJ} = 0.005357 \text{ mg Ni/m}^3$$

where: POD_{ADJ} = POD from an animal study, adjusted to a continuous exposure duration
POD = POD from an animal study, based on discontinuous exposure duration
D = exposure duration, hours per day
F = exposure frequency, days per week

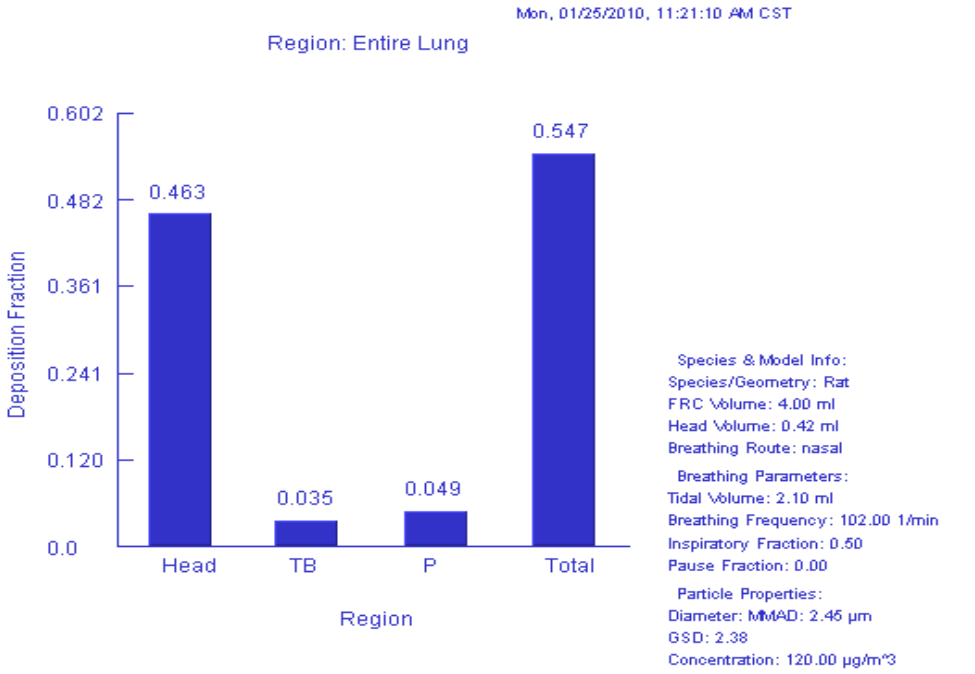
4.1.5.2 Default Dosimetry Adjustment from Animal-to-Human Exposure

Since NTP (1996c) was conducted in laboratory animals, a dosimetric adjustment factor for PM must be applied to the POD_{ADJ} to convert the animal concentration to a POD_{HEC}. Per TCEQ (2006), the TD used the Multiple Pass Particle Dosimetry (MPPD) Model (version 2.0) (CIIT 2002) to derive a deposition fraction that is used in the regional deposited dose ratio (RDDR), which is an appropriate model for rats. Study-specific parameters necessary for the MPPD model were provided by NTP (1996c), which included the MMAD, σ_g, and the NOAEL (120 µg/m^3 nickel sulfate hexahydrate). The default minute ventilation (V_E) used by MPPD for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation below. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation and are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. Therefore, the TD used human tidal volume and breathing frequency values from de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation for input into the MPPD model (Appendix F). All remaining values used were default. The target region for divalent nickel was considered to be the pulmonary region. The input and output terms are presented in Figure 2.

Figure 2. MPPD Model Input and Output for Nickel Sulfate Data



Human Output



Rat Output

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

$$RDDR = [(V_E)_A/(V_E)_H] \times [DF_A / DF_H] \times [NF_H / NF_A]$$

$$RDDR\ (pulmonary) = [(214.2\ mL/min)/(13{,}800\ mL/min)] \times [(0.049)/(0.092)] \times [(54\ m^2)/(0.34\ m^2)] = 1.313$$

where: RDDR = Regional Deposited Dose Ratio
V_E = Minute ventilation used in MPPD run (tidal volume (mL/ breath) × breathing frequency (breaths/minute))
DF = Depositional fraction in the respiratory tract target region from MPPD output (i.e., pulmonary region)
NF = Normalizing factor (Table 4-4 of USEPA 1994)
A = Animal
H = Human

The RDDR of the pulmonary region was selected as the appropriate output to use to develop a POD_{HEC} because the adverse effect noted in the key animal study is chronic active inflammation and lung fibrosis. So, to derive a POD_{HEC} for nickel, the RDDR of 1.313 for the pulmonary region was multiplied by the nickel equivalent POD_{ADJ} from the NTP (1996c) study:

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 0.005357\ mg\ Ni/m^3 \times 1.313$$
$$= 0.007034\ mg\ Ni/m^3$$

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

4.1.6 Adjustments of the POD_{HEC} and Critical Effect

4.1.6.1 Uncertainty Factors (UFs)

The MOA by which soluble forms of nickel may produce toxicity is not fully elucidated (see Section 4.1.2). 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/nonlinear MOA).

The following UFs were applied to the POD_{HEC} from the chronic key study NTP (1996c) to derive the chronic noncarcinogenic ReV:

- A UF_L is not applicable and is not shown in the equation below since the POD was a NOAEL;

- A UF_A of 3 was used because default dosimetric adjustments using the MPPD model were conducted to account for toxicokinetic differences but not toxicodynamic differences;
- A UF_H of 10 was used for intrahuman variability to account for potentially sensitive human subpopulations;
- A UF_D of 1 was applied because there are multiple animal studies that examine a wide variety of toxic effects using different forms of nickel, which provide strong evidence that the lung is the most sensitive target of chronic nickel toxicity.

A total UF of 30 was applied to the POD_{HEC} to derive the chronic ReV:

$$\begin{aligned} \text{chronic ReV} &= POD_{HEC} / (UF_A \times UF_H \times UF_D) \\ &= 0.007034 \text{ mg Ni/m}^3 / (3 \times 10 \times 1) \\ &= 0.000234 \text{ mg Ni/m}^3 \\ &= 0.234 \ \mu\text{g Ni/m}^3 \end{aligned}$$

4.1.6.2 Critical Effect

As indicated in Section 4.1.1.2, available animal data indicate chronic active pulmonary inflammation and its associated lesions (e.g., fibrosis) are the most sensitive endpoints for long-term exposure to soluble forms of nickel compounds. These effects are considered relevant to humans. Similar to ATSDR (2005) and Haber *et al.* (2000), the TD utilized data on these critical effects as the basis for chronic noncarcinogenic inhalation values.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV of 0.234 µg Ni/m^3 was rounded to two significant figures at the end of all calculations which yields a chronic ReV of 0.23 µg Ni/m^3. The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{nonlinear(nc)}$. At the target hazard quotient (HQ) of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 0.07 µg Ni/m^3 (Table 5).

Table 5. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameters	**Summary**
Study	NTP (1996c)
Study Population	Male and Female F344 rats
Study Quality	High
Exposure Method	0, 0.12, 0.25, and 0.5 mg/m^3 nickel sulfate hexahydrate (equivalent to 0, 0.03, 0.06, 0.11 mg Ni/m^3) in an inhalation chamber
Critical Effects	Chronic active lung inflammation and associated lesions
POD (original study NOAEL)	0.03 mg Ni/m^3 (NOAEL)
Exposure Duration	6h/day, 5 days/week for 2 years
POD_{ADJ}	5.357 µg Ni/m^3
POD_{HEC}	7.034 µg Ni/m^3
Total uncertainty factors (UFs)	30
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL UF	*Not applicable*
Incomplete Database UF *Database Quality*	*1* *High*
Chronic ReV (HQ = 1)	**0.23 µg/m3**
chronicESLnonlinear(nc) (HQ = 0.3)	**0.07 µg/m3**

4.1.8 Comparison of Results

CalEPA (1999) published a chronic REL for nickel and nickel compounds of 0.05 µg Ni/m^3 based on a LOAEL of 60 µg Ni/m^3 for active pulmonary inflammation, macrophage hyperplasia, alveolar proteinosis, fibrosis, lymph node hyperplasia, olfactory epithelial in NTP (1996c). ATSDR (2005) published a chronic MRL for nickel of 0.9 µg Ni/m^3 based on the NOAEL of 0.03 mg Ni/m^3 from NTP (1996c). However, ATSDR used a different RDDR than TD which was a result of using different models and inputs. The chronic ReV falls between the CalEPA chronic REL of 0.05 µg Ni/m^3 and the ATSDR chronic MRL of 0.9 µg Ni/m^3.

4.2 Carcinogenic Potential

4.2.1 Weight of Evidence (WOE) from Epidemiological and Animal Studies

There have been numerous epidemiological studies in nickel-exposed workers which indicate certain forms of nickel have carcinogenic potential. A discussion on the carcinogenic potential of four nickel species (soluble nickel (including nickel sulfate and nickel chloride), sulfidic nickel (including nickel subsulfide), oxidic nickel, and metallic nickel) in humans, taken from Section 3.2.1.7 of ATSDR (2005) with table references removed, is provided below. See ATSDR (2005) for the cited references.

> A large number of epidemiology studies have assessed the carcinogenic potential of nickel; it has been estimated that over 100,000 nickel workers have been examined in epidemiology studies (Seilkop and Oller 2003). These workers have been employed in nickel refinery facilities, nickel mining and smelting facilities, nickel alloy production facilities, stainless steel production facilities, nickel-cadmium battery production facilities, or as stainless steel welders. In the mid 1980s, a committee of epidemiologists was formed to investigate the human health risks associated with nickel exposure and to determine the specific forms of nickel that are associated with an increased risk of respiratory cancer (ICNCM 1990). The investigators updated the existing data from 10 previously examined cohorts and estimated levels of exposure to various nickel species. Since no measurements of nickel concentrations were available for workers employed prior to 1950, the investigators estimated total nickel exposure levels using recent monitoring data and historical data on the industrial processes. Based on information on the chemistry of the industrial process, total nickel exposure levels were divided into exposure to four nickel species: soluble nickel (including nickel sulfate and nickel chloride), sulfidic nickel (including nickel subsulfide), oxidic nickel, and metallic nickel. It is noted that interpretation of the results of many of the epidemiology studies of nickel workers is confounded by poor nickel exposure characterization, exposure to relatively high concentrations of other metals, including arsenic, and in some cases, exposure to irritant gases including hydrogen sulfide, ammonia, chlorine, and sulfur dioxide (IARC 1990).
>
> Statistically significant increases in the risk of nasal and/or lung cancer were found among nickel refinery workers (Andersen *et al.* 1996; Anttila *et al.* 1998; Chovil *et al.* 1981; Doll *et al.* 1977; Enterline and Marsh 1982; Grimsrud *et al.* 2003; ICNCM 1990; Karjalainen *et al.* 1992; Magnus *et al.* 1982; Muir *et al.* 1994; Pedersen *et al.* 1973; Peto *et al.* 1984; Roberts *et al.* 1989a). In general, the nickel refinery workers were exposed to high levels of sulfidic and oxidic nickel and low levels of soluble and metallic nickel (ICNCM 1990). At one nickel refinery facility (New Caledonia), the risk of respiratory tract cancers was not significantly elevated in the nickel-exposed workers (Goldberg *et al.* 1987, 1994; ICNCM 1990). This refinery facility differs from other refineries in that the workers were primarily exposed to silicate oxide ore and oxidic nickel with very little exposure to sulfidic or soluble nickel. Sunderman and associates

(Sunderman *et al.* 1989a) examined the histopathological diagnosis of 100 cases of sinonasal cancer and 259 cases of lung cancer among workers at three nickel refinery facilities. The primary sinonasal cancers were squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), and adenocarcinomas (6%). In an analysis of lung cancer, the cancers were primarily squamous cell carcinomas (67%), anaplastic, small cell, and oat cell carcinomas (15%), and adenocarcinomas (8%). The types of sinonasal and lung cancers were similar to those found in the general population, suggesting a lack of nickel-specific tumor types.

In contrast to the findings of nickel refinery workers, most studies in other groups of nickel workers have not found significant increases in the risk of lung cancer among workers employed in nickel mining and smelting facilities (ICNCM 1990; Shannon *et al.* 1984b, 1991), workers employed at a hydrometallurgical refinery (Egedahl and Rice 1984, Egedahl *et al.* 1991, 2001), workers employed at nickel alloy and stainless steel production facilities (Cornell 1984; Cornell and Landis 1984; Cox *et al.* 1981; Enterline and March 1982; ICNCM 1990; Jakobsson *et al.* 1997; Moulin *et al.* 1993; Sorahan 2004), workers employed as stainless steel welders (Danielsen *et al.* 1996; Gerin *et al.* 1993; Hansen *et al.* 1996; Simonato *et al.* 1991), workers involved in nickel-chromium electroplating (Pang *et al.* 1996), or workers employed at a barrier production facility (Cragle *et al.* 1984; Godbold and Tompkins 1979; ICNCM 1990). Although some studies of these workers did find significant increases in respiratory tract cancers (Becker 1999; Moulin *et al.* 1990), the increased risk was attributed to exposure to other carcinogenic agents, such as polycyclic aromatic hydrocarbons or asbestos. Redmond (1984) and Arena *et al.* (1998) reported significant increases in lung cancer risks among high nickel alloy production workers as compared to the U.S. population. However, when the local population was used as the comparison group, the increase in lung cancer risk was no longer statistically significant (Arena *et al.* 1998). In general, workers employed in these industries were exposed to lower levels of sulfidic or oxidic nickel than the nickel refinery workers who were primarily exposed to metallic nickel (Cragle *et al.* 1984; Godbold and Tompkins 1979) or soluble nickel (Pang *et al.* 1996).

Because nickel workers are exposed to several nickel species, it is difficult to assess the carcinogenic potential of a particular nickel species. The ICNCM 1990 investigators used cross-classification analyses to examine the dose-response to a specific nickel species independent of variations in other species. The most comprehensive cross-classification analyses were performed for cohorts of workers in different departments at the Mond/INCO (Clydach) nickel refinery and at the Falconbridge (Kristiansand) nickel refinery (only analyzed for metallic nickel). The strongest evidence of carcinogenicity of a particular nickel species is for sulfidic nickel. The highest cancer risk levels were found in cohorts with the highest sulfidic nickel exposure levels, although high oxidic and soluble nickel levels were also found at these same facilities. The increased cancer risks in workers with high sulfidic nickel exposure and low oxidic and soluble nickel exposure suggests that sulfidic nickel is the causative agent. The evidence for oxidic nickel is

weaker. No differences in cancer risks were seen among groups of workers with low sulfidic and soluble nickel exposures when the levels of oxidic nickel were varied. However, when high soluble nickel levels are present, oxidic nickel appears to be carcinogenic. The available weight of evidence does not suggest that exposure to soluble nickel, in the absence of carcinogenic compounds, will increase the risk of cancer. At low sulfidic and oxidic nickel levels, increasing soluble nickel levels do not increase the cancer risk in the Clydach cohort. However, at high oxidic nickel levels, increasing the soluble nickel levels resulted in at least a 2-fold increase in the cancer risk. There is no evidence that metallic nickel is associated with increased lung or nasal cancer risks in nickel workers based on the results of the cross-classification analyses for two cohorts of nickel refinery workers and the lack of increased cancer risk in the workers exposed to metallic nickel alone at the barrier production facility (Cragle *et al.* 1984; Godbold and Tompkins 1979). The ICNCM 1990 concluded that lung and nasal cancers were related primarily to exposure to less soluble nickel compounds at concentrations of ≥10 mg Ni/m^3 (primarily oxidic and sulfidic compounds). Exposure to soluble nickel compounds at concentrations of >1 mg Ni/m^3 appeared to enhance the carcinogenicity of insoluble nickel compounds.

Significant increases in cancer risks at sites other than the respiratory tract have been found in some cohorts of nickel workers. The ICNCM 1990 noted that if nickel exposure was associated with nonrespiratory tract cancer, increased risks would be seen among the workers with the highest nickel exposures (cohorts that also had increased levels of respiratory tract cancer). Among the three cohorts with the highest nickel exposures (Clydach, INCO Ontario sinter plants, and Kristiansand), no consistent patterns of increased nonrespiratory tract cancer risks were found. When the three cohorts were combined, significant increases in pharynx (SMR 201; 95% confidence interval 117–322) and bone (SMR 206; 95% confidence interval 111–353) cancers were found. The investigators noted that cancers of the ethmoid and maxillary sinuses are sometimes classified as bone cancer and that bone cancer is sometimes listed on death certificates if the primary lung cancers are occasionally unrecognized and death is attributed to the site of metastasis. Among workers with low-level nickel exposures without significant increases in respiratory tract cancer, no significant increases in cancer risks were found. Thus, the investigators concluded that there was insufficient evidence that nickel exposure results in tumors outside of the respiratory tract (ICNCM 1990). Two studies published after this analysis found significant increases in the incidence of stomach cancer among nickel refinery workers (Antilla *et al.* 1998) and nickel platers (Pang *et al.* 1996). These data are insufficient to conclude whether the increases in stomach cancer risks are due to exposure to nickel, other agents, or chance. A meta-analysis of occupational exposure studies on pancreatic cancer (Ojajärvi *et al.* 2000) found a significant association between exposure to nickel and pancreatic cancer risk. However, the Ojajärvi *et al.* (2000) meta-analysis has been criticized (Sielkop 2001) for excluding a study of nickel mining and smelting workers (Shannon *et al.* 1991) and a study of nickel alloy production workers (Arena *et al.* 1998). The addition of these studies

> lowered the meta-analysis ratio from 1.9 (95% confidence interval 1.2–3.2) to 1.3 (95% confidence interval 0.9–1.9); Ojajärvi accepted Sielkop's comments. Overall, there does not appear to be sufficient evidence that exposure to airborne nickel is associated with increased cancer risks outside of the respiratory tract.

However, ATSDR (2005) appears not to have accurately summarized the conclusions of the ICNCM (1990) when it states that the study, "concluded that lung and nasal cancers were related primarily to exposure to less soluble nickel compounds at concentrations of ≥ 10 mg Ni/m^3 (primarily oxidic and sulfidic compounds). Exposure to soluble nickel compounds at concentrations of > 1 mg Ni/m^3 appeared to enhance the carcinogenicity of insoluble nickel compounds." This inaccurate summary has the effect of discounting that study's conclusions regarding the association between soluble nickel and respiratory cancer risk, seemingly limiting the role of soluble nickel to enhancing the carcinogenicity of insoluble nickel compounds. The ICNCM (1990) actually states (*italics* added for emphasis) that, "*respiratory cancer risks are primarily related to exposure to soluble nickel at concentrations in excess of 1 mg Ni/m^3* and to exposure to less soluble nickel compounds at concentrations greater than 10 mg Ni/m^3." In regard to soluble nickel, that study concludes that in addition to the evidence that soluble nickel exposure increases the risk of respiratory cancer, it may enhance risk associated with exposure to less soluble forms. A more recent review article (Goodman *et al.* 2009) indicates that soluble nickel is unlikely to be carcinogenic alone, but may be a carcinogenic promoter. In summary, based on the ten cohorts evaluated, the ICNCM (1990) indicates that more than one form of nickel gives rise to respiratory cancer risk, and that the following were associated with increased risk: a mixture of oxidic and sulfidic nickel at very high concentrations; high oxidic nickel concentrations in the absence of sulfidic nickel; soluble nickel; and soluble nickel enhancing the risk associated with less soluble forms. More recent studies (e.g., Grimsrud *et al.* 2002, 2003, Oller *et al.* 2008, NTP 1996a,b,c) were not available for review by ICNCM (1990) in examining the potential of various forms of nickel to increase lung tumors.

In regard to inhalation animal studies which have examined the carcinogenic potential of various forms of nickel (e.g., nickel subsulfide, nickel oxide, and nickel sulfate), generally, only chronic inhalation exposure to nickel subsulfide and nickel oxide resulted in lung tumors (adenocarcinomas, squamous cell carcinomas, and fibrosarcoma) in rats, and no significant alterations in tumor incidences were observed in mice (ATSDR 2005). NTP (1996b) showed clear evidence of the carcinogenic activity of nickel subsulfide in male and female Fisher 344 rats as a result of chronic exposure (e.g., alveolar/bronchiolar adenoma and carcinoma). For chronic exposure to nickel oxide, NTP (1996a) showed some evidence of carcinogenic activity in male and female Fisher 344 rats (e.g., alveolar/bronchiolar adenoma/carcinoma combined), with equivocal evidence in female B6C3F1 mice (e.g., marginal increases in alveolar/ bronchiolar adenoma/carcinoma combined). NTP (1996c) provided no evidence of carcinogenic activity of nickel sulfate in chronically exposed Fisher 344 rats and B6C3F1 mice. See Section 3.2.1.7 of ATSDR (2005) or NTP (1996a,b,c) for more detailed discussions of the inhalation animal studies which have examined the potential of various forms of nickel to increase lung tumors. Additionally, a recent inhalation study by Oller *et al.* (2008) provided no evidence of respiratory

tract carcinogenesis in Wistar rats chronically exposed to metallic nickel. The results of this study support the lack of evidence (mentioned above in quote from ATSDR 2005) for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers.

4.2.2 WOE Classifications

It is not known with certainty which forms of nickel pose a carcinogenic risk to humans (Grimsrud *et al.* 2002). The difficulty in assessing the carcinogenic potential of a particular nickel species in humans is that nickel workers are exposed to several nickel species (ATSDR 2005). Additionally, largely unknown differences such as differences in the reliability of exposure estimates for various nickel species in individual cohorts/workplaces/departments (e.g., sample collection, preservation, and speciation methods, coexposure to emissions from adjacent areas) may contribute to inconsistent results between studies as to the carcinogenicity of a particular nickel species (Goodman *et al.* 2009).

ATSDR (2005) indicates that the strongest evidence of carcinogenicity of a particular nickel species is for sulfidic nickel. While this may be the case, the exact role of sulfidic nickel exposure in the increased respiratory cancer risks observed in refinery workers is somewhat unclear as high concentrations of sulfidic nickel were associated with high concentrations of other nickel species, including oxidic and soluble nickel (i.e., Copper Cliff sinter plant; linear calcining at Clydach; leaching, calcining, and sintering department at Port Colborne). Additionally, for three groups of workers with similar cumulative exposure levels for soluble, metallic, and oxidic nickel (i.e., Clydach, Kristiansand, Huntington), only the Clydach data suggested a relationship between cumulative sulfidic nickel exposure and respiratory cancer (ICNCM 1990). Possible explanations for this are beyond the scope of this assessment. The point is that because workers were exposed to mixtures of nickel species (in varying proportions) and there is some variability across epidemiological studies as to what form(s) of nickel are considered to be most closely associated with increased respiratory cancer risk (e.g., water-soluble at Kristiansand, Norway; sulfidic at Clydach, Wales), there is some uncertainty as to which form(s) or mixtures of nickel are carcinogenic (or most carcinogenic and at what exposure concentrations).

While ATSDR considers evidence for the carcinogenicity of sulfidic nickel to be strongest, IARC (1990) indicates, “there is sufficient evidence in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry.” While the interpretation of this conclusion varies, as this sentence is written, neither words nor sentence structure infer that exposure to another form of nickel is required for nickel sulfate to be carcinogenic. The sentence refers to two separate types of exposure as being carcinogenic, nickel sulfate exposure, and separately, exposure to combinations of nickel sulfides and oxides. As a result, the TD can only interpret this sentence to mean that IARC (1990) concluded there is sufficient evidence in humans that nickel sulfate (soluble nickel) is carcinogenic. This interpretation is consistent with that of Goodman *et al.* (2009) which states, “In its 1990 evaluation, IARC determined there was 'sufficient evidence' in humans for the carcinogenicity of nickel sulfate.” Several epidemiologic studies of nickel workers (Easton *et al.*

1992; Andersen *et al.* 1996; Grimsrud *et al.* 2000, 2002, 2003, 2005) have reported a positive association between water-soluble nickel species and lung cancer. Additionally, the ICNCM (1990) indicates there is strong evidence that exposure to soluble nickel is associated with respiratory cancer risk (i.e., Kristiansand electrolysis worker data, somewhat supported by Clydach hydrometallurgy worker data). Recently, Grimsrud *et al.* (2002) conducted a case-control study of Norwegian (Kristiansand) nickel-refinery workers and examined dose-related associations between lung cancer and cumulative exposure to soluble, sulfidic, oxidic, and metallic nickel. A clear dose-related effect was seen for water-soluble nickel, with no dose-dependent risk observed for less soluble forms, suggesting an important role for soluble nickel in nickel-induced cancer. Grimsrud *et al.* (2003) completed a retrospective cohort study of 5,297 workers which confirmed the earlier case-control study results that there was a strong dose-related risk from nickel exposure, most clearly seen for soluble nickel. However, because nickel workers were exposed to several forms of nickel, it was not possible to definitively determine whether the risk was related to a single form or to several forms of nickel, and researchers may disagree regarding the extent to which a carcinogenic response may be attributed to a particular form of nickel. For example, a recent review article by Goodman *et al.* (2009) indicates that only limited data suggest that exposure to soluble nickel compounds increases cancer risk in the presence of certain forms of insoluble nickel. The weight of evidence does not indicate that soluble nickel compounds are complete carcinogens (although they could act as tumor promoters), and that soluble nickel should be considered only possibly carcinogenic to humans. This may be viewed as somewhat in contrast to the assessments of soluble nickel by IARC (1990), ICNCM (1990), and the reported results of Grimsrud *et al.* (2002, 2003).

Based on the evaluation of the combined results of epidemiological studies, animal carcinogenicity studies, and other relevant data, IARC (1990) considers nickel compounds as a group (soluble and insoluble forms) to be carcinogenic to humans (Group 1), and metallic nickel as possibly carcinogenic to humans (Group 2B). According to Goodman *et al.* (2009), IARC is in the process of reassessing the carcinogenicity of soluble and insoluble nickel.

USEPA has classified nickel refinery dust and nickel subsulfide as Group A human carcinogens (USEPA 1986). Inhalation unit risk factors (URFs) of 2.4E-04 and 4.8E-04 per $\mu g/m^3$ were derived based on occupational data for nickel refinery dust and nickel subsulfide, respectively. The URFs were derived in USEPA (1986).

The Department of Health and Human Services (NTP 2005) has classified metallic nickel as reasonably anticipated to be a human carcinogen, and nickel compounds as known human carcinogens (ATSDR 2005). ACGIH currently classifies insoluble nickel subsulfide and nickel oxide as confirmed human carcinogens (A1), metallic nickel as not suspected as a human carcinogen (A5), and soluble nickel chloride and nickel sulfate as not classifiable as a human carcinogen (A4) (Goodman *et al.* 2009).

According to the new cancer guidelines (USEPA 2005a) and consistent with IARC (1990) and NTP (2005), the TD considers nickel compounds as a group to be “Carcinogenic to Humans” via

inhalation. Regarding metallic nickel alone, information relevant to the WOE may be viewed as consistent with descriptors from "Likely to Be Carcinogenic to Humans" to "Not Likely to Be Carcinogenic to Humans." For "Likely to Be Carcinogenic to Humans," USEPA (2005a) indicates that adequate evidence consistent with this descriptor covers a broad spectrum, including when an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans. Metallic nickel has tested positive in laboratory animal experiments in multiple species (e.g., rats, hamsters), at multiple sites and by multiple exposure routes (e.g., subcutaneous, intramuscular, intraperitoneal, intratracheal) (NTP 2005). While metallic nickel meets this criterion given as an example by USEPA (2005a), USEPA indicates that this and other example criteria cited in the document are neither checklists nor limitations and that additional information may change the choice of descriptor. For the purposes of this document, the TD is interested specifically in the inhalation route of exposure, which is not among the multiple routes by which metallic nickel has yielded positive results in animal experiments. Regarding inhalation in particular, the absence of respiratory tract carcinogenesis in the chronic Oller *et al.* (2008) rat study (sensitive species) supports the lack of evidence (mentioned above in the Section 4.2.1 quote from ATSDR 2005) for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers. Additionally, in regard to inhalation exposure to metallic nickel, Oller *et al.* (2008) indicates that the combination of relatively low retained dose, poor intracellular uptake, and low intracellular dissolution (i.e., the particles need to be oxidized) results in a "low" predicted nuclear bioavailability for nickel ion from metallic nickel *in vivo*, which is relevant to the carcinogenic MOA discussion in Section 4.2.3 below. USEPA (2005a) indicates that the "Not Likely to Be Carcinogenic to Humans" descriptor may apply to circumstances where data indicate that an agent is not likely to be carcinogenic by one exposure route (e.g., inhalation), although it may be carcinogenic by another (e.g., subcutaneous). For the inhalation of metallic nickel, an argument could be made that this descriptor is supported by the chronic inhalation rat study, epidemiology studies, and MOA information (Oller *et al.* 2008). However, low theoretical nuclear bioavailability for nickel ion from inhaled metallic nickel is not tantamount to an *in vivo* demonstration of zero nuclear bioavailability (e.g., *in vivo* information on cellular uptake and intracellular dissolution for nickel-containing substances was not available to Oller *et al.* 2008), and taken together, the data that support both these two descriptors may be viewed as adequately supporting a third descriptor, "Suggestive Evidence of Carcinogenic Potential." More specifically, the rationale is that while positive animal study results for other exposure routes, some level of potential nuclear bioavailability following inhalation (albeit "low"), and other possible carcinogenic MOAs (see Section 4.2.3 below) raise a potential concern for carcinogenicity in humans, the negative results for metallic nickel in the inhalation rat study by Oller *et al.* (2008) and the general lack of evidence for metallic nickel risk from epidemiology studies (ATSDR 2005, Goodman *et al.* 2009) prevent a stronger conclusion for inhalation exposure. The TD interprets the overall WOE, including the latest scientific studies (e.g., Oller *et al.* 2008, Goodman *et al.* 2009, Grimsrud *et al.* 2002), as at most adequately supporting that there is "Suggestive Evidence of Carcinogenic Potential" for metallic nickel via inhalation. The TD will consider the potential conservativeness of applying URFs in evaluations when it is known that exposure will be to metallic nickel alone, given the negative results from

the inhalation rat study (Oller *et al.* 2008) and the lack of evidence for metallic nickel being associated with increased lung or nasal cancer risks in nickel workers (ATSDR 2005).

4.2.3 Carcinogenic MOA

Based on human and animal data, not all forms of nickel appear to have equal carcinogenic potential and potency. Generally, evidence for the carcinogenicity of some insoluble nickel compounds (e.g., nickel subsulfide, nickel oxide) is judged as sufficient, while that for soluble forms of nickel (e.g., nickel sulfate, nickel chloride) is more limited and more subject to scientific debate. Information on possible carcinogenic MOAs may help understand differences in carcinogenic potential and potency. While a full detailed review of the abundant information available and potentially relevant to the MOA is beyond the scope of this document, such reviews may be found in the published literature (ATSDR 2005, Goodman *et al.* 2009, 2011). A summary of the information that is available and critical to an understanding of mechanisms believed to be relevant to the carcinogenic MOA, based primarily on ATSDR (2005) and Goodman *et al.* (2009), is presented below.

The mechanisms of nickel carcinogenesis have not been firmly established, although a variety of mechanisms are likely to be involved. Available mechanistic evidence suggests that nickel-induced carcinogenicity likely results from genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals, hypoxia-inducible transcription factor-1 (HIF-1)) epigenetic factors. While *in vitro* and *in vivo* studies in mammals indicate that nickel is genotoxic, generally, it has low mutagenic potential (ATSDR 2005). However, both insoluble and soluble nickel compounds have been shown to be mutagenic and genotoxic (e.g., DNA damage, chromosomal aberrations, sister chromatid exchanges, cell transformation, DNA strand breaks, DNA-protein cross-links, 8-hydroxyguanosine adducts), with varying degrees of potency and consistency (Goodman *et al.* 2009). Nickel-induced DNA damage has resulted in the formation of chromosomal aberrations, which could result in deletion of senescence or tumor suppressor genes. Additionally, nickel ions may inhibit DNA repair, although the mechanism is unclear (ATSDR 2005).

For nickel to exert any genotoxic effects, the nickel ion must reach the cell nucleus and interact with DNA. Nickel particles cannot enter the nucleus while nickel ions can, which suggests that the nickel ion bioavailable in the nucleus may be the ultimate carcinogen. The nickel ion does not form pre-mutagenic lesions in isolated DNA. Differences in the respiratory tract clearance, cellular uptake, and intracellular dissolution of different forms of nickel may affect the amount of nickel ion available at the nucleus and may be related to the carcinogenic potential of different nickel forms (e.g., insoluble forms likely result in higher nickel ion at the nucleus). For example, while soluble nickel compounds undergo dissolution to form nickel ions in biological fluids that are transported to cell cytoplasm via calcium or magnesium channels or the proton-coupled divalent cation transporter insoluble nickel compounds such as nickel subsulfide (somewhat soluble in biological fluids) may be phagocytosed as one *in vitro* study (Benson *et al.* 1992) suggests that lung epithelial cells are capable of phagocytic activity towards nickel subsulfide (Goodman *et al.* 2009). Assuming these as the primary methods of nickel transport, differences

in carcinogenic potency may exist due to differences in resulting nucleus nickel ion concentrations caused by the extracellular generation of nickel ions (perhaps greater opportunity to form complexes with cytoplasmic proteins) by soluble nickel compounds (and nickel subsulfide to some extent) versus perhaps greater nucleus nickel ion concentrations from the intracellular generation of ions following possible phagocytosis, cytoplasmic vacuolization, and vacuolar/lysosomic dissolution of insoluble forms by lung epithelial cells (Goodman *et al.* 2009).

In regard to nongenotoxic effects as possible MOAs, nickel can bind to biological macromolecules, which may be involved in nickel carcinogenesis. Although nickel has a relatively weak affinity for DNA, it has a high affinity for chromatin proteins, histones and protamines specifically (ATSDR 2005). The nickel ion has an affinity for amino acids that is several orders of magnitude higher than that for DNA, which favors interaction with heterochromatin due to its high protein content (Goodman *et al.* 2009). The binding of nickel ions with heterochromatic DNA, which is transcriptionally inactive, may result in a number of alterations that can disrupt gene expression. More specifically, the interaction between the nickel ion and histones in heterochromatic DNA may produce reactive oxygen species leading to DNA strand breaks, base modifications, or epigenetic effects such as gene silencing (e.g., tumor suppressor genes) through DNA hypermethylation or histone hypoacetylation (see Figure 3 of Goodman *et al.* 2009). The oxidation of DNA can also result in altered DNA methylation, a mechanism by which epigenetic carcinogens may exert their effects, causing genes to no longer be expressed due to incorporation into heterochromatin (e.g., inactivation of tumor suppressor genes). Soluble nickel (i.e., nickel sulfate) has been shown to cause DNA hypermethylation in rat lung cells *in vitro*. Soluble nickel has also been shown to inhibit DNA repair. While these effects require nickel ion in the nucleus, a nongenotoxic effect which does not require nickel ion in the nucleus is the induction of gene expression changes via activation of signal transduction pathways which promote cell survival and proliferation (e.g., those with precancerous changes). In other words, altered gene expression caused by the activation of transcription factors does not require nickel ions in the nucleus. For example, interference with iron homeostasis outside the nucleus can lead to the induction of the hypoxia-inducible transcription factor (HIF-1), which can affect the expression of many genes, particularly those related to angiogenesis (important for tumor promotion) (Goodman *et al.* 2009). This transcription factor is over-expressed in both primary and metastatic tumors, and is involved in the regulation of hypoxia-inducible genes involved in cell transformation, tumor promotion and progression, angiogenesis, altered metabolism, and apoptosis (ATSDR 2005). For example, induction of HIF-1 leads to the transactivation of the HIF-1-dependent gene encoding the putative cellular differentiation factor Cap43 and genes encoding the angiogenesis promoters: vascular endothelial growth factor, plasminogen activator inhibitor-1 (promotes thrombosis), and erythropoietin (regulates red blood cell proliferation and differentiation) (Goodman *et al.* 2009). Nickel-induced signal transduction effects (e.g., HIF-1) can be equally elicited by both soluble and insoluble nickel (ATSDR 2005, Goodman *et al.* 2009).

Additionally, certain nickel compounds have been shown to promote cell proliferation. For example, nickel sulfate has been shown to induce proliferin, which belongs to a gene family that encodes growth hormone- and mitogen-regulated proteins, and other *in vitro* studies have shown that soluble nickel compounds can induce cell proliferation. The induction of cell proliferation increases the likelihood of converting a repairable DNA lesion into a non-repairable mutation (ATSDR 2005, Goodman *et al.* 2009). In other words, cell division can "fix" cancer-initiating DNA damage into heritable mutations (both insoluble and soluble nickel compounds have been shown to be mutagenic). However, evidence that a chemical (e.g., nickel sulfate) can stimulate cell proliferation does not necessarily preclude the possibility that the chemical may have a MOA which to some extent includes both nongenotoxic activity (e.g., induction of cell proliferation in/clonal expansion of initiated cells) and genotoxic activity (e.g., DNA reactivity capable of initiating cells). For example, a strong tumor promoter may also elicit weak tumor-initiating activity (Melnick *et al.* 1996). While Goodman *et al.* (2009) interpret available MOA and other information (e.g., induction of cell proliferation, proliferin, and certain signal transduction, animal study results) as at most only supporting soluble nickel compounds as respiratory tract tumor promoters with a nongenotoxic MOA, study authors concede that a genotoxic MOA is possible based on positive genotoxicity tests for soluble nickel compounds (although they may be less potent mutagens *in vivo* compared to insoluble nickel compounds).

See Section 3.5.2 of ATSDR (2005) and Goodman *et al.* (2009, 2011) for additional information on possible MOAs. As the available relevant data are limited, the carcinogenic MOA for nickel is yet to be fully elucidated. Therefore, the TD uses linear low-dose extrapolation to calculate unit risk factors (URFs) as a conservative default assumption.

4.2.4 Nickel Emissions from Texas Facilities

Because data indicate that nickel species differ in their carcinogenic potency and available epidemiological studies differ in the total and relative amounts of nickel species to which workers were exposed (i.e., exposure profile), it is important that the URF is developed based on studies with nickel species exposure profiles that are most similar to nickel emissions from Texas facilities and other sources. As indicated in Section 4.2 above, most studies in groups other than nickel refinery workers have not found significant increases in the risk of lung cancer (e.g., nickel mining and smelting, hydrometallurgical refining, nickel alloy and stainless steel production, stainless steel welders, nickel-chromium electroplating). *Generally, nickel refinery workers were exposed to high levels of sulfidic and oxidic nickel and low levels of soluble and metallic nickel (ATSDR 2005).* Mining may also involve high levels of sulfidic and oxidic nickel (Vincent *et al.* 1995).

As detailed information on the forms of nickel to which Texans are personally exposed is lacking, the Toxics Release Inventory (TRI) and scientific literature provide the best information available regarding the forms to which Texans and the general population would be expected to be exposed. Per ATSDR (2005), there are no nickel refining or mining operations in the United States. According to the 2005 TRI (USEPA TRI Explorer 2005), Texas does not have any nickel refineries, and twelve other facility types emitted over 97% of the total nickel emissions in Texas

(Table 6). Available information from the 2005 TRI indicates that Texas nickel emissions would predominantly be metallic (e.g., railroad equipment, steel foundries, aircraft engines, metal forging, oil/gas field machinery, plate work), along with soluble nickel (e.g., electric utilities) and nickel oxides (e.g., electric utilities, steel foundries and works, aircraft engines) (personal communications with Dr. Adrianna Oller (Nickel Institute), Richard Wilds (Union Tank Car), and Randy Hamilton (TCEQ) 2008). For example, railroad equipment facilities accounted for the vast majority of nickel emissions in Texas in 2005, and a representative of the largest railroad equipment emitter indicated that these emissions were primarily due to metal grinding (metallic nickel) (personal communication with Richard Wilds (Union Tank Car 2008)). More recent 2008 TRI data (USEPA TRI Explorer 2008) indicate that the top three sources of nickel and nickel compounds were "all other basic inorganic chemical manufacturing," petroleum refineries, and fossil fuel electric power generation. These sources could include varying percentages (35–65%) of metallic nickel, nickel sulfate, or nickel oxide (personal communication with Dr. Adrianna Oller, Nickel Institute 2008, 2010). Subsequently, the 2005 number one emitter, the railroad equipment facility type, dropped to the eleventh top nickel emitter in 2008 and accounted for less than 1.5% of the total nickel emissions in Texas for that year (see Tables 6 & 7). Therefore, based on TRI data, Texas nickel emissions are expected to be low in (or perhaps devoid of) sulfidic nickel.

Table 6 Texas Facility Types with Total Nickel Emissions (USEPA's TRI 2005)

Facility Type	Nickel Emissions (lbs/year)
Railroad Equipment	81235
Electric Utilities	7958
Petroleum refining	6960
Production of industrial organic chemicals	2345
Steel Foundries	1034
Aircraft Engines and Engine Parts	1030
Noferrous Metal Forging	1000
Steel Works, Blast Furnaces (Including Coke Ovens), and Rolling Mills	915
Sheet Metal Work	896
Oil and Gas Field Machinery and Equipment	891
Production of industrial inorganic chemicals	667
Fabricated Plate Work (Boiler Shops)	600

Table 7 Texas Facility Types with Total Nickel Emissions (USEPA's TRI 2008)

Facility Type	Nickel Emission (lbs/year)
All Other Basic Inorganic Chemical Manufacturing	9915
Petroleum Refineries	9611
Fossil Fuel Electric Power Generation	6672
All Other Basic Organic Chemical Manufacturing	1611
Other Nonferrous Foundries (except Die-Casting)	1563
Plate Work Manufacturing	1355
Steel Foundries (except Investment)	1312
Iron and Steel Forging	1312
Sheet Metal Work Manufacturing	923
Secondary Smelting, Refining, and Alloying of Nonferrous Metal (except Copper and Aluminum)	605
Railroad Rolling Stock Manufacturing	520
Cement Manufacturing	409

In regard to available information other than TRI about the forms of nickel commonly found in ambient air (e.g., in areas which may not be located near a nickel source reporting to TRI), generally, the major nickel species in ambient air is a soluble form, nickel sulfate (Schaumlöffel 2005, USEPA 1985). For example, Galbreath (2003) reports on a 6-day Davie, Florida nickel data set which indicates that nickel in the respirable PM_{10} fraction is dominated by nickel sulfate hexahydrate (followed by far lower concentrations of nickel ferrite $NiFe_2O_4$). Although other nickel compounds including nickel subsulfide were analyzed for, these compounds were not detected in PM_{10}.

Based on the above information, Texas nickel emissions are expected to be low in (or perhaps devoid of) sulfidic nickel. Therefore, the emissions profile from Texas facilities and background sources is expected to differ from the nickel species profile of nickel refineries, which is high in sulfidic nickel and has been shown to be carcinogenic in epidemiological studies. Thus, the URF will be developed based on epidemiological studies where workers were exposed to low levels of sulfidic nickel (Section 4.2.5 Epidemiological Studies Used to Develop URFs).

4.2.5 Epidemiological Studies used to Develop URFs

Human epidemiological studies are available and preferable over animal studies for the assessment of the carcinogenic potential of nickel and the development of a URF. There are numerous epidemiological studies that have investigated the association of nickel exposure and cancer, but not all of these studies are adequate to define the dose-response relationship. USEPA's carcinogenic assessment (USEPA 1986) analyzed lung cancer data from epidemiological studies of four groups of workers:

- Copper Cliff, Ontario (Chovil *et al.* 1981);
- Clydach, Wales (Peto *et al.* 1984);
- Huntington, WV (Enterline and Marsh 1982); and
- Kristiansand, Norway (Magnus *et al.* 1982).

Summary information on the above-mentioned epidemiological studies (shown in Table 8), and other available epidemiological studies, was provided by Seilkop and Oller (2003). As indicated in Section 4.2.4 above, it is important that the URF is developed based on studies with nickel species exposure profiles that are most similar to nickel emissions from Texas facilities and other sources (i.e., the forms of nickel expected in Texas air). This criterion for study selection helps ensure generalizability to the public to the extent possible. Obviously, the availability of adequate data for dose-response assessment is also a requisite for selection of a study by the TD for URF derivation and, as indicated above, human data are preferable.

Workers in two of these studies (Clydach, Wales and Copper Cliff, Ontario) were exposed to relatively high levels of sulfidic nickel, generally both in terms of absolute and relative concentrations (Seilkop and Oller 2003). More specifically, these studies involved higher absolute sulfidic nickel levels (> 10 mg/m^3 sulfidic nickel) than the Huntington, WV and Kristiansand, Norway studies (< 0.01 to > 0.5 mg/m^3 sulfidic nickel). In addition, although there is some uncertainty in the calculations, the Clydach, Wales and Copper Cliff, Ontario studies have estimated overall relative percents for sulfidic nickel of 39% and 48%, respectively, while the Huntington, WV and Kristiansand, Norway studies have lower relative percents (less than 15%) (see Table 8). Based on available information discussed in Section 4.2.4, nickel sources in Texas are not expected to emit high sulfidic nickel relative to other species. Therefore, epidemiological studies of workers exposed to high absolute and relative sulfidic nickel concentrations (i.e., Clydach, Wales and Copper Cliff, Ontario) were not considered for development of a URF as their nickel species exposure profile is expected to be even more significantly different than the emissions profiles of facilities (and other sources) in Texas than epidemiological studies with low sulfidic nickel.

Workers in two of the studies utilized by USEPA (1986) were exposed to lower levels of sulfidic nickel and a mixture of other forms of nickel (Table 8), so exposure profiles for these studies were considered by the TD to be more relevant to nickel emissions in Texas: Huntington, WV (Enterline and Marsh 1982) and Kristiansand, Norway (Magnus *et al.* 1982). Grimsrud *et al.* (2000) estimated cumulative nickel exposure from the Kristiansand, Norway cohort (Magnus *et al.* 1982) using a job exposure matrix and monitored levels of nickel. The Grimsrud *et al.* (2003) cohort study is an update of Magnus *et al.* (1982) through 2000, uses more accurate data pertaining to cumulative nickel exposure, contains sufficient information to estimate the carcinogenic potency of nickel, and will be used along with the Enterline and Marsh (1982) study to develop a URF and the carcinogenic-based ESL ($^{chronic}ESL_{linear(c)}$). Grimsrud *et al.* (2003) will be used for the carcinogenic assessment instead of the Grimsrud *et al.* (2002) case-control study because unlike the 2002 case-control study, the 2003 cohort study provides risk

results for multiple dose groups based on cumulative total nickel exposure, which will be used as the dose metric in the dose-response assessment (as discussed in Section 4.2.6 below). Additionally, Grimsrud *et al.* (2003) reports standardized incidence ratios (SIRs) and relative risks/ rate ratios (RRs), which are more appropriate for dose-response model fitting than the odds ratios presented by Grimsrud *et al.* (2002), and reports these results for several lower total nickel dose groups that may be more relevant to exposure and risk at environmental exposures. Enterline and Marsh (1982) report appropriate data to estimate the carcinogenic potency of nickel, including standardized mortality ratios (SMRs). Use of worker studies with exposure profiles most relevant to that in Texas air increases confidence in the URF estimates. However, although the exposure profiles for workers evaluated in Enterline and Marsh (1982) and Grimsrud *et al.* (2003) are considered by the TD to be more relevant to nickel in Texas than those in other studies, important differences exist. Most notably, available information indicates that Texans are not expected to be exposed to nickel subsulfide, while workers in these cohorts were exposed to nickel subsulfide, for which there is clear evidence of carcinogenicity. As a result, although the two studies with exposure profiles most relevant to that in Texas air were utilized, the significant difference in nickel subsulfide exposure between cohort workers and that expected for the Texas general population may drive URF estimates towards conservatism (i.e., overestimate risks).

Table 8. Summary of Epidemiological Studies with Adequate Dose-Response Data (Seilkop and Oller 2003)

Occupational Location and Exposure Period	Number of Workers	Lung cancer p value	Nickel Species	Typical Exposure Concentration (mg Ni/m3)	Estimated Relative Percent Sulfidic Nickel f
Clydach, Wales refinery before 1930 (1902-1930 [b])	1348	394 SMR [a] p < 0.001	Sulfidic Oxidic Soluble Metallic	> 10 > 10 > 1 > 0.5	38.6% overall
Clydach, Wales refinery after 1930 (1931-1984 [e])	1173	124 SMR	Sulfidic Oxidic Metallic	> 1 > 5 > 1	38.6% overall
Copper Cliff, Ontario sinter plants (1926-1972 [e])	3769	261 SMR p < 0.001	Sulfidic Oxidic Soluble Metallic	> 10 > 10 > 1 > 0.01	47.6%
Kristiansand, Norway refinery (1916-1983 [c])	4764	300 SIR [d] p < 0.001	Sulfidic Oxidic Soluble Metallic	> 0.5 > 2 > 0.5 > 0.5	14.3% [g]
Huntington Alloys, WV (1922-1984 [e])	3208	97 SMR	Sulfidic Oxidic Metallic	generally < 0.01 (> 3 in one dept) 0.001-0.5 0.0-0.4	generally 2.2%

[a] SMR, standardized mortality ratio; reported results from most recent study.
[b] Worker follow-up was carried out through 1984.
[c] Follow-up through 1993; operations continue to present day, but with lower exposures.
[d] SIR, standardized incidence ratio.
[e] End of worker follow-up; operations continue to present day.
[f] Generally, estimates based on (> sulfidic value / sum of > values for all forms) × 100; for Clydach, Wales the > values for the two times periods were combined for an overall estimate; for Huntington, WV the < sulfidic value was combined with the middle of the ranges for oxidic and metallic for the estimate.
[g] Typically ≤ 5% per Grimsrud *et al.* (2003).

4.2.6 Dose-Response Assessment

Grimsrud *et al.* (2003) evaluated *lung cancer incidence* by cumulative nickel exposure level, while Enterline and Marsh (1982) examined *respiratory cancer mortality* (i.e., larynx, bronchus, trachea, lung, and other (residual)) by cumulative nickel exposure level. Lung cancer will be considered the cancer endpoint of interest for these two studies, which is the same endpoint in the USEPA (1986) analysis of cancer potency estimates from various epidemiological studies. Because Enterline and Marsh (1982) do not present lung cancer incidence information, the respiratory cancer mortality data they do provide are used instead of lung cancer incidence, as more than 93% of the observed (65 of 69) and expected (57.71 of 61.47) respiratory cancers were lung cancers. Additionally, as lung cancer mortality, and consequently respiratory cancer mortality, are reasonably predictive of lung cancer incidence (i.e., five-year survival is only about 15% (American Cancer Society 2005)), the TD considers the cancer potency estimates based on the two studies and the resulting calculations as comparable (i.e., lung cancer incidence and mortality rates are sufficiently similar to respiratory cancer mortality rates as to be comparable for purposes of this assessment; see Figure 3).

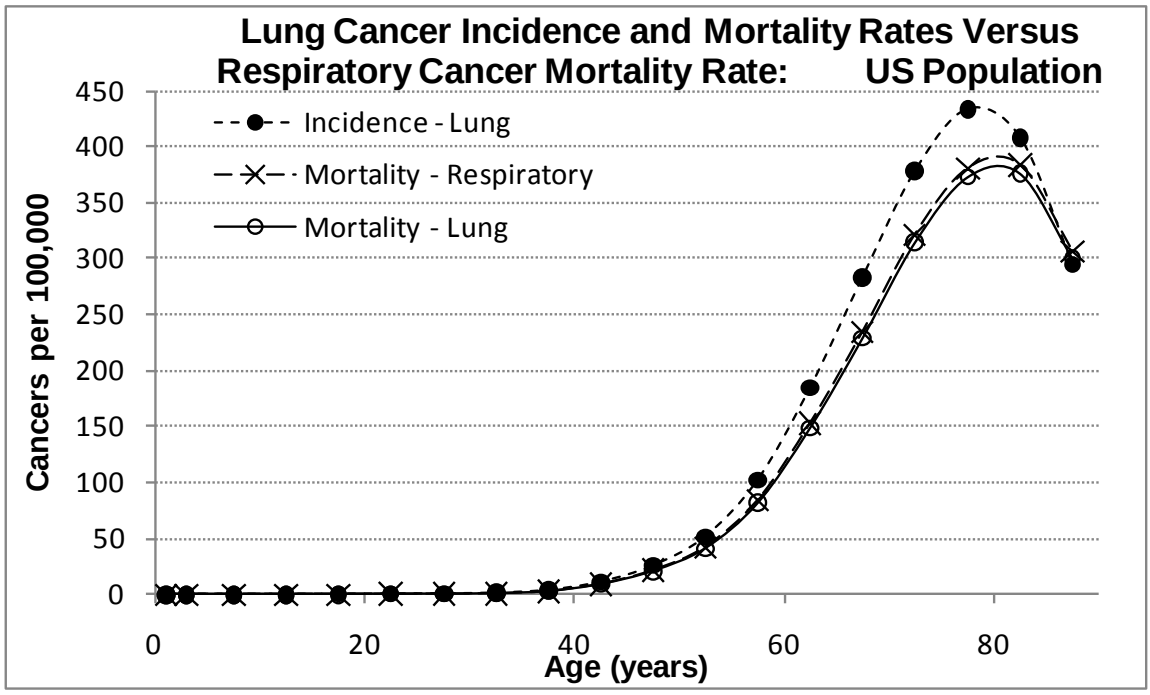


Figure 3 Lung Cancer Incidence and Mortality vs Respiratory Cancer Mortality

The dose metric used for the dose-response assessment is cumulative total nickel exposure (mg/m^3-year) because it is the only measure available from both sources and because there are no definitive biological/mechanistic data or statistical evidence which indicates that another available dose metric is more appropriate. Using cumulative exposure to total nickel as the dose metric inherently treats all nickel species as toxicologically equivalent based on nickel content and is consistent with the TD considering nickel compounds as a group to be "Carcinogenic to

Humans." Additionally, use of this dose metric alleviates the significant uncertainty associated with attempting to definitively attribute cancer risk to a particular form of nickel (e.g., sulfidic versus soluble) as study findings vary in regard to the most closely-associated form(s) and the carcinogenic response may be due to more than one form (i.e., there is no scientific consensus regarding only one form being carcinogenic which can then be used as the dose metric). In summary, the TD considers use of total nickel as the most reasonable dose metric for the carcinogenic assessment considering: (1) the potential interaction of nickel forms (i.e., the potential role of mixtures) in nickel-induced carcinogenicity; (2) the uncertainty regarding the most carcinogenic form(s) of nickel; (3) the generally robust association between total nickel and increased respiratory cancer risk in nickel epidemiological studies; (4) it is the only measure available from both cohorts; and (5) it is consistent with the TD considering nickel compounds as a group to be "Carcinogenic to Humans." The TD recognizes, however, that use of total nickel as the dose metric has associated uncertainty as it inherently assumes that the nickel species the workers were exposed to may be considered carcinogenically equivalent on a nickel content basis. That is, the risk assessment assumes that total nickel sufficiently represents the total carcinogenic potential of the nickel mixture to which the workers were exposed given both the carcinogenicity of specific nickel forms and possible interactions (e.g., possible promoter activity of nickel compounds which may not be complete carcinogens themselves).

Grimsrud *et al.* (2003) and Enterline and Marsh (1982) only provide summary data and did not conduct standard regression analysis approaches (Poisson regression or Cox regression) to calculate the slope parameter (β) and variance. The TD used the linear multiplicative relative risk model and Poisson regression modeling (Appendix B) to obtain maximum likelihood estimates of β (Section B.2, Appendix B) and the asymptotic variance for β (Section B.3, Appendix B) when cumulative nickel exposure levels versus observed and expected deaths (Enterline and Marsh 1982) or observed and expected incidence cases (Grimsrud *et al.* 2003) were provided. Grimsrud *et al.* (2003) also provided smoking-adjusted and smoking-unadjusted rate ratios.

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. In addition to the more plausible assumptions regarding the amount of increase in risk with age, the multiplicative relative risk model naturally results from the Poisson regression and Cox proportional hazards models. These standard regression analysis approaches (Poisson regression and Cox regression) to calculate the β and variance are considered more reliable and less restricted (e.g., can adjust for covariate effects and use internally-derived background hazard

rates) when the necessary detailed data are available, which is not the case for these studies as only summary data are available.

USEPA (1986) had to use the average relative risk model to calculate a URF from the Magnus *et al.* (1982) data, to which Grimsrud *et al.* (2003) is an update, because data were not available to use a more robust model (e.g., relative risk dose-response model). In addition to other analyses (e.g., multiplicative relative risk model), USEPA (1986) also used the average relative risk model for Enterline and Marsh (1982). The average relative risk model in USEPA (1986) calculates the URF using:

- the average continuous environmental concentration calculated across exposure groups using a weighting factor (e.g., number of workers per exposure group);
- the overall relative risk for all exposure groups combined (i.e., total observed cancers/total expected); and
- the background rate for the cancer endpoint.

The average relative risk equation from USEPA (1986) is:

> URF = background rate for lung cancer × [(relative risk -1)/average lifetime exposure level]

The average relative risk model used by USEPA for Magnus *et al.* (1982) and Enterline and Marsh (1982) is a simplistic approach which provides only a rough estimate of incremental risk per unit dose and should only be used when more detailed information is lacking and better methods cannot be used (e.g., only one dose-response data point). The simplicity of the USEPA average relative risk model may produce biased estimates of the URF for at least three reasons. First, it does not reflect time-dependent exposure and dose-response information. Second, it ignores age-dependent competing causes of death when calculating the URF. Lastly, it does not allow for an estimate of the confidence limits on the URF.

The TD did not use the average relative risk model for the Grimsrud *et al.* (2003) update of Magnus *et al.* (1982), or for Enterline and Marsh (1982), because the multiplicative relative risk model with Poisson regression modeling or least squares linear regression to approximate the relative risk model along with the BEIR IV methodology can be used and provides a better analysis for estimating lifetime excess risk. For example, the BEIR IV methodology accounts for competing causes of death and age-specific background population risks, and may also be used to incorporate other potentially important factors (e.g., exposure lag, windows of exposure). It is not justifiable or desirable to use the average relative risk model when there are sufficient data for the TD to use the multiplicative relative risk model.

4.2.6.1 Grimsrud et al. (2000, 2002, 2003)

The aim of Grimsrud *et al.* (2003) was to investigate the risks of cumulative nickel exposure on updated worker lung cancer incidence information. A total of 5,297 individuals met the inclusion

criteria for the cohort study and worked for at least one year at the Kristiansand, Norway refinery between 1910 and 1989. Nickel exposure estimates were based on a job-exposure matrix, 5,900 personal measurements of total nickel in air between 1973 and 1994, and the identification of soluble, sulfidic, oxidic, and metallic nickel in refinery dusts and aerosols during the 1990s (Grimsrud *et al.* 2000). For years prior to 1973, more than 500 stationary samples were available and exposure levels were back-calculated using multiplication factors based on important modifications in production technology or chemistry, or reported changes in the working environment. The average cumulative exposure was determined for each worker. While there are always uncertainties associated with estimating exposure concentrations for workers in epidemiology studies, such as speciating total nickel into different forms of nickel, Grimsrud *et al.* (2000) provides the most extensive nickel exposure dataset to date, including speciation data. It is also the only cohort for which smoking data are available. Although Goodman *et al.* (2009) suggests that soluble nickel may have been overestimated and insoluble nickel underestimated for this cohort, TD's use of total nickel as the dose metric alleviates: (1) any uncertainty associated with speciating total nickel into soluble and insoluble forms (e.g., analytical methods); (2) potential exposure misclassification as to the form(s) to which workers were exposed which may have occurred in a dose-response assessment conducted on a form-specific basis; and (3) the significant uncertainty associated with attempting to attribute cancer risk to a particular form or forms of nickel. Use of cumulative exposure to total nickel as the dose metric for the dose-response assessment inherently assumes that the nickel species the workers were exposed to may be considered carcinogenically equivalent on a nickel content basis. That is, it is assumed that total nickel sufficiently represents the total carcinogenic potential of the nickel mixture to which the workers were exposed when considering both the carcinogenicity of specific nickel forms and possible interactions (e.g., possible promoter activity of nickel compounds which may not be complete carcinogens themselves). This simplifying assumption was necessary given the significant uncertainty associated with any attempt to attribute all cancer risk in epidemiological studies to a particular form or forms of nickel without inappropriately excluding possible interactions between forms, and given the limited form-specific cumulative exposure levels provided in Grimsrud *et al.* (2003) (i.e., cumulative exposure levels only given for water-soluble, nickel oxide, and total).

Grimsrud *et al.* (2003) reported a clear dose-response relationship between lung cancer and cumulative nickel exposure, the strongest relationship being for soluble nickel, with elevated risk for all three exposed worker groups. Relative risks for lung cancer were calculated with internal analyses using cumulative exposure (mg/m^3-years) to either total, soluble, or oxidic nickel. The RRs for various cumulative (dose) levels are presented in Table 8 of Grimsrud *et al.* (2003) and were calculated using Poisson regression models adjusted for age, with or without adjustment for smoking. For a cohort study, the RR is the ratio of the cumulative incidence of the disease (lung cancer) in the exposed workers relative to that in the unexposed workers. The RRs for lung cancer were elevated for all exposed groups and statistically significantly greater than one at the 5% significance level for the two highest dose groups. There was a monotonic increase in RRs with cumulative exposure for total nickel and soluble nickel, but not for nickel oxide, although the two highest exposure groups for nickel oxide had higher RRs than the lowest exposure group.

For 11 of the 18 elevated RRs, the 95% confidence intervals (95% CI) did not include a RR of 1.0, and the seven RRs which had 1.0 in their 95% CI were for the lowest exposure groups.

Standardized incidence ratios (SIRs) are presented in Table 7 of Grimsrud *et al.* (2003) for the same cumulative dose levels for total and soluble nickel. Basically, the SIRs compare the lung cancer incidence in the cohort to that of the general population, considering five-year age group cancer rates and observation years, and number of person-years at risk. Separate SIRs were calculated based on two periods of first exposure (1910-1967 and 1968+) and both periods combined. The point estimates of the SIRs for lung cancer were elevated for all exposed groups. There was a monotonic increase in SIRs with cumulative exposure for both total nickel and soluble nickel. For 15 of the 18 SIRs for nickel-exposed workers, the 95% CI did not include a SIR of 1.0, and none of the elevated SIRs had 1.0 in their 95% CI for both exposure periods combined.

As information on specific nickel species is typically not available when evaluating air permit application modeling results or ambient air data, the RRs and SIRs for *total nickel* were used to estimate various β values for lung cancer.

4.2.6.1.1 Slope Parameter (β) Estimates

As previously mentioned, the procedures for calculating β estimates for summary data for RRs and SIRs differ, and will be discussed separately. Appendix C, which is from a personal communication with Grimsrud (March 30, 2008 Email), provides additional data not available in Grimsrud *et al.* (2003) that the TD used to estimate β values:

- Expected number of deaths for Table 7 (Grimsrud *et al.* 2003);
- A Stata output file that was used to determine the midpoints of the cumulative dose exposure ranges.

The estimation of the β parameters based on the RRs and SIRs is discussed in Sections 4.2.6.1.1.1 and 4.2.6.1.1.2, respectively. The TD used linear models to fit the RRs and the SIRs. The models used by the TD are the best linear models for a dose-response analysis of the Grimsrud *et al.* (2003) RR and SIR data and are definite improvements over the average relative risk model used by USEPA (1986) for this cohort. Although the models fit to the data are not statistically significantly satisfactory (Appendix H), the models fits are considered health protective and therefore acceptable for this assessment for several reasons: (1) the models fit to the RR and SIR data are the best linear models (i.e., no other multiplicative linear models fit the data better); (2) these models use data that take into consideration how incidence rates change with exposure levels to nickel and are therefore statistically preferable to models based on data that do not reflect changes in incidence rates with exposure levels; (3) the models used are superior to the simple average relative risk approach used by EPA (1986) in that EPA's approach did not include any regression diagnostic analyses, did not incorporate competing risks, incorrectly used Norwegian background hazard rates instead of the correct US background rates, ignored data regarding changes in the SMRs, SIRs and RRs with exposure levels to nickel, and

assumed all exposed workers had identical average cumulative nickel exposures; and (4) use of the model may confer greater health-protectiveness than discarding data from one of the two studies considered to have exposure profiles most similar to that expected for Texas since it ultimately results in a more conservative (i.e., higher) URF. Consideration of these factors indicates the models used by the TD are the best available choice for a dose-response analysis of the Grimsrud *et al.* (2003) RR and SIR data, a definite improvement over the average relative risk model used by USEPA (1986) for this cohort, and are used in the interest of protecting public health.

4.2.6.1.1.1 Estimates For β Based on RR Summary Data

For the RRs and cumulative dose levels presented in Table 8 of Grimsrud *et al.* (2003), least squares linear regression was used to approximate the linear relative risk model. Data from Table 8 of Grimsrud *et al.* (2003) that are relevant for calculation of the β are presented in Table 9 below.

Table 9. Lung Cancer Rate Ratios from Grimsrud *et al.* (2003)

Total Nickel Cumulative Exposure (mg/m3-years)	Midpoint of Exposure Range (mg/m3-years)	Number of Cases	Rate Ratio (adjusted for smoking)	Rate Ratio (unadjusted for smoking)
0	0	11	1.0	1.0
0.01-0.41	0.21	37	1.2	1.2
0.42-1.99	1.205	72	2.1	2.3
2.0+	14.2284 [a]	147	2.4	2.7

[a] weighted average estimated using piecewise linear cumulative distribution functions based on Grimsrud *et al.* (2002) (Appendix D).

Grimsrud *et al.* (2003) provides total nickel exposure ranges for the two lowest nickel-exposed groups, allowing use of the midpoints of these ranges as approximations of the averages for these two dose groups in calculation of the β. However, as the high end of the range for the highest exposed group (>2 mg/m^3-years) was not provided, a midpoint for this dose group was not readily available. The TD used piecewise linear cumulative distribution functions to estimate the average exposure level for the cases (14.0927 mg/m^3-years) and controls (14.2958 mg/m^3-years) in the high dose group as of 1995 based on the Stata output from the Grimsrud *et al.* (2002) case-control study (Appendix C). In occupational case-control studies, controls are workers without the health outcome (e.g., lung cancer) that are otherwise comparable to cases. Both cases and controls may have been unexposed or exposed to different levels of the chemical of interest (e.g., various levels and forms of nickel). Calculations for the midpoint of the highest dose group for controls are provided as an example in Appendix D. The expected number of cases (124) and controls (249) in the high-dose group were then used as weighting factors to calculate a weighted average for the high-dose group (cases and controls combined; 14.2284 mg/m^3-years) for use in

least squares linear regression for calculation of the β, although the estimated average exposure levels for cases and controls in the high-dose group were very similar. The estimate of the average for the high dose group is expected to be conservative as it only considers exposure up to 1995, whereas the lung cancer incidence and exposure data in Grimsrud *et al.* (2003) are through 2000. This may result in an underestimate of the cumulative exposure through 2000 for the high-dose group, which would tend to increase the slope β of the model (i.e., would tend to increase risk estimates).

For this relative risk model assessment, an estimate of the y-intercept (α) is used to normalize to the background lung cancer incidence observed in unexposed workers when using least squares linear regression to fit the RRs and calculate the central estimate (β) for lung cancer potency, as shown by the following equation:

$$\text{Rate Ratio (i)} = \alpha \times [1 + \beta \times \text{dose(i)}],\ i=1,...,4 \quad (A)$$

which is equivalent to

$$\text{Rate Ratio (i)} = \alpha + s \times \text{dose(i)},\ i=1,...,4, \quad (B)$$

where $s = \alpha \times \beta$ and the model in equation (B) can be easily estimated using standard least squares regression methods to solve for s = slope of the line and α = y-intercept. The β estimate is then calculated as follows:

$$\beta \text{ estimate} = s / \alpha$$

The central estimate β calculated using least squares linear regression to approximate the relative risk model based on RRs is presented in Table 11. Consistent with USEPA (2005a) and TCEQ (2006) guidelines, 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 presented in Table 11. The estimated β values based on the RRs unadjusted for smoking are presented for comparison purposes only. Smoking-unadjusted RRs use the same data as smoking-unadjusted SIRs to evaluate excess lung cancer incidence risk, only with a different reference population (internal for RRs versus external for SIRs). However, the β values based on the smoking-unadjusted SIRs are preferred over those based on smoking-unadjusted RRs for reasons cited in Section 4.2.6.1.4.

4.2.6.1.1.2 Estimates of β Based on SIR Summary Data

For the smoking-unadjusted SIRs and cumulative dose levels presented in Table 7 of Grimsrud *et al.* (2003), maximum likelihood estimation procedures with Poisson regression modeling were used to calculate the maximum likelihood estimate (MLE) β (Appendix B).Relevant data from Table 7 of Grimsrud *et al.* (2003) are presented in Table 10. 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 B), as with the data in Table 7 of Grimsrud *et al.* (2003). The multiplicative relative risk model used to

calculate the β value included a term (α) to account for differences in lung cancer incidence background rates between the study population and the reference population used to determine the number of expected lung cancer incidences. This 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 B, 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 incidence cases for exposure group j

E_{oj} = expected number of background lung cancer incidence cases for exposure group j

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

d_j = cumulative exposure for exposure group j

α = accounts for differences in lung cancer incidence background rates between the study population and the reference population

Table 10. Lung Cancer Rate Standardized Incidence Ratio (SIR) from Grimsrud *et al.* (2003)

Total Nickel Cumulative Exposure (mg/m3-years)	Midpoint of Exposure Range (mg/m3-years)	Number of Cases	Expected Number b	SIR
0	0	11	9.295	1.2
0.01-0.41	0.21	37	24.458	1.5
0.42-1.99	1.205	72	24.672	2.9
2.0+	14.2284 [a]	147	45.036	3.3

[a] weighted average estimated using a piecewise linear cumulative distribution function (Appendix D)

[b] provided by study author in personal communication (Appendix C).

As with the β calculation for the RRs from Grimsrud *et al.* (2003), the midpoints of the ranges were used for the two lowest dose groups along with the average exposure concentration for the high-dose group, estimated using a piecewise linear cumulative distribution function. The MLE β, SE, β (95% LCL), and β (95%UCL) based on the SIRs are presented in Table 11. In addition to the β (95% LCL) and β (95%UCL) values presented in Table 11 based on the estimated variance of the maximum likelihood parameter estimate, upper and lower confidence limits based on the more robust profile likelihood method are presented in the footnotes for comparison and are mostly similar.

Table 11. Beta (β) Values and Standard Error (SE) Based on Lung Cancer Incidence from Grimsrud *et al.* (2003)

Incidence Rate Basis	SE	β (95% LCL) [a]	β (MLE) [a]	β (95% UCL) [a]
Estimates based on the rate ratios using least squares regression				
Smoking-Adjusted RRs	4.10E-05	-6.54E-05 [b, f]	**5.44E-05**	1.74E-04 [c, g]
Smoking-Unadjusted RRs	4.91E-05	-7.85E-05 [b, f]	6.48E-05	2.08E-04 [c, g]
Estimates based on the standardized incidence ratios using Poisson regression				
Smoking-Unadjusted SIRs	1.58E-05	2.33E-05 [d, f]	**4.92E-05**	7.51E-05 [e, g]

[a] Excess relative risk estimates are per $\mu g/m^3$-years.
[b] 95%LCL = β - (2.920 × SE) for a t-distribution with 2 degrees of freedom.
[c] 95%UCL = β + (2.920 × SE) for a t-distribution with 2 degrees of freedom.
[d] 95%LCL = β - (1.645 × SE) for a standard normal distribution.
[e] 95%UCL = β + (1.645 × SE) for a standard normal distribution.
[f] The 95% LCLs based on the profile-likelihood are -4.57E-06, 8.10E-06, and 3.38E-05 for Smoking-Adjusted RRs, Smoking-Unadjusted RRs, and Smoking-Unadjusted SIRs, respectively.
[g] The 95% UCLs based on the profile-likelihood are 1.13E-04, 1.22E-04, and 6.61E-05 for Smoking-Adjusted RRs, Smoking-Unadjusted RRs, and Smoking-Unadjusted SIRs, respectively.

4.2.6.1.2 Dosimetric Adjustments

Consistent with TCEQ (2006), occupational concentrations ($Concentration_{OC}$) were converted to environmental concentrations for the general population ($Concentration_{HEC}$) using the following equation:

$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

where:

$Concentration_{HEC}$ = human equivalent concentration for the general public ($\mu g/m^3$)

$Concentration_{OC}$ = occupational exposure concentration ($\mu g/m^3$)

VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)

VE_h = non-occupational/environmental ventilation rate for a 24-h day (20 m^3/day)

days per $week_{oc}$ = occupational weekly exposure frequency (5 days per week)

days per $week_{res}$ = residential weekly exposure frequency (7 days per week)

4.2.6.1.3 Unit Risk Factors (URFs) and Air Concentrations at 1 in 100,000 Excess Lung Cancer Risk

URFs express cancer potency in units of risk per air concentration (e.g., risk per µg/m^3) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is unknown, which is the case for nickel (Section 4.2.3). When a dose-response curve is modeled for tumor data (see Figure 4 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.

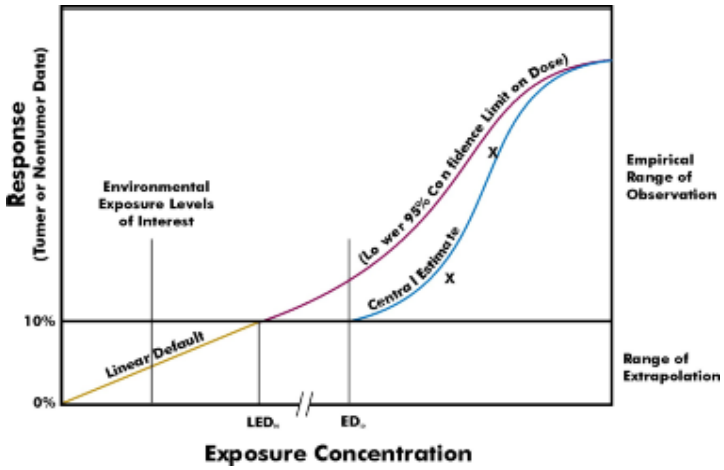


Figure 4 Example of Linear Approach for Low-Dose Extrapolation

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, an extrapolated URF using a high POD is approximately equal to a URF estimated using a low POD.

Table 12 shows estimates of URFs and air concentrations at 1 in 100,000 excess cancer risk based on β (MLE), β (95% LCLs), and β (95% UCLs) from Table 11, which were calculated from the Grimsrud *et al.* (2003) study. 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 2006), and were solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). The BEIR IV methodology for calculating excess risk is mathematically correct when the specified response is mortality and mortality rates are used, but not when the specified response is incidence rates, as shown in Appendix E. Therefore, the BEIR IV methodology was adjusted to correctly account for incidence dose-response based on equations in Appendix E.

For comparison purposes, calculations are shown using both United States (US) and Texas background incidence rates and survival probabilities:

- US incidence rates for 1975-2005 for lung cancer (Surveillance, Epidemiology, and End Results database (SEER 2007) (Appendix A);
- US survival rates for 2004 (Arias 2007) (Appendix A); and
- Texas-specific incidence rates for 2001-2005 for lung cancer and Texas-specific survival rates for 2005 were kindly provided by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry (Appendix A).

URFs and nickel air concentrations at an excess lung cancer incidence risk of 1 in 100,000 were calculated using β values for both smoking-adjusted and unadjusted RRs. URFs and air concentrations at a 1 in 100,000 excess lung cancer incidence risk were also calculated using β values based on the SIRs, unadjusted for smoking, which are preferred over those based on unadjusted RRs (see Section 4.2.6.1.4).

Table 12. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Lung Cancer Incidence

Incidence Rate Basis	Background Rates	URF (95% LCL) Air Concentration @ 1 in 100,000 Excess Risk a	URF (MLE) Air Concentration @ 1 in 100,000 Excess Risk a	URF(95% UCL) Air Concentration @ 1 in 100,000 Excess Risk a
Smoking-Adjusted RRs	TX	NA	2.83E-04/ μg/m^3 0.0354 μg/m^3	9.04E-04/ μg/m^3 0.0111 μg/m^3
	US	NA	2.64E-04/ μg/m^3 0.0379 μg/m^3	8.44E-04/ μg/m^3 0.0119 μg/m^3
Smoking-Unadjusted RRs	TX	NA	3.37E-04/ μg/m^3 0.0297 μg/m^3	1.08E-03/ μg/m^3 0.00925 μg/m^3
	US	NA	3.14E-04/ μg/m^3 0.0318 μg/m^3	1.01E-03/ μg/m^3 0.00992 μg/m^3
Smoking-Unadjusted SIRs	TX	1.21E-04/ μg/m^3 0.0826 μg/m^3	2.56E-04/ μg/m^3 0.0391 μg/m^3	3.90E-04/ μg/m^3 0.0256 μg/m^3
	US	1.13E-04/ μg/m^3 0.0885 μg/m^3	2.39E-04/ μg/m^3 0.0419 μg/m^3	3.64E-04/ μg/m^3 0.0275 μg/m^3

[a] Calculation of air concentrations at 1 in 100,000 excess risk used the unrounded URF.
NA = as the 95%LCL β value was negative, suggesting zero excess risk, calculation of an air concentration at 1 in 100,000 excess risk was not possible.

4.2.6.1.4 Preferred Potency Estimates (Grimsrud *et al.* 2003)

The TD used the following considerations in selecting the preferred potency values to represent the carcinogenic potency of total nickel based on this study:

- URFs based on Texas-specific incidence and survival rates are preferred over US rates as they are more applicable to the general population of Texas (although there were minor differences in the URFs calculated with Texas-specific versus US rates);
- Use of the URF (MLE) based on the central estimate β was preferred over use of the URF (95%UCL) as incidence data were available and utilized as opposed to mortality data, consistent with TCEQ (2006) (i.e., use of the URF (95%UCL) was not considered necessary in consideration of incidence being more prevalent than mortality as incidence was modeled), and use of this study to estimate risk based on Texas ambient air sample results is likely already conservative given differences in exposure profiles between the exposed workers and the forms of nickel likely emitted in Texas (also, controls were unexposed (as opposed to low exposed) and did not bias risk low);

- As smoking is an important confounder for lung cancer incidence, the URF of 2.83E-04 per µg/m^3 based on smoking-adjusted RRs (value shaded in Table 12) is preferred by the TD over the URF based on smoking-unadjusted RRs;
- Although not adjusted for smoking, the TD will also utilize the URF of 2.56E-04 per µg/m^3 based on available SIRs (value shaded in Table 12) as the variability of the estimated parameter based on the SIRs is smaller (e.g., there is only about a 1.5 fold difference between the URFs calculated using the SIR-based β and β (95%UCL) and the β (95%LCL) is still positive, while there is a 3.2 fold difference between the URFs calculated using the RR-based β and β (95%UCL) and the β (95%LCL) is actually negative). Additionally, the URF based on SIR data may be somewhat more robust because it was calculated using a β obtained from the multiplicative relative risk model and Poisson regression instead of a least squares linear regression which approximates the relative risk model.

Based on the above considerations, the TD believes the two URF values of 2.83E-04 per µg/m^3 (smoking-adjusted RR-based β) and 2.56E-04 per µg/m^3 (SIR-based β) (values shaded in Table 12) are the most appropriate for use in estimating the carcinogenic potency of nickel based on Grimsrud *et al.* (2003). There is only a 10% difference between these two URF values. Because each of the two values has an advantageous characteristic that the other does not have (i.e., one is adjusted for smoking while the other has less variability), the TD will use both in determining the final URF and ${}^{chronic}ESL_{linear(c)}$ (Section 4.2.6.4).

4.2.6.1.5 Comparison of TCEQ's URF to USEPA's URF

The URFs selected by the TD for Grimsrud *et al.* (2003) (2.83E-04 and 2.56E-04 per µg/m^3) are greater than (i.e., more conservative than) the range of the average relative risk URFs calculated by USEPA (1986) for this cohort based on Magnus *et al.* (1982) (1.9E-05 to 1.9E-04 per µg/m^3). The difference in the URFs calculated by the TD and the USEPA are due to various factors, including but not limited to:

- The availability of updated and more refined exposure estimates (Grimsrud *et al.* 2000);
- TD estimate is based on lung cancer incidence while USEPA is based on lung cancer mortality;
- TD using a more refined and scientifically-defensible methodology (linear multiplicative relative risk model and BEIR IV life-table approach) than USEPA (average relative risk);
- TD using updated whole population lung cancer background incidence rates for the US and Texas versus USEPA using a background lung cancer mortality rate for Norwegian males.

Calculation of a URF based on respiratory/lung cancer in Enterline and Marsh (1992) is presented below and will be used in conjunction with the URFs selected based on Grimsrud *et al.* (2003) in deriving the final URF and ${}^{chronic}ESL_{linear(c)}$ (see Section 4.2.6.4).

4.2.6.2 Enterline and Marsh (1982)

4.2.6.2.1 Estimates for β

This study of workers at a Huntington, West Virginia refinery divided workers by those exposed to nickel subsulfide (refinery workers) and those not expected to have been exposed to nickel subsulfide (non-refinery workers). Refinery workers in Enterline and Marsh (1982) were exposed to lower subsulfide levels relative to the Clydach, Wales and Copper Cliff, Ontario studies which USEPA (1986) also used to calculate risk (Table 8). USEPA (1986) utilized data from Table 10 of Enterline and Marsh (1982) to calculate a range of URFs for lung cancer. More specifically, USEPA (1986) examined lung cancer risks from refinery workers hired before 1947 and non-refinery workers hired before 1947 separately, and calculated several URFs using various risk models. While many of the SMRs reported for respiratory cancer (including lung) in Table 10 and other tables were elevated for workers in various exposure groups, the SMRs were generally not statistically elevated at a p-value of <0.05. 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) notes 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 for TCEQ to characterize cancer risk due to nickel exposure in the interest of public health, and there is regulatory agency precedent for use of such studies for risk characterization (e.g., USEPA 1986). A SMR is basically the number of observed deaths due to a particular disease (e.g., lung cancer) in a group divided by the number that would be expected had the group developed the disease at the same rate as a standard population (e.g., unexposed group, general population), taking into account the number of person-years in each age group of a cohort and age group rates in the standard population. Ultimately, the ranges of URFs cited by USEPA's IRIS for refinery workers (1.5E-05 to 3.1E-05 per $\mu g/m^3$) and non-refinery workers (9.5E-06 to 2.1E-05 per $\mu g/m^3$) in this study were based on results from the relative risk model and the average risk model.

As mentioned in Section 4.2.6, the average relative risk model was used in USEPA (1986), and is a simplistic approach which provides only a rough estimate of incremental risk per unit dose. It should only be used when insufficient dose-response data points are available (i.e. only one dose-response data point). Therefore, the TD used the multiplicative relative risk model with Poisson regression modeling and the BEIR IV methodology (mortality) as they provide a better analysis for estimating lifetime excess risk.

Observed and expected deaths with SMRs for respiratory cancer are presented in Table 9 of Enterline and Marsh (1982) according to cumulative exposure (mg/m^3-months) to total nickel for the following four groups:

- refinery workers hired before 1947;
- non-refinery workers hired before 1947;

- workers hired after 1946; and
- all workers combined.

The data used for β development from Table 9 of Enterline and Marsh (1982) are presented in Table 13 below. Workers hired after 1946 were exposed to much lower nickel levels, but were not included separately in the USEPA (1986) risk analysis or the TD analyses. These workers were not evaluated separately because:

- they are included in the preferred "all worker" analysis,
- there were only three exposure groups to model, as opposed to six for the other analyses (i.e., less information for a dose-response assessment), and
- this group of workers had no exposure to nickel subsulfide emissions from the calciner, the part of the old refinery to which the study authors generally attribute elevated cancer death rates.

For comparison purposes, however, workers hired after 1946 were combined with non-refinery workers hired before 1947 (91.4% of whom were never exposed to calcining operations) to represent a larger group of workers with six exposure groups mainly unexposed to nickel subsulfide from refining calcining operations. The URF based on this exposure group will not be used to calculate the ${}^{chronic}ESL_{linear(c)}$ as the possibility of some exposure to nickel subsulfide emissions cannot be excluded.

Enterline and Marsh (1982) provides total nickel exposure ranges for all but the highest nickel-exposed group, allowing use of the midpoints of these ranges as approximations of the averages for these dose groups in calculation of the β. However, as the high end of the range for the highest exposed group (≥ 200 mg/m^3-months) was not provided, the TD used the average value for this exposure group from Table 10 of the study as an estimate of the midpoint for the range. This is conservative (i.e., tends to increase β estimates) as Table 10 cumulative exposure data include an exposure lag period and therefore exclude some exposure, resulting in an underestimate of the average cumulative exposure for the highest non-lagged exposure group. USEPA (1986) used Table 10 data and referred to it as "20-year lag time" data. However, the TD did not use the Table 10 data because:

- the methods used by Enterline and Marsh (1982) to evaluate lagged exposure are not standard (i.e., there was not a fixed-exposure lag period, it varied for each person-year for each worker who worked past 20 years; only exposure during the first 20 years from date of hire was considered by study authors and related to mortality 20 years or more after date of hire);
- the data cannot be incorporated into the standard BEIR IV methodology to calculate excess risk as an unrealistic assumption would be required (i.e., one would have to assume that only nickel exposures from birth to age 20 could be related to lung cancer); and

- the Table 10 analysis by Enterline and Marsh (1982) resulted in a dose-response relationship that was somewhat weaker in contrast to data in Table 9.

Instead, the TD used Table 9 data as it can properly be used to estimate slopes for the multiplicative relative risk model.

Table 13. Observed (Obs) and Expected (Exp) Deaths and Standard Mortality Rates (SMR) from Respiratory Cancer by Cumulative Nickel Exposure Level

		All workers			Refinery hired before 1947			Nonrefinery hired before 1947			Workers hired after 1946		
Cumulative Nickel Exposure (mg/m^3-months) [a]	**Midpoint of Exposure Range (mg/m^3-months)** [b]	**Obs**	**Exp**	**SMR**	**Obs**	**Exp**	**SMR**	**Obs**	**Exp**	**SMR**	**Obs**	**Exp**	**SMR**
<10	5	10	16.45	60.8	0	0.05	-	7	11.48	61.0	3	4.92	61.0
10-24	17.5	8	11.00	72.7	0	0.33	-	4	8.18	48.9	4	2.49	160.5
25-49	37.5	19	14.94	127.2	0	0.76	-	16	11.99	133.5	3	2.19	136.8
50-99	75	17	14.18	119.9	3	2.48	121.2	14	10.78	129.9	0	0.92	-
100-199	150	7	5.93	118.0	2	1.80	111.1	5	3.94	126.8	0	0.19	-
≥200	563.80 [c]	8	6.46	123.8	5	2.67	187.6	3	3.75	79.9	0	0.04	-

[a] Data from Table 9 of Enterline and Marsh (1982).
[b] mg/m^3-months were converted to $\mu g/m^3$-years for calculating the β by multiplying by 1,000 μg/mg × 1 year/12 months.
[c] This is the average value for this exposure group from Table 10 of Enterline and Marsh (1982).

For the SMRs and cumulative dose levels presented in Table 9 of Enterline and Marsh (1982), Poisson regression modeling with maximum likelihood estimation procedures was used to calculate the MLE of β for respiratory cancer (Appendix B). Adequate model fit was obtained (Appendix H). The multiplicative relative risk model used to calculate the β value included a term (α) to account for differences in respiratory cancer mortality background rates between the study population and the reference population used to determine the number of expected respiratory cancer deaths. This may account for potential issues such as the healthy worker effect and any differences between internally- and externally-derived background rates. 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 respiratory cancer deaths for exposure group j

E_{oj} = expected number of background respiratory cancer deaths for exposure group j

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

d_j = cumulative exposure for exposure group j

α = accounts for differences in respiratory cancer mortality background rates between the study population and the reference population

The β (MLE), SE, β (95%LCL), and β (95%UCL) values are presented in Table 14 below. In addition to the β (95% LCL) and β (95%UCL) values presented in Table 14 based on the estimated variance of the maximum likelihood parameter estimate, upper and lower confidence limits based on the more robust profile likelihood method are presented in the footnotes for comparison and are similar.

Table 14. β Values and SE Based on Respiratory Cancer Mortality from Enterline and Marsh (1982)

Worker Group	SE	β (95% LCL) [a, b, d]	β (MLE) [a]	β (95% UCL) [a, c, e]
All Workers	1.25E-05	-9.07E-06	**1.15E-05**	3.22E-05
Refinery Hired Before 1947	5.97E-05	-5.66E-05	4.16E-05	1.40E-04
Non-refinery Hired Before 1947	1.28E-05	-1.90E-05	2.01E-06	2.30E-05
Refinery + Non-refinery Hired Before 1947	1.32E-05	-9.36E-06	1.23E-05	3.40E-05
Hired After 1946 + Non-refinery Hired Before 1947	1.23E-05	-1.88E-05	1.43E-06	2.17E-05

[a] Estimates are excess relative risk per $\mu g/m^3$-years.
[b] 95%LCL = β - (1.645 × SE).
[c] 95%UCL = β + (1.645 × SE).
[d] The 95% LCLs based on the profile likelihood are zero for all groups.
[e] The 95% LCLs based on the profile likelihood are 3.15E-05, 9.37E-05, 2.62E-05, 3.27E-05, and 2.51E-5 for the first, second, …, and fifth worker groups listed in the table, respectively.

4.2.6.2.2 Dosimetric Adjustments

Consistent with TCEQ (2006), occupational concentrations were converted to environmental concentrations for the general population using the equation in Section 4.2.6.1.2.

4.2.6.2.3 Calculation of URFs and Air Concentrations at 1 in 100,000 Excess Respiratory Cancer Risk

Table 15 shows estimates of URFs and air concentrations at 1 in 100,000 excess respiratory cancer mortality risk based on β (MLE) and β (95% UCLs) from Table 9 of Enterline and Marsh (1982). Air concentrations were based on extra risk and a lifetime exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2006), and solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). Air concentrations at 1 in 100,000 excess respiratory cancer risk are shown in Table 15 using both US and Texas mortality and survival rates provided in Appendix A.

URFs and air concentrations at a 1 in 100,000 excess respiratory cancer mortality risk were calculated using β values based on various worker population subsets for completeness and comparison purposes in Table 15 below. Since the β (95% LCL) values were negative (Table 14), suggesting zero excess risk, calculation of a URF (95% LCL) and corresponding air concentration at 1 in 100,000 excess risk was not possible.

Table 15. URFs and Air Concentrations Corresponding to 1 in 100,000 Excess Respiratory Cancer Mortality

Worker Group	Background Rates	URF (MLE) a Air Concentration @ 1 in 100,000 Excess Risk	URF (95% UCL) a Air Concentration @ 1 in 100,000 Excess Risk
All Workers	US	4.55E-05/ µg/m^3 0.220 µg/m^3	1.27E-04/ µg/m^3 0.0788 µg/m^3
	TX	4.34E-05/ µg/m^3 0.230 µg/m^3	1.21E-04/ µg/m^3 0.0826 µg/m^3
Refinery Hired Before 1947	US	1.64E-04/ µg/m^3 0.0608 µg/m^3	5.53E-04/ µg/m^3 0.0181 µg/m^3
	TX	1.57E-04/ µg/m^3 0.0637 µg/m^3	5.28E-04/ µg/m^3 0.0189 µg/m^3
Non-refinery Hired Before 1947	US	7.94E-06/ µg/m^3 1.26 µg/m^3	9.09E-05/ µg/m^3 0.110 µg/m^3
	TX	7.58E-06/ µg/m^3 1.32 µg/m^3	8.68E-05/ µg/m^3 0.115 µg/m^3
Refinery + Non-refinery Hired Before 1947	US	4.86E-05/ µg/m^3 0.206 µg/m^3	1.34E-04/ µg/m^3 0.0744 µg/m^3
	TX	4.64E-05/ µg/m^3 0.215 µg/m^3	1.28E-04/ µg/m^3 0.0780 µg/m^3
Hired After 1946 + Non-refinery Hired Before 1947	US	5.65E-06/ µg/m^3 1.77 µg/m^3	8.58E-05/ µg/m^3 0.117 µg/m^3
	TX	5.40E-06/ µg/m^3 1.85 µg/m^3	8.19E-05/ µg/m^3 0.122 µg/m^3

[a] Since the β (95% LCL) value was negative (Table 14), suggesting zero excess risk, calculation of a URF (95% LCL) and corresponding air concentration at 1 in 100,000 excess risk was not possible.

4.2.6.2.4 Preferred β and Potency (URF) Estimates (Enterline and Marsh 1982)

Considering TCEQ's important role in the protection of public health and that the possibility of some nickel subsulfide exposure due to emissions from Texas facilities cannot be entirely excluded, a health-protective science policy-decision was made to select the β value based on the dataset for all workers combined as the preferred β (as opposed to just non-refinery workers or workers hired after 1946 + non-refinery workers), which includes workers exposed to nickel subsulfide. While a conservative decision in the face of uncertainty, the preferred β (all workers) may tend to overestimate risk for the Texas population (e.g., the β for workers hired after 1946 +

non-refinery workers is about an order of magnitude lower). Additionally, the dataset for all workers is the most robust for development of the β. The TD utilized respiratory cancer mortality data from Enterline and Marsh (1982) because lung cancer incidence data were not provided. However, respiratory cancer mortality rates are reasonable surrogates for lung cancer mortality rates since more than 93% of the observed (65 of 69) and expected (57.71 of 61.47) respiratory cancers are lung cancers, and lung cancer mortality reasonably predicts lung cancer incidence since 5-year survival is only about 15% (American Cancer Society 2005). Therefore, use of the β (MLE) was preferred over use of the β (95%UCL) as the TD essentially considers the endpoint lung cancer incidence, consistent with TCEQ (2006). Based on these considerations, the TD believes the β (MLE) for all workers (1.15E-05 per $\mu g/m^3$-years) to be the most appropriate for use in estimating the carcinogenic potency of total nickel based on Enterline and Marsh (1982).

Additionally, the TD prefers a URF (MLE) based on Texas-specific mortality and survival rates over one based on US rates as Texas-specific mortality and survival rates are more applicable to the general population of Texas. Based on the β (MLE) and mortality/survival rates selected by the TD for Enterline and Marsh (1982), the preferred URF is 4.34E-05 per $\mu g/m^3$. This URF will be used in determining the final URF and ${}^{chronic}ESL_{linear(c)}$ (Section 4.2.6.4).

4.2.6.2.5 Comparison of TCEQ's URF to USEPA's URF

The URF selected by the TD for all workers (4.34E-05 per $\mu g/m^3$) is greater than (i.e., more conservative than) the relative risk model URFs calculated by USEPA (1986) for refinery workers (1.5E-05 per $\mu g/m^3$) and non-refinery workers (9.5E-06 per $\mu g/m^3$) (see Tables 8-51 and 8-52 of USEPA 1986). The difference in the URFs calculated by TD and USEPA may be due to various factors, including but not limited to:

- Various methodology/calculation errors made by USEPA (1986) (e.g., the expected number of respiratory cancers (larynx, bronchus, trachea, lung, and other) are used to predict the number of observed lung cancers, which is a different cancer endpoint);
- TD estimate is based on all worker's period of follow-up and cumulative nickel exposure (Table 9 in Enterline and Marsh) while USEPA estimates are based on nickel workers 20 years after first exposure and cumulative nickel exposure up to 20 years from onset of exposure (i.e., nonstandard lagged exposure data) (Table 10 in Enterline and Marsh);
- TD estimate is based on all workers while USEPA estimates are based on refinery workers hired before 1947 and on non-refinery workers hired before 1947;
- TD using updated whole population survival and lung cancer background mortality rates for the US and Texas, as opposed to the 1978 rates used by USEPA which were already outdated as of the 1986 USEPA assessment; and
- TD using a BEIR IV life-table approach versus the equation used by USEPA, although the methodology is very similar.

To elaborate on the example in the first bullet above, USEPA (1986) subtracted nasal cancers from the observed respiratory cancers to derive the number of *observed lung cancers*, but did not

make this same adjustment for expected cancers in order to limit the expected cancers to lung, instead using the number of *expected respiratory cancers*. This resulted in the number of expected cancers being somewhat higher than it should have been given that the observed cancers were limited to those of the lung, and tended to bias risk results low. Because of this error, the USEPA (1986) multiplicative relative risk and additive risk analyses for both the refinery and non-refinery workers are incorrect. The TD did not duplicate this error and used respiratory cancer for *both* the observed and expected number of cancers for Enterline and Marsh (1982).

A more specific accounting for the differences between the URFs calculated by TD and USEPA is not possible as important information is missing from USEPA (1986) (e.g., specific age at which incremental risk is calculated, specific survival rates and background lung cancer mortality rates used). The URF based on Enterline and Marsh (1992) will be used in conjunction with the URFs selected based on Grimsrud *et al.* (2003) in deriving the final URF and ${}^{chronic}ESL_{linear(c)}$ (see Section 4.2.6.4).

4.2.6.3 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005) 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. The mechanisms of nickel carcinogenesis have not been firmly established, although a variety of mechanisms are likely to be involved as discussed in Section 4.2.3.

Nickel has not been identified by USEPA as having a mutagenic MOA, and data are not sufficient to definitively determine the specific carcinogenic MOA. The MOA for nickel-induced lung cancer has not been determined to be mutagenic by the scientific community. Therefore, consistent with TCEQ guidance (TCEQ 2006), ADAFs will not be applied to the URF. This issue will be reevaluated periodically as new scientific information on nickel's carcinogenic MOA becomes available.

4.2.6.4 Final URF and ${}^{chronic}ESL_{linear(c)}$

The final URF is derived here using a meta-analysis approach that combines URFs based on the preferred individual epidemiological studies. Though meta-analyses usually combine results of primary research, herein the meta-analysis combines URFs estimated from published data of primary epidemiological research studies. The purpose of this meta-analysis is to integrate the findings based on the preferred individual studies into a final URF that objectively incorporates the value of the data (measured by the size of the study) and the significance of the results (measured by the precision or variance of the model fit to the data).

The two preferred URFs based on Grimsrud *et al.* (2003) were 2.83E-04 and 2.56E-04 per $\mu g/m^3$, and the URF based on Enterline and Marsh (1982) was 4.34E-05 per $\mu g/m^3$. The URFs selected by the TD for Grimsrud *et al.* (2003) and Enterline and Marsh (1982) are considered appropriate estimates of the carcinogenic potency of nickel based on their respective studies. The

TD believes use of any of these three URFs would result in adequate protection of public health given available information on the nickel species likely emitted in Texas. Additionally, all three are more conservative than the corresponding URFs calculated by USEPA (1986) for these studies (see Sections 4.2.6.1.5 and 4.2.6.2.5). URFs based on Grimsrud *et al.* (2003) are for lung cancer incidence (they did not report data on respiratory cancer mortality), while the URFs based on Enterline and Marsh (1982) are for respiratory cancer mortality (they did not report data on lung cancer incidence). In order to incorporate the available information, the TD combined these URFs based on slightly different endpoints to estimate the final URF because incidence rates for lung cancer are reasonably predictive of respiratory cancer mortality rates.

The two preferred URFs from Grimsrud *et al.* (2003) and the preferred URF from Enterline and Marsh (1982) were combined for the final URF using weighting factors relevant to relative confidence in these three URFs. The number of person-years of follow up (153,952.9 for Grimsrud *et al.* 2003 and 77,323.6 for Enterline and Marsh 1982) indicate the total number of years the workers in the cohorts were at risk or had the opportunity of developing cancer. Generally, there is more confidence in cohort studies with large worker populations and/or long follow-up periods, which increase person-years at risk. Variance in the β values used to derive the preferred URFs reflects uncertainty in the β estimates and can also be used as a weighting factor. Generally, there is more confidence in β values with smaller variance. These two weighting factors seem not to be highly correlated for these particular studies as the preferred β value for the smaller Enterline & Marsh (1982) study has the least variance of the three. Inclusion of the number of person-years of follow up as a weighting factor for cohorts helps to ensure that information on carcinogenic potency (i.e., URFs) from larger, more data-robust studies is not potentially drastically outweighed by a very large β variance weighting factor from a smaller study due to lesser β variance, which would essentially be tantamount to discarding a URF from a large, data-rich study for purposes of calculating a final URF. Similarly, inclusion of the β variance weighting factor helps to ensure that URFs from smaller studies are not drastically outweighed in the final URF calculation solely based on relative cohort size, as the URFs from smaller studies may be potentially given additional weight commensurate with lesser uncertainty in the underlying β value. The TD believes that combining both of these readily-available weighting factors (i.e., person-years of follow up and β variance) into overall weighting factors for the three preferred URFs provides a better weighting procedure than use of either of these weighting factors alone since such combined overall weighting factors pertain to two considerations relevant to relative confidence in the URFs (i.e., cohort size and length of follow-up, variance/uncertainty in the underlying β values).

The three preferred URFs were not estimated independently, and therefore, cannot be weighted in a way that assumes independence. The URFs estimated using the Grimsrud *et al.* (2003) data are based on the same cohort and, consequently, are not independent. In order to combine the three preferred URFs, the TD first calculated a pooled URF from the two preferred URFs derived from the Grimsrud *et al.* (2003) data analyses and then this pooled URF was combined with the URF derived from the Enterline and Marsh (1982) study. As a result, the row labeled “Pooled Adjusted RRs and Unadjusted SIRs” in Table 16 below shows the URF that results from pooling

the URFs based on the Grimsrud *et al.* (2003). The two Grimsrud *et al.* (2003) URFs were weighted by multiplying each by the person-years of follow up (which is the same for both URFs and were used for the sake of consistency with the next step in the combination of URFs) and the reciprocal of the variance for the associated β (i.e., number of person-years of follow up × 1/β variance). The reciprocal of the variance is used so that the resulting weighting factor is larger for the β value with the smallest variance (uncertainty). The URFs based on βs with smaller variance receive greater weights as confidence is increased because relatively lesser variances are an indication of higher statistically significance. The overall weight for a URF (see the last column of Table 16) is the percentage of the sum of URF weighting factors that is represented by the product of the number of person-years of follow up in the cohort and the reciprocal of the variance of the estimated β for that URF (i.e., (individual URF weighting factor/sum of weighting factors for URFs being pooled) × 100 = overall weight % for a given URF). The resulting pooled URF of 2.59E-04 per $\mu g/m^3$ for Grimsrud *et al.* (2003) is equal to the weighted average (using overall weight percents expressed in decimal form) of the two individual URFs:

Pooled URF for Grimsrud *et al.* (2003) based on the Smoking-Adjusted RRs and Unadjusted SIRs = (URF × overall weight for Smoking-Adjusted RRs) + (URF × overall weight for Smoking-Unadjusted SIRs)

= (2.83E-04 × 0.1293) + (2.56E-04 × 0.8707)

= 2.59E-04 per $\mu g/m^3$

The standard error of the pooled estimate of β (1.47E-05) is similarly calculated by using the definition of a weighted sum of variances:

SE of β for Pooled Grimsrud *et al.* (2003) URF =

$$[\ (\text{SE} \times \text{overall weight for Smoking-Adjusted RRs})^2 + (\text{SE} \times \text{overall weight for Smoking-Unadjusted SIRs})^2\ ]^{1/2}$$

$$= [\ (4.10\text{E-}05 \times 0.1293)^2 + (1.58\text{E-}05 \times 0.8707)^2\ ]^{1/2}$$

$$= 1.47\text{E-}05$$

After the pooled URF based on the Grimsrud *et al.* (2003) cohort was obtained, it was combined with the preferred URF based on Enterline and Marsh (1982). These two URFs were weighted by multiplying each by the number of person-years of follow up in the cohort and the reciprocal of the variance for the associated β (i.e., number of years of follow up × 1/β variance). By this combined weighting, the URF based on the cohort with the largest number person-years of follow up (Grimsrud *et al.* 2003) is given more weight based on this factor, while at the same time the URF with the least variance in the underlying β (Enterline and Marsh 1982) is given additional weight. The combination of the relative difference between the cohorts in number of person-years of follow up and the relative differences in variance of the β values upon which the preferred URFs were based determines the overall weighting for the preferred URFs from these

studies. As shown in the last two rows of Table 16, Grimsrud *et al.* (2003) had a larger number of person-years weighting factor, but as the β for the Enterline and Marsh (1982) URF had a smaller variance, the β variance weighting factor (i.e., 1/β variance) for Enterline and Marsh (1982) was slightly larger. The net result is that the overall weighting factor for the Enterline and Marsh (1982) URF is smaller. The final weight for the pooled URF based on the Grimsrud *et al.* (2003) cohort (i.e., 58.87%) is larger than the weight for the preferred URF based on the Enterline and Marsh (1982) cohort (i.e., 41.13%).

Table 16. Weighting of Preferred URFs from Grimsrud *et al.* (2003) and Enterline and Marsh (1982)

Study	Preferred URF	Total Person-Years	Standard Error (SE) of β e	1 / SE2 e	URF Weighting Factor f	Overall Weight of URF (%) g
Grimsrud et al. (2003)						
Smoking-Adjusted RRs	2.83E-04/ μg/m^3 [a]	153,952.9 [c]	4.10E-05	5.95E+08	9.16E+13	12.93
Smoking-Unadjusted SIRs	2.56E-04/ μg/m^3 [a]	153,952.9 [c]	1.58E-05	4.01E+09	6.17E+14	87.07
Pooled URF and SE from two estimates based on the study of Grimsrud et al. (2003)						
Combined Adjusted RRs and Unadjusted SIRs	2.59E-04/ μg/m^3 [h]	153,952.9	1.47E-05 [i]	4.60E+09	7.08E+14	58.87
URF and SE estimates based on the study of Enterline and Marsh (1982)						
All Workers	4.34E-05/ μg/m^3 [b]	77,323.6 [d]	1.25E-05	6.40E+09	4.95E+14	41.13

[a] See Table 12.
[b] See Table 15.
[c] See Appendix C.
[d] See Table 3 in Enterline and Marsh (1982).
[e] See Tables 11 and 14 for the values of the SE of β.
[f] Weighting factor = total person-years × 1/SE^2.
[g] Overall weight of URF (%) = (weighting factor/sum of weighting factors) × 100.
[h] combined URF = 0.1293×2.83E-04 + 0.8707×2.56E-04
[i] SE of β for combined URF = [(0.1293×4.10E-05)^2 + (0.8707×1.58E-05)^2]$^{1/2}$.

The calculation of the final URF can be performed using the pooled URF for Grimsrud *et al.* (2003) and the preferred URF (all workers) for Enterline and Marsh (1982) (second column of Table 16) and the overall weight percents (expressed in decimal form) from the last column of Table 16:

Final URF = Combined Grimsrud *et al.* (2003) URF × overall weight +
Enterline and Marsh (1982) URF × overall weight

= 2.59E-04 × 0.5887 + 4.34E-05 × 0.4113

= 1.70E-04 per μg/m^3

The final URF, when rounded to two significant figures, is 1.7E-04 per µg/m^3, and the resulting air concentration at a 1 in 100,000 excess lung cancer risk rounded to two significant figures is 0.059 µg/m^3. *Therefore, the* ${}^{chronic}ESL_{linear(c)}$ *is 0.059µg/m*^{3}.

4.2.7 Uncertainty Analysis

4.2.7.1 Dose-Response Modeling

The ${}^{chronic}ESL_{linear(c)}$ of 0.059 µg/m^3 is based on best estimates of parameters in models fit to the most appropriate available epidemiological data of workers exposed to nickel species most similar to the nickel emissions in Texas. The derivation of the final ${}^{chronic}ESL_{linear(c)}$ includes the use of the most appropriate statistical analyses for the given epidemiological data available. Though some of the statistical methodology used may be more refined than the available data warrant, the analysis methodology guarantees that the uncertainty and variability already present in the epidemiological data would not be increased. In consideration of the remaining variability and uncertainty inherent in all epidemiological studies, and especially here for different nickel species, the TD decided to include estimates based on incidence of lung cancers in the estimation of the final ${}^{chronic}ESL_{linear(c)}$. The final ${}^{chronic}ESL_{linear(c)}$ includes some degree of variability and uncertainty that cannot be eliminated or further reduced with the available data. The excess risk of lung cancer incidence for the final ${}^{chronic}ESL_{linear(c)}$ could be as high as approximately 2 in 100,000 if the β (95%UCL) values were used instead of the maximum likelihood estimates, and could be as low as zero excess lung cancers if the β (95%LCL) were used instead of the maximum likelihood estimates. The sections below highlight particular areas of uncertainty due to different dose-response modeling methods.

For the Enterline and Marsh (1982) study, dose-response modeling was conducted with a multiplicative relative risk model and linear Poisson regression modeling including a term to account for differences between study and reference population background mortality rates. Linear Poisson regression is commonly used to investigate dose-response relationships derived from occupational cohort epidemiologic studies based on mortality and is generally considered to be biologically-plausible for lung cancer. For the Grimsrud *et al.* (2003) study, RRs adjusted for smoking were used to conduct a linear regression dose-response modeling to approximate the linear relative risk model. Maximum likelihood estimation procedures with Poisson regression modeling were used to calculate the MLE β using smoking-unadjusted SIRs and cumulative dose levels. While the models used by the TD are the best linear models available for a dose-response analysis of the Grimsrud *et al.* (2003) data and are definite improvements over the average relative risk model used by USEPA (1986) for this cohort, the model fits to the data are not statistically significantly satisfactory (Appendix H). Although this may introduce some uncertainty, use of the models is considered health protective and in the interest of public health for reasons cited in Sections 4.2.6.1.1.1 and 4.2.6.1.1.2.

URFs calculated with slope β parameter estimates for both the MLE and 95% UCL estimates were reported for each cohort in order to provide information on uncertainty in the risk estimates based on the different cohorts. Since the β (95% LCL) values were negative in both studies,

indicating the possibility of zero excess risk, calculation of a URF (95% LCL) was not possible. Regarding the preferred URFs from each study:

- For the Grimsrud *et al.* (2003) study, URF estimates for smoking-adjusted RRs ranged from 2.83E-04 per $\mu g/m^3$ (MLE) to 9.04E-04 per $\mu g/m^3$ (95% UCL), a ratio of 3.2;
- For the Grimsrud *et al.* (2003) study, URF estimates for smoking-unadjusted SIRs ranged from 2.56E-04 per $\mu g/m^3$ (MLE) to 3.90E-04 per $\mu g/m^3$ (95% UCL), a ratio of 1.5; and
- For the Enterline and Marsh (1982) study, URF estimates for all workers range from 4.34E-05 per $\mu g/m^3$ (MLE) to 1.21E-04 per $\mu g/m^3$ (95% UCL), a ratio of 2.8.

For these analyses, the ratio of the URF (95% UCL) to the URF (MLE) for the individual cohorts ranged from 1.5 to 3.2, which indicates the precision of the estimates. Across cohorts for these analyses, the ratio of the highest URF (MLE) of 2.83E-04 per $\mu g/m^3$ (from Grimsrud *et al.* 2003) to the lowest URF (MLE) of 4.34E-05 per $\mu g/m^3$ (from Enterline and Marsh 1982) was 6.5, which indicates good agreement between dose-response modeling from the different cohort studies.

4.2.7.2 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, 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 nickel was evaluated based on healthy male workers employed in smelters. The model may underestimate excess risks for subpopulations that are particularly more sensitive than smelter workers to nickel exposures. Although workers are often healthier than the general population, the approach used by TD estimates how the risk of lung cancer changes with exposure to nickel while adjusting for the differences between the workers and the general population background lung cancer rates (i.e., Texas general population lung cancer incidence and mortality background rates were used as opposed to those for the workers). The estimates of excess risks 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 excess risk per unit increase in the dose metric (i.e., cumulative exposure or weighted cumulative exposure to nickel) is the same for the workers and for the target population. Subpopulations with higher background lung cancer mortality rates will have higher estimated URFs.
- The general population does not have the same exposure levels as occupational workers, who are generally exposed to significantly higher concentrations. Lung cancer risk in refinery workers exposed to high concentrations of nickel are elevated based on occupational exposure.

- In addition, occupational workers (e.g., nickel refiners) may be exposed to different species of nickel than the general population, as discussed in section 4.2.4. For example, while there is a strong relationship between sulfidic nickel exposure and the increased risk of lung cancer in highly-exposed smelter workers, Texans are expected to be exposed to little or no sulfidic nickel.

4.2.7.3 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 and mean exposure levels). Grimsrud *et al.* (2000, 2002, 2003) investigated the dose-response relationship between exposure to different species of nickel and lung cancer incidence. However, the TD used total nickel estimates, and not nickel species estimates, because of:

- the significant uncertainty associated with attempting to definitively attribute cancer risk to a particular form of nickel as study findings vary in regard to the most closely-associated form(s) and the carcinogenic response may be due to more than one form (i.e., there is no scientific consensus regarding only one form being carcinogenic which can then be used as the dose metric);
- the potential interaction of nickel forms (i.e., the potential role of mixtures) in nickel-induced carcinogenicity;
- the generally robust association between total nickel and increased respiratory cancer risk in nickel epidemiological studies; and
- it is the only measure available for both cohorts.

Additionally, there is the potential for estimation error for individual species of nickel. For example, a recent review (Goodman *et al.* 2009) discussed that unknown differences may occur in exposure estimates due to differences in the reliability of exposure estimates for various nickel species in individual cohorts/workplaces/departments (e.g., sample collection, preservation, and speciation methods, coexposure to emissions from adjacent areas). Uncertainty in the exposure estimates for the Grimsrud *et al.* studies are discussed specifically (see Goodman *et al.* 2009 for more information). The TD recognizes that use of total nickel as the dose metric has associated uncertainty as it inherently assumes that the nickel species the workers were exposed to may be considered approximately equivalent for carcinogenic potential on a nickel content basis, or alternatively, that total nickel sufficiently represents the total carcinogenic potential of the nickel mixture to which the workers were exposed given both the carcinogenicity of specific nickel forms and possible interactions (e.g., possible promoter activity of nickel compounds which may not be complete carcinogens themselves).

In regard to the Enterline and Marsh (1982) cohort, the authors indicated, “Estimates have been derived by the use of limited historical sample data obtained by the midget impinger-particle counting technique and converted to modern gravimetric expression. In addition, data derived from several hundred recent gravimetric samples were used to estimate historic exposures.

Whenever possible and/or applicable, the modern data were adjusted on the basis knowledge of process changes and environmental controls that were implemented over the years. The unadjusted extrapolation of modern sample data to historical exposures is imperfect, but it can be assumed that the historical exposures were the same or, in most cases, of greater magnitude." If historical exposures were of greater magnitude than concentration estimates used to derive URFs, risk due to exposure to nickel would tend to be overestimated.

4.2.7.4 Uncertainty Due to Co-Exposures to other Compounds

IARC (1990) has noted that nickel workers may be exposed to high concentrations of other metals, including arsenic, and in some cases, exposure to irritant gases including hydrogen sulfide, ammonia, chlorine, and sulfur dioxide. Enterline and Marsh (1982) noted that workers from the nickel refinery at Huntington, West Virginia, were exposed to substances commonly found in the alloys and processing: chromium, iron, copper, grinding dust, solvents, and acid mists. Grimsrud *et al.* (2003) provide the following discussions on the role in lung cancer due to co-exposures to arsenic, asbestos, mists containing sulfuric acid, and cobalt:

> Exposure to other carcinogens at the refinery has been suggested as playing a role in the lung cancer problem. Accumulation of arsenic in the process intermediates between 1930 and 1952 was a matter of great concern at the time, and it represents a potential confounder that could affect the risk estimates among those who were at work in this period. However, the risks observed in workers who were employed before 1930 and after 1955 suggest that arsenic, at most, was a minor contributor to the lung cancer risk. Asbestos has been a widely spread industrial carcinogen in Norway. Through the year 2000 only 3 cases of pleural mesothelioma were diagnosed in the nickel-refinery cohort, which is in line with the expected number based on the general male population (SIR ~ 0.9, 95% CI 0.2, 2.8). Thus, exposure to asbestos only seems to have had a small impact on the lung cancer incidence. Mists containing sulfuric acid have been classified as carcinogenic to humans *(IARC 1992, as cited in Grimsrud et al. 200*3). The levels of exposure to sulfuric acid were not particularly high at the refinery, and they were limited to the copper electrolysis and some associated departments. The analyses of risk by department do, in fact, suggest a higher risk in these areas but do not take account of possible differences in nickel exposure. Cobalt is found together with nickel in small amounts throughout the refinery process. Water-soluble cobalt compounds have been shown to induce cancer by inhalation in rodent experiments *(Bucher et al. 1999, as cited in Grimsrud et al. 2003).* Most of the cobalt was removed from the nickel electrolyte and subsequently discarded until 1952, when an electrolytic cobalt production was started. During the period 1980–1994 cobalt generally was present at low levels, with concentrations amounting to some 5 to 20 percent of the nickel. With the present approach it was not possible to assess the potential effect of exposure to cobalt. Similar lung cancer hazards have been identified.

The risk estimates can therefore be confounded by co-exposure to other pollutants and/or smoking, which is common in epidemiological studies. Many of the workers were smokers.

Enterline and Marsh (1982; 1995) did not investigate confounding by smoking. Grimsrud *et al.* (2002) stated that the most important potential confounder is tobacco smoking with its strong impact on lung cancer risk. Grimsrud *et al.* (2002) found that RRs adjusted for smoking were lower than RRs unadjusted for smoking. The TD used both smoking-adjusted RRs and smoking-unadjusted SIRs in the analyses (see Section 4.2.6.1).

4.2.7.5 Use of Mortality Rates to Predict Incidence

As previously discussed in Section 4.2.6, Grimsrud *et al.* (2002) investigated lung cancer incidence whereas Enterline and Marsh (1982) examined respiratory cancer mortality. Using respiratory cancer mortality data from Enterline and Marsh (1982) may potentially overestimate lung cancer mortality since there were four additional deaths in the respiratory cancer category other than lung cancer. However, as potency (β) estimates for Enterline and Marsh (1982) were based on respiratory cancer mortality and lung cancer incidence was used as the common cancer endpoint for these two cohorts, lung cancer incidence may be slightly underestimated (see Figure 3).

4.3 Welfare-Based Chronic ESL

No data were found regarding vegetative effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- chronic ReV = 0.23 $\mu g/m^3$
- ${}^{chronic}ESL_{nonlinear(nc)}$ = 0.07 $\mu g/m^3$
- ${}^{chronic}ESL_{linear(c)}$ = 0.059 $\mu g/m^3$

The long-term ESL for air permit evaluations is the ${}^{chronic}ESL_{linear(c)}$ of 0.059 $\mu g/m^3$ (Table 2). As indicated previously, to protect against sensitization, exceedances of the short-term or long-term ESL during the air permit review should be discouraged for any chemicals identified as respiratory sensitizers (TCEQ 2006).

For evaluation of long-term ambient air monitoring data, the ${}^{chronic}ESL_{linear(c)}$ of 0.059 $\mu g/m^3$ is lower than the chronic ReV of 0.23 $\mu g/m^3$ (Table 1), although both values may be used for the evaluation of air data as well as the URF of 1.7E-04 per $\mu g/m^3$. The ${}^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 5 References

5.1. References Cited in DSD

ACS. 2005. American Cancer Society. Cancer facts and figures. Available at www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf, (accessed May 2009).

Adkins, B., Jr., J. H. Richards, and D. E. Gardner. 1979. Enhancement of experimental respiratory infection following nickel inhalation. *Environ Res* 20 (1):33-42.

AEGL. 2006. Acute Exposure Guideline Level for Nickel Carbonyl. Interim. available at www.epa.gov/oppt/aegl, (accessed May 2009).

Andersen, A., S. R. Berge, A. Engeland, and T. Norseth. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup Environ Med* 53 (10):708-13.

Arias, E. 2007. United States life tables, 2004. National Vital Statistics Reports 56(9): 3, Table B. http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_09.pdf (accessed August 2008).

ATSDR. 2005. Toxicological profile for nickel. Place Published: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp15.html(accessed May 2009).

Benson, J. M., D. G. Burt, R. L. Carpenter, A. F. Eidson, F. F. Hahn, P. J. Haley, R. L. Hanson, C. H. Hobbs, J. A. Pickrell, and J. K. Dunnick. 1988. Comparative inhalation toxicity of nickel sulfate to F344/N rats and B6C3F1 mice exposed for twelve days. *Fundam Appl Toxicol* 10 (1):164-78.

Berge, S. R., and K. Skyberg. 2003. Radiographic evidence of pulmonary fibrosis and possible etiologic factors at a nickel refinery in Norway. *J Environ Monit* 5 (4):681-8.

Brera, S., and A. Nicolini. 2005. Respiratory manifestations due to nickel. *Acta Otorhinolaryngol Ital* 25 (2):113-5.

Cal_EPA. 1995. California Environmental Protection Agency . Acute REL (http://oehha.ca.gov/air/acute_rels/pdf/NiA.pdf); Chronic REL (http://oehha.ca.gov/air/chronic_rels/pdf/NiComp.pdf). Accessed October 2008.

Camner, P., and A. Johansson. 1992. Reaction of alveolar macrophages to inhaled metal aerosols. *Environ Health Perspect* 97:185-8.

Chovil, A., R. B. Sutherland, and M. Halliday. 1981. Respiratory cancer in a cohort of nickel sinter plant workers. *Br J Ind Med* 38 (4):327-33.

CIIT. 2002 Multiple path particle dosimetry model (MPPD v 2.0): A model for human and rat airway particle dosimetry: Centers for Health Research (CIIT) and National Institute for Public Health and the Environment (RIVM).

Cirla, A.M., F Bernabeo, and F Ottoboni. 1985. Nickel induced occupational asthma: Immunological and clinical aspects. In *Progress in Nickel Toxicology*, edited by S. S. Brown and F. W. Sunderman. Boston Blackwell Scientific Publications.

Coogan, T. P., D. M. Latta, E. T. Snow, and M. Costa. 1989. Toxicity and carcinogenicity of nickel compounds. *Crit Rev Toxicol* 19 (4):341-84.

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

Czerczak, S., and J.P. Gromiec. 2001. Nickel ruthenium, rhodium, palladium, osmium, and platinum. In *Patty's toxicology*, edited by E. Bingham, B. Cohrssen and C. H. Powell. Edition: 5th ed. / Eula Bingham: Barbara Cohrssen, Charles H. Powell, editors.

Davies, J. E. 1986. Occupational asthma caused by nickel salts. *J Soc Occup Med* 36 (1):29-31.

de Winter-Sorkina, R., and F.R. Cassee. 2002. From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. *RIVM report 650010031/2002*:1 - 36.

Dolovich, J., S. L. Evans, and E. Nieboer. 1984. Occupational asthma from nickel sensitivity: I. Human serum albumin in the antigenic determinant. *Br J Ind Med* 41 (1):51-5.

Dunnick, J. K., J. M. Benson, C. H. Hobbs, F. F. Hahn, Y. S. Cheng, and A. F. Eidson. 1988. Comparative toxicity of nickel oxide, nickel sulfate hexahydrate, and nickel subsulfide after 12 days of inhalation exposure to F344/N rats and B6C3F1 mice. *Toxicology* 50 (2):145-56.

Easton, D.F, J. Peto, and LG Morgan. 1992. Respiratory cancer mortality in Welsh nickel refiners: which nickel compounds are responsible? In *Nickel and Human Health: Current Perspectives. Advances in Environmental Sciences and Technology*, edited by E. Nieboer and J. O. Nrigau. New York: John Wiley and Sons, Ltd.

Enterline, P. E., and G. M. Marsh. 1982. Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. *J Natl Cancer Inst* 68 (6):925-33.

Fernandez-Nieto, M., S. Quirce, J. Carnes, and J. Sastre. 2006. Occupational asthma due to chromium and nickel salts. *Int Arch Occup Environ Health* 79 (6):483-6.

Gardner, D. E., F. J. Miller, J. W. Illing, and J. M. Kirtz. 1977. Alterations in bacterial defense mechanisms of the lung induced by inhalation of cadmium. *Bull Eur Physiopathol Respir* 13 (1):157-74.

Goodman, J. E., R. L. Prueitt, D. G. Dodge, and S. Thakali. 2009. Carcinogenicity assessment of water-soluble nickel compounds. *Crit Rev Toxicol* 39 (5):365-417.

Goodman, J. E., R. L. Prueitt, S. Thakali, and A. R. Oller. 2011. The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung. *Crit Rev Toxicol* 41 (2):142-74.

Graham, J. A., D. E. Gardner, F. J. Miller, M. J. Daniels, and D. L. Coffin. 1975. Effect of nickel chloride on primary antibody production in the spleen. *Environ Health Perspect* 12:109-13.

Graham, J. A., F. J. Miller, M. J. Daniels, E. A. Payne, and D. E. Gardner. 1978. Influence of cadmium, nickel, and chromium on primary immunity in mice. *Environ Res* 16 (1-3):77-87.

Grimsrud, T. K., S. R. Berge, T. Haldorsen, and A. Andersen. 2002. Exposure to different forms of nickel and risk of lung cancer. *Am J Epidemiol* 156 (12):1123-32.

Grimsrud, T. K., S. R. Berge, T. Haldorsen, and A. Andersen. 2005. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? *Epidemiology* 16 (2):146-54.

Grimsrud, T. K., S. R. Berge, J. I. Martinsen, and A. Andersen. 2003. Lung cancer incidence among Norwegian nickel-refinery workers 1953-2000. *J Environ Monit* 5 (2):190-7.

Grimsrud, T. K., S. R. Berge, F. Resmann, T. Norseth, and A. Andersen. 2000. Assessment of historical exposures in a nickel refinery in Norway. *Scand J Work Environ Health* 26 (4):338-45.

Haber, L. T., L. Erdreicht, G. L. Diamond, A. M. Maier, R. Ratney, Q. Zhao, and M. L. Dourson. 2000. Hazard identification and dose response of inhaled nickel-soluble salts. *Regul Toxicol Pharmacol* 31 (2 Pt 1):210-30.

Hamilton, R.A. 2008. TCEQ's Office of Permitting and Registration, Air Permits Division, Personal communication via e-mail.

Hansen, K., and R.M. Stern. 1984. Toxicity and transformation of nickel compounds in vitro. In *Nickel in the human environment : proceedings of a joint symposium held at IARC, Lyon, France, 8-11 March 1983 ,IARC scientific publications*, edited by F. W. Sunderman and A. Aitio. Lyon : International Agency for Research on Cancer: New York.

IARC. 1990. *IARC monographs on the evaluation of carcinogenic risks to humans Vol. 49, Chromium, nickel and welding*. Lyon: International Agency for Research on Cancer.

ICNCM. 1990. Report of the International Committee on Nickel Carcinogenesis in Man. *Scand J Work Environ Health* 16 (1 Spec No):1-82.

ILO. 1980. Guidelines for us of the ILO International Classification of Radiographs of Pneumoconiosis, (Occupational Safety and Health Series. No 22. Revised), International Labour Office (ILO), Geneva.

Ishihara, Y., H. Kyono, F. Serita, T. Toya, H. Kawashima, and M. Miyasaka. 2002. Inflammatory responses and mucus secretion in rats with acute bronchiolitis induced by nickel chloride. *Inhal Toxicol* 14 (4):417-30.

Ishii, S., K. Ishii, N. Imatanaka, Y. Fujino, K. Sasaki, and M. Nakadate. 2009. Evaluation for skin sensitization based on published literatures (existing information) of major PRTR designated chemical substances in Japan. Regul Toxicol Pharmacol 55 (1):43-51.

Lombardo, L. J., and J. R. Balmes. 2000. Occupational asthma: a review. *Environ Health Perspect* 108 Suppl 4:697-704.

Magnus, K., A. Andersen, and A. C. Hogetveit. 1982. Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer* 30 (6):681-5.

Mastromatteo, E. 1986. Yant memorial lecture. Nickel. *Am Ind Hyg Assoc J* 47 (10):589-601.

Nicklin, S., and G.D. Nielsen. 1992. Nickel and the immune system: Current Concepts. In *Nickel and Human Health: Current Perspectives. Advances in Environmental Sciences and Technology*, edited by E. Nieboer and J. O. Nrigau. New York: John Wiley and Sons, Inc.

NRC. 1988. *Health risks of radon and other internally deposited alpha-emitters : BEIR IV*. Washington, D.C.: National Acadamy Pr.

NTP. 1996a. NTP technical report on the toxicology and carcinogenesis studies of nickel oxide (CAS no. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). In *NIH publication; no. 96-3367.; National Toxicology Program technical report series; no. 451*. Place Published: [Research Triangle Park, N.C.] : U.S. Dept of Health and Human Services, Public Health Service, National Institutes of Health ; Springfield, Va. : Available from the National Technical Information Service. http://purl.access.gpo.gov/GPO/LPS77424 (accessed May 2009).

NTP. 1996b. NTP technical report on the toxicology and carcinogenesis studies of nickel subsulfide (CAS no. 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). In *NIH publication; no. 96-3369.; National Toxicology Program technical report series;*

no. 453. Place Published: [Research Triangle Park, N.C.] : U.S. Dept of Health and Human Services, Public Health Service, National Institutes of Health ; Springfield, Va. : Available from the National Technical Information Service. http://purl.access.gpo.gov/GPO/LPS77231 (accessed May 2009).

NTP. 1996c. NTP technical report on the toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS no. 10101-97-0) in F344/N rats and B6C3F1s mice (inhalation studies). In *NIH publication; National Toxicology Program technical report series; no. 454*. Place Published: Springfield, Va. http://purl.access.gpo.gov/GPO/LPS77230(accessed May 2009).

Oller, A. R. 2002. Respiratory carcinogenicity assessment of soluble nickel compounds. *Environ Health Perspect* 110 Suppl 5:841-4.

Oller, A. R., D. T. Kirkpatrick, A. Radovsky, and H. K. Bates. 2008. Inhalation carcinogenicity study with nickel metal powder in Wistar rats. *Toxicol Appl Pharmacol* 233 (2):262-75.

Peto, J, H. Chuckle, and R Doll. 1984. Respiratory cancer mortality of Welsh nickel refinery workers. In *Nickel in the human environment : proceedings of a joint symposium held at IARC, Lyon, France, 8-11 March 1983 ,IARC scientific publications*, edited by F. W. Sunderman and A. Aitio. Lyon : International Agency for Research on Cancer: New York.

Ries, L., D. Melbert, and M. Krapcho. 2007. Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/ based on November 2007 SEER data submission, posted to the SEER web site, 2008.

Schaumloffel, D. 2005. Speciation of Nickel. In *Handbook of Element Speciation II, Species in the Environment, Food, Medicine and Occupational Health*, edited by R. Cornelis, J. Caruso, H. Crews and K. Heumann: John Wiley & Sons, Ltd.

Schlede, E., Aberer, W., Fuchs, T., Gerner, I., Lessmann, H., Maurer, T., Rossbacher, R., Stropp, G., Wagner, E., Kayser, D. 2003. Chemical substances and contact allergy-244 substances ranked according to allergenic potency. Toxicology (3):219-59.

SEER. 2006. Surveillance, Epidemiology, and End Results, Crude total US mortality rates, leukemia, for 1998-2003 by race and sex, www.seer.cancer.gov, (accessed May 2009).

Seilkop, S. K., and A. R. Oller. 2003. Respiratory cancer risks associated with low-level nickel exposure: an integrated assessment based on animal, epidemiological, and mechanistic data. *Regul Toxicol Pharmacol* 37 (2):173-90.

Serita, F. 1999. An animal exposure system using ultrasonic nebulizer that generates well controlled aerosols from liquids. *Ind Health* 37 (1):82-7.

Sivulka, D. J., and S. K. Seilkop. 2009. Reconstruction of Historical Exposures in the U.S. Nickel Alloy Industry and the Implications for Carcinogenic Hazard and Risk Assessments. *Regul Toxicol Pharmacol*.

Snow, E.T., and M. Costa. 1992. Nickel toxicity and carcinogenesis. In *Environmental and Occupational Medicine*, edited by W. N. Rom.

Stayner, L., Bailer, A.J., Smith, R., Gilbert, S., Rice, F., Kuempel, E. 1999. Sources of uncertainty in dose-response 14 modeling of epidemiological data for cancer risk assessment. *Ann NY Acad Sci* 895: 212-222.

Sunderman, F.W., and A. Oskarsson. 1991. In *Metals and their compounds in the environment : occurrence, analysis, and biological relevance*, edited by E. Merian: Weinheim [u.a.] VCH.

TCEQ. 2006. Guidelines to develop effects screening levels, reference values, and unit risk factors. Chief Engineer's Office. RG-442: Texas Commission on Environmental Quality

TDSHS. 2005. Texas Department of State Health Services, Texas Life Table http://www.dshs.state.tx.us/CHS/VSTAT/vs05/anrpt.shtm, (accessed August 2008).

USEPA. 1986. *Health assessment document for nickel and nickel compounds: final report*. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

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. 2005. Guidelines for carcinogen risk assessment. Place Published: Risk Assessment Forum, U.S. Environmental Protection Agency. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283 (accessed May 2009).

USEPA. 2005 & 2008 Toxics Release Inventory Explorer. TRI at EPA (accessed July 2010)

Vincent, J. H., G. Ramachandran, and S. M. Kerr. 2001. Particle size and chemical species 'fingerprinting' of aerosols in primary nickel production industry workplaces. *J Environ Monit* 3 (6):565-74.

Vincent, J.H., P.J. Tsai, and J.S. Warner. 1995. Sampling of inhalable aerosol with special reference to speciation. *Analyst* 120:675-9.

Vyskocil, A., V. Senft, C. Viau, M. Cizkova, and J. Kohout. 1994. Biochemical renal changes in workers exposed to soluble nickel compounds. *Hum Exp Toxicol* 13 (4):257-61.

Weischer, C. H., W. Kordel, and D. Hochrainer. 1980. Effects of NiCl2 and NiO in Wistar rats after oral uptake and inhalation exposure respectively. *Zentralbl Bakteriol Mikrobiol Hyg [B]* 171 (4-5):336-51.

Wilds, R. 2008. Union Tank Car Environmental Manager. Personal communication via telephone.

5.2. References Not Cited in DSD

ATSDR. 1997. Agency for Toxic Substances and Disease Registry. Toxicological profile for Nickel. U.S. Department of Health and Human Services Public Health Service. Atlanta, GA.

Heim, K. E., H. K. Bates, R. E. Rush, and A. R. Oller. 2007. Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. *Toxicol Appl Pharmacol* 224 (2):126-37.

Appendix A. Lung Cancer Mortality/Incidence Rates and Survival Probabilities

	US Total Population 2000-2003	**Texas Statewide 2001-2005**	**US Total Population 1975-2005**	**Texas Statewide 2001-2005**
	Total Lung Cancer Mortality Rates per 100,000 [1]	**Total Lung Cancer Mortality Rates per 100,000** [2]	**Total Lung Cancer Incidence Rates per 100,000** [3]	**Total Lung Cancer Incidence Rates per 100,000** [4]
Years	**Rate**	**Rate**	**Rate**	**Rate**
00	0.0	0.0	0.0	0.0
01-04	0.0	0.0	0.0	0.0
05-09	0.0	0.0	0.0	0.0
10-14	0.0	0.0	0.0	0.0
15-19	0.0	0.0	0.1	0.1
20-24	0.1	0.1	0.3	0.3
25-29	0.2	0.2	0.5	0.5
30-34	0.6	0.4	1.1	1.2
35-39	2.5	1.6	3.6	3.0
40-44	8.8	7.9	10.9	12.2
45-49	20.6	18.6	25.5	28.0
50-54	40.9	36.7	51.5	54.1
55-59	81.5	75.1	102.3	107.2
60-64	148.8	143.8	184.9	199.2
65-69	229.3	225.0	283.7	307.9
70-74	315.0	312.4	378.8	403.0
75-79	373.3	376.1	433.9	456.2
80-84	376.4	384.1	408.6	427.4
85+	300.3	294.8	294.9	289.6

[1] Appendix E. United States Lung Cancer Mortality Rates. US Total Population (Table XV-7, SEER Cancer Statistics Review 1975-2005) Total Lung Cancer Mortality Rates per 100,000.

[2] Age-specific lung cancer (C34) mortality rates. Prepared by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry. Data Request # 08240 08/12/2008 Source: Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry Mortality, 1990-2005, created 03-31-08, SEER Pop-Adj, SEER*Prep 2.4.

[3] Table XV-7, SEER Cancer Statistics Review 1975-2005 Surveillance, Epidemiology, and End Results database.

[4] Age-specific lung cancer (C34) incidence rates. Prepared by the Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry. Data Request # 08240 08/12/2008 Source: Texas Department of State Health Services, Cancer Epidemiology and Surveillance Branch, Texas Cancer Registry, Incidence, 1995-2005, NPCR-CSS Sub 01-31-08, SEER Pop-Adj, SEER*Prep 2.4.0

2004 US All Life Tables [1]		2005 Total Texas Population Life Tables [2]	
Age	**Survival**	**Age**	**Survival**
0	1	0	1
1	0.9932	1	0.99348
5	0.99202	5	0.99227
10	0.99129	10	0.99149
15	0.99036	15	0.99052
20	0.98709	20	0.98739
25	0.98246	25	0.9828
30	0.97776	30	0.97823
35	0.9725	35	0.97305
40	0.96517	40	0.9661
45	0.95406	45	0.95449
50	0.93735	50	0.93756
55	0.91357	55	0.91315
60	0.88038	60	0.87949
65	0.83114	65	0.82873
70	0.76191	70	0.75979
75	0.66605	75+	0.66292
80	0.53925		
85	0.38329		

[1] Arias, E., United States Life Tables, 2004. National Vital Statistics Reports. 2007. 56(9): 3, Table B. Available from the CDC website

[2] Table 24, Appendix D. Texas Life Table, last update: 8/12/08

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

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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.

B.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.

B.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.

In order to obtain the relative risk modeling results for Section B.2 Estimating the Slope Parameter, β, in the Relative Risk Model Adjusting for Differences in Background Rates and B.3 B.3 Estimating the Asymptotic Variance for the Slope Parameter in the Relative Risk Model, please send an email providing the name of the DSD and requesting these sections to the following email: tox@tceq.texas.gov.

Appendix C. Data Contained in the March 30, 2008 Email from Tom K. Grimsrud

The person-years and expected numbers relating to Grimsrud et al, 2003, Table 7, last 3 columns (Total nickel, all exposure periods).

In order to obtain this data, please send an email providing the name of the DSD and requesting Appendix C to the following email: tox@tceq.texas.gov.

Appendix D. Estimating Conditional Expected Values from Percentiles of a Distribution

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TCEQ Contract 582-7-80174

In a personal communication to Dr. Roberta Grant of TCEQ, Dr. Tom K, Grimsrud sent the output of a Stata run with several percentiles of the distribution of total nickel exposures for workers employed at the nickel refinery in Kristiansand, Norway (Appendix C and Grimsrud *et al.* 2002). The Stata output provided by Dr. Grimsrud included percentiles for the distribution of cumulative exposures to total nickel for a set of 525 control workers; i.e., workers without lung cancer. Similarly, the percentiles for the distribution of cumulative exposures to total nickel for a set of 213 cases (i.e., workers with lung cancer) were also in the Stata output. Along with the percentiles were given summary statistics, including the estimates of the mean and standard deviation. The means and standard deviations of the cumulative exposure to total nickel for the 525 controls and the 213 cases were provided (means of 6.56 for controls versus 7.96 for cases and standard deviations of 14.28 for controls versus 13.46 for cases.)

The mean and standard deviation of cumulative exposure to total nickel from a sample of workers can be better estimated if the values for each of the workers were available. However, when the information is limited to some percentiles of the distribution, some inferences about means and standard deviations can still be made.

The problem of computing statistics from percentiles of a distribution becomes particularly more difficult when the statistics are conditional. For example, the mean for workers with cumulative exposure to total nickel greater than a specified value is a conditional statistic. There are at least two techniques that can be used to compute conditional statistics from a list of percentiles. Monte Carlo simulation, which is computer intensive, and an analytical distribution approximation using the definition of expected value result in approximately the same estimates.

Estimation Based on Monte Carlo Simulation

Using Monte Carlo simulation, the estimation of the conditional mean can be accomplished by specifying the piecewise linear cumulative distribution function made with the percentiles given

in the Stata output and generating random variables. Either the conditional distribution for values greater than 2 can be specified or the full distribution can be specified but reject all the random values less than 2 in the calculation of the average. Either way should result in approximately the same answer.

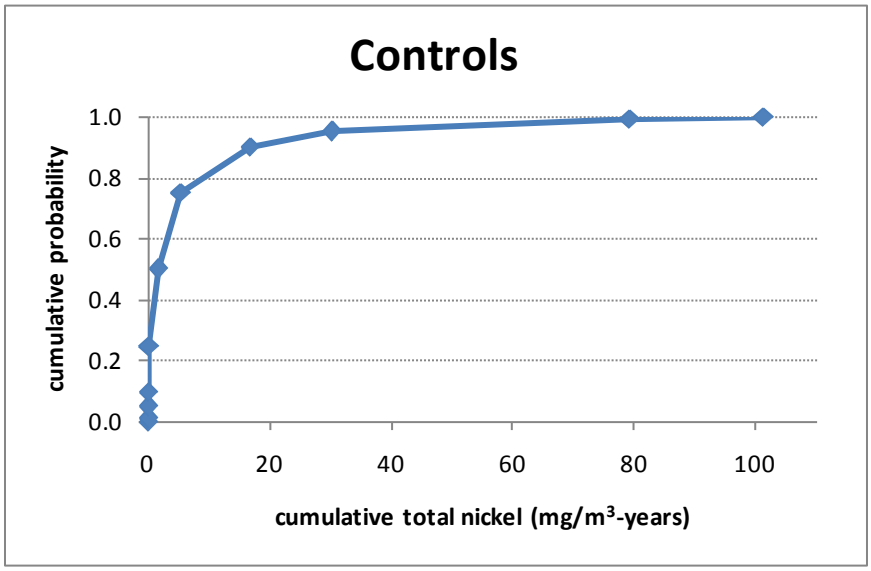
Estimation Based on Definition of Expected Value

Using an analytical approach, the estimation of the conditional mean can be accomplished applying the definition of expected value and the definition of conditional distribution function. There are a couple of equivalent definitions of the expected value function. Here, we will show an example using the more familiar definition of expected value; namely $E[X] = \sum_i x_i P(X=x_i)$ for discrete random variables or $E[X] = \int xf(x)dx$ for continuous random variables. The distribution of cumulative exposure to total nickel is a continuous random variable because exposures can take any non-negative value (i.e., can be 0 or any number greater than zero).

For illustrations purposes let us get the expected value for the controls first. The Stata output shows the distribution of total nickel for the controls as

```
. by caco: summarize totnikum, detail

-----------------------------------------------------------------
-> caco = 0

                          totnikum
-------------------------------------------------------------
      Percentiles      Smallest
 1%            0              0
 5%            0              0
10%            0              0       Obs                 525
25%      .2492623              0       Sum of Wgt.         525

50%     1.605923                      Mean           6.556545
                        Largest       Std. Dev.      14.27872
75%     5.509768       87.12912
90%     16.80044       87.12912       Variance       203.8818
95%     30.23084       97.95537       Skewness       3.928408
99%     79.30529       101.3714       Kurtosis       20.06698

-----------------------------------------------------------------
```

Note that the 0th percentile is zero (the smallest value) and the 100th percentile is 101.3714 (the largest value). The cumulative distribution function for the controls is as follows:



The cumulative distribution function is being approximated using a piecewise linear function. The probability density function corresponding to the cumulative distribution function for the controls is given by a step function with the intervals and corresponding probabilities given in the next table

Values	Probability	Cumulative Probability
0	0.10	0.10
Between 0.0 and 0.2492623	0.15	0.25
Between 0.2492623 and 1.605923	0.25	0.50
Between 1.605923 and 5.509768	0.25	0.75
Between 5.509768 and 16.80044	0.15	0.90
Between 16.80044 and 30.23084	0.05	0.95
Between 30.23084 and 79.30529	0.04	0.99
Between 79.30529 and 101.3714	0.01	1.00

Using the step function given above, then the expected value can be easily calculated using the definition for a continuous random variable and seeing that the integration is easily calculated for a step function. The expected value is then given by:

$$E[X] = [(0.0+0.0)/2]\times0.10 + [(0.2492623+0.0)/2]\times0.15 + (1.605923+0.2492623)/2]\times0.25 + [(5.509768+1.605923)/2]\times0.25 + [(16.80044+5.509768)/2]\times0.15 + [(30.23084+16.80044)/2]\times0.05 + [(79.30529+30.23084)/2]\times0.04 + [(101.3714+79.30529)/2]\times0.01$$

$$E[X] = 7.083208$$

This expected value is close to the expected value (6.556545) given in the Stata output and the difference is because the expected value calculated here is only an approximation in that the piecewise linear cumulative distribution function is an approximation to the true distribution.

In order to compute the expected value of the cumulative exposure to total nickel for individuals exposed to 2 mg/m^3-year or more, the conditional distribution is needed. The definition of the expected value of the conditional random variable is similar to the definition give above, namely $E[X|X>2] = \int x f(x|X>2)dx$. Thus, once the conditional distribution $f(x|X>2)$ is given, the expected value can be readily calculated. The conditional distribution can be easily obtained and is $f(X|X>2) = f(X)/P(X>2)$. The probability of $X>2$ ($P(X>2)$) can be estimated using linear interpolation in the piecewise linear cumulative distribution function defined above. We know that for the control workers the probability of cumulative exposures less than or equal to 2 is somewhere between the 50th and the 75th percentile. Thus, using linear interpolation, the probability of values less than or equal to 2 is equal to

$$P(X\leq 2) = 0.50 + [\ (0.75-0.50)/(\ 5.509768-1.605923)\ ] \times (2 - 1.605923) = 0.525236$$

That implies that the probability of values greater than 2 is 0.474764 (=1-0.525236). Similarly, the probability of values between 2 and 5.509768 is equal to 0.224764 (=0.75-0.525236). The conditional probability density function ($f(x|X>2)$) is then given as in the following table:

Values	Probability
Between 2 and 5.509768	0.224764 / 0.474764
Between 5.509768 and 16.80044	0.15 / 0.474764
Between 16.80044 and 30.23084	0.05 / 0.474764
Between 30.23084 and 79.30529	0.04 / 0.474764
Between 79.30529 and 101.3714	0.01 / 0.474764

The expected value in control workers of the cumulative exposures to total nickel greater than 2 mg/m^3-year is then equal to:

$$\begin{aligned} E[X|X>2] = {} & [(5.509768+2)/2]\times(0.224764/0.474764) + \\ & [(16.80044+5.509768)/2]\times(0.15/0.474764) + \\ & [(30.23084+16.80044)/2]\times(0.05/0.474764) + \\ & [(79.30529+30.23084)/2]\times(0.04/0.474764) + \\ & [(101.3714+79.30529)/2]\times(0.01/0.474764) \\ E[X|X>2] = {} & 14.2958. \end{aligned}$$

The conditional expected value of the cumulative exposure to total nickel for the control workers is 14.2958 mg/m^3-years. The total number of control workers with more than 2 mg/m^3-years cumulative exposure to total nickel is approximately equal to 249 (525 control workers multiplied by 0.474764 -- the probability of the cumulative exposure to total nickel being greater than 2 mg/m^3-years for the control workers).

The same procedure can be applied to the cases given in the Stata output provided by Dr. Grimsrud. The expected value of the cumulative exposure to total nickel is 14.0927 mg/m^3-years for cases with more than 2 mg/m3-years. The total number of cases with more than 2 mg/m^3-years cumulative exposure to total nickel is approximately equal to 124 (213 workers with lung cancer multiplied by 0.5810 -- the probability of the cumulative exposure to total nickel being greater than 2 mg/m^3-years for the cases).

APPENDIX E. CALCULATING EXCESS RISK WHEN SPECIFIED RESPONSE IS MORTALITY VERSUS INCIDENCE

Issues in Quantitative Epidemiology

Calculating Excess Risk When Specified Response is Mortality

Vs When the Specified Response is Incidence

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January 17, 2007

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The BEIR IV methodology for calculating excess risk is mathematically correct when the specified response is mortality; however, the BEIR IV methodology is mathematically incorrect when the specified response is incidence (not death).

The following slides are divided into two presentations. The first presentation provides a step-by-step derivation of the BEIR IV methodology when the specified response is mortality. This presentation directly parallels the same derivation in BEIR IV. The second presentation provides a step-by-step derivation that is “parallel” to that in the first presentation except that in the second presentation the specified response is incidence (not death). However, the steps and result are fundamentally different when the specified response is incidence (not death) than when the response is death.

The fact that the “result” (i.e., the mathematical formula for calculating excess risk) is different when the response is mortality than it is when the response is incidence, means that when the response is incidence (not death) the excess risk cannot be validly calculated using the formula (BEIR IV methodology) for death.

The First Presentation: Issues in Quantitative Epidemiology: Calculating Excess Risk: When Specified Response is Mortality

Calculating Excess Risk using Actuarial Method or Life Table Method. This way of calculating excess risks from a RR function is the implementation of the methodology described

in “BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Committee on the Biological Effects of Ionizing Radiations. Board on Radiation Effects Research Commission of Life Sciences. National Research Council. National Academy Press, Washington, DC, 1988.”

In order to obtain the slides on calculating excess risk using the BEIR IV methodology, please send an email providing the name of the DSD and requesting Appendix E to the following email: tox@tceq.texas.gov.

Appendix F. Estimating Tidal Volume and Breathing Frequency Values Corresponding to the Default USEPA Human Minute Ventilation for Input into the MPPD Model

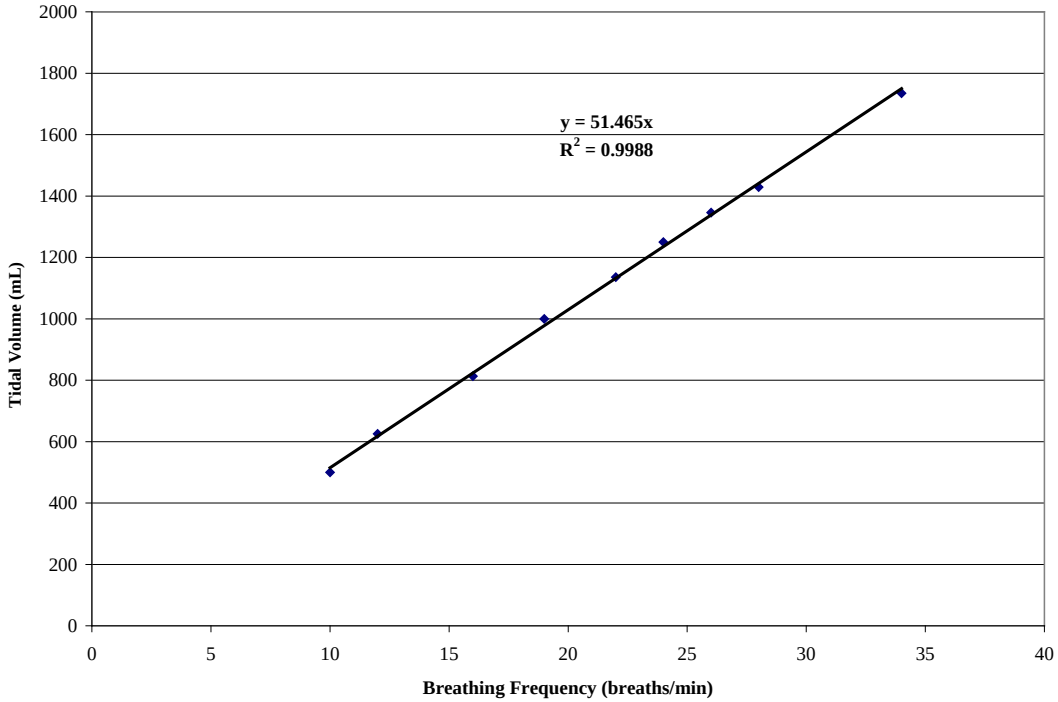
The default minute ventilation (V_E) used by the MPPD model for humans (7,500 mL/min) does not correspond to the default value (13,800 mL/min) given by USEPA (1994), which is used in the RDDR calculation. Neither USEPA (1994) nor cited USEPA background documents provide the human tidal volume (mL/breath) and breathing frequency (breaths/min) values which correspond to the default USEPA minute ventilation. However, they are needed for input into the MPPD so that both the MPPD model and RDDR calculation use the same human minute ventilation. de Winter-Sorkina and Cassee (2002) calculated tidal volume and breathing frequency values corresponding to various minute ventilation values for use in the MPPD model. Therefore, the TD used human tidal volume and breathing frequency data from Table 2 of de Winter-Sorkina and Cassee (2002) to determine the quantitative relationship between the two and calculate the tidal volume and breathing frequency values corresponding to the default USEPA minute ventilation (13,800 mL/min) for input into the MPPD model. More specifically, the TD used data for exertion levels of rest through heavy (see below), below the switch to oronasal (mouth and nose) breathing around a minute ventilation of 35 L/minute, as the USEPA (1994) default of 13.8 L/minute falls within this range and is associated with nasal breathing.

Human Tidal Volume and Breathing Frequency Data from Table 2 of de Winter-Sorkina and Cassee (2002)

Breathing Frequency (breaths/min)	Tidal Volume (mL)	Associated Minute Ventilation (L/min)	Exertion Level
10	500	5	Rest
12	625	7.5	Rest
16	813	13.0	Light
19	1000	19.0	Light
22	1136	25.0	Light
24	1250	30.0	Modest
26	1346	35.0	Modest
28	1429	40.0	Modest
34	1735	59.0	Heavy

Based on values represented in the 2002 paper, tidal volume and breathing frequency are highly linearly related (r^2=0.9988), with breathing frequency (breaths/min) multiplied by 51.465 being approximately equal to tidal volume (mL/breath) (see graph below). As the relationship is linear, this process is very similar to interpolation.

Relationship Between Human Tidal Volume and Breathing Frequency based on Table 2 of de Winter-Sorkina and Cassee (2002)



Based on the above linear relationship between tidal volume and breathing frequency, because minute ventilation (mL/min) equals tidal volume (mL/breath) times breathing frequency (breaths/min), the breathing frequency and tidal volume associated with a desired minute ventilation within this range (< 35,300 mL/minute) may be calculated from equations 3 and 4, respectively:

(1) minute ventilation (mL/min) = tidal volume (mL/breath) * breathing frequency (breaths/min)

(2) From the equation of the line in the graph above (y=51.465x), tidal volume (y-axis) equals 51.465x and breathing frequency (x-axis) equals x, so multiplying them together per equation (1) yields a product of $51.465x^2$. Substituting this value into the equation for "tidal volume * breathing frequency"

minute ventilation = tidal volume * breathing frequency = $51.465x^2$

(3) Solving the above equation 2 "minute ventilation = $51.465x^2$" for x (breathing frequency)

breathing frequency (breaths/min) = (minute ventilation)^0.5 / (51.465)^0.5

(4) Tidal volume may then be calculated

tidal volume (mL/breath) = 51.465 * breathing frequency (calculated using equation 3 above)

Using the default USEPA (1994) human minute ventilation value (13,800 mL/min), the associated breathing frequency and tidal volume may be calculated from equations 3 and 4 above:

breathing frequency (breaths/min) = (minute ventilation)^0.5 / (51.465)^0.5

$= 13{,}800^{0.5} / (51.465)^{0.5} = 117.4734 / 7.173911 = 16.375$ breaths/min

tidal volume (mL/breath) = 51.465 * breathing frequency = 51.465 * 16.375 = 842.74 mL/breath

[confirmation calculation: minute ventilation (mL/min) = tidal volume (mL/breath) * breathing frequency (breaths/min) = 842.74 mL/breath * 16.375 breaths/min = 13,800 mL/min = USEPA default]

Appendix G. Benchmark Concentration (BMC) Modeling of Rat Lesions Associated with Chronic Active Inflammation in NTP (1996c)

To support selection of the NOAEL (0.03 mg/m^3) for chronic inflammation in rats (NTP 1996c) as the point of departure (POD) for the chronic noncarcinogenic assessment, BMC modeling was performed for the lesions considered components of chronic inflammation. Study authors of NTP (1996c) indicated that fibrosis, macrophage hyperplasia, and alvelolar proteinosis are considered various components of chronic active inflammation. Male and female rat dose-response data from Table 14 of NTP (1996c) were used for BMC modeling of these endpoints using USEPA Benchmark Dose Software (Version 2.1). Goodness of fit was evaluated by visual inspection with scaled residuals < 2 and goodness-of-fit p values > 0.1. While adequate model fits were obtained for hyperplasia and proteinosis, no models adequately fit the fibrosis data. For proteinosis and hyperplasia, much better model fits were obtained, and more models adequately fit the data, when modeling male and female data separately. Therefore, only gender-specific BMC modeling results are shown. The severity of these lesions was generally graded between minimal to mild on average (NTP 1996c), so a benchmark response level of 10% was used for BMC modeling. Gender-specific results for proteinosis and hyperplasia are presented below.

Male Rats: Alveolar Proteinosis (NTP 1996c 2-year study)

Nickel Sulfate Dose (mg/m^3)	Nickel Equivalent Dose (mg/m^3)	Number in Dose Group	Number Responding	% Positive	Models with Adequate Fit	P-value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
0	0	54	0	0	Log-Probit	0.8431	117.975	0.05001	0.04273
0.12	0.03	53	0	0	Gamma	0.6836	118.621	0.04988	0.04211
0.25	0.06	53	12	22.64	Log-Logistic	0.6435	118.891	0.04985	0.04224
0.5	0.11	53	41	77.36	Weibull	0.4242	120.172	0.04900	0.04025
					Probit	0.2867	121.075	0.05059	0.04225
					Logistic	0.1569	122.921	0.05137	0.04319

Female Rats: Alveolar Proteinosis (NTP 1996c 2-year study)

Nickel Sulfate Dose (mg/m^3)	Nickel Equivalent Dose (mg/m^3)	Number in Dose Group	Number Responding	% Positive	Models with Adequate Fit	P-value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
0	0	52	1	1.92	Log-Probit	0.1555	124.104	0.04305	0.03711
0.12	0.03	53	0	0	Log-Logistic	0.1084	125.034	0.04312	0.03694
0.25	0.06	53	22	41.51					
0.5	0.11	54	49	90.74					

Male Rats: Macrophage Hyperplasia (NTP 1996c 2-year study)

Nickel Sulfate Dose (mg/m^3)	Nickel Equivalent Dose (mg/m^3)	Number in Dose Group	Number Responding	% Positive	Models with Adequate Fit	P-value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
0	0	54	7	12.96	Log-Logistic	0.2545	198.285	0.02970	0.02217
0.12	0.03	53	9	16.98	Log-Probit	0.2299	198.438	0.02983	0.02267
0.25	0.06	53	35	66.04					
0.5	0.11	53	48	90.57					

Female Rats: Macrophage Hyperplasia (NTP 1996c 2-year study)

Nickel Sulfate Dose (mg/m^3)	Nickel Equivalent Dose (mg/m^3)	Number in Dose Group	Number Responding	% Positive	Models with Adequate Fit	P-value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
0	0	52	9	17.31	Log-Probit	0.1809	226.902	0.03041	0.02138
0.12	0.03	53	10	18.87	Log-Logistic	0.1602	227.087	0.02942	0.02021
0.25	0.06	53	32	60.38	Multistage	0.1269	230.068	0.02738	0.01346
0.5	0.11	54	45	83.33					

While several models had an adequate fit for proteinosis in male rats, the log-probit model fit best based on visual inspection and AIC values, as was the case for proteinosis in female rats. The benchmark concentrations low (BMCLs) corresponding to the 10% response level ($BMCL_{10}$) for males (0.04273 mg/m^3) and females (0.03711 mg/m^3) from this model were averaged to yield a representative $BMCL_{10}$ of 0.03992 mg/m^3 for proteinosis. For hyperplasia in male and female rats, the log-logistic and log-probit models provide very similar fits and results. The average of these $BMCL_{10}$ values for males and females yields a representative $BMCL_{10}$ of 0.02161 mg/m^3 for this endpoint.

As macrophage hyperplasia and alvelolar proteinosis were considered components of chronic active inflammation in NTP (1996c), a representative $BMCL_{10}$ based on these endpoints was used for comparison to the NOAEL for chronic inflammation (0.03 mg/m^3). More specifically, the representative $BMCL_{10}$ values based on these endpoints (see preceding paragraph) were averaged for an overall $BMCL_{10}$ of 0.03076 mg/m^3 for these lesions associated with chronic inflammation (NTP 1996a). Rounding this value results in a $BMCL_{10}$ of 0.03 mg/m^3, which happens to be identical to the NOAEL for chronic inflammation (and associated lesions) of 0.03 mg/m^3. This comparison supports use of the NOAEL for chronic inflammation as an appropriate POD for derivation of the chronic noncarcinogenic ReV and ${}^{chronic}ESL_{nonlinear(nc)}$.

Appendix H. Goodness of Model Fit Information

Goodness of Model Fit to SMRs in Enterline and Marsh (1982):

The multiplicative linear dose-response Poisson models used for the epidemiological data in Enterline and Marsh were fit using maximum likelihood estimation. These models fit the data adequately according to a likelihood ratio test. This statistical test compares the logarithm of the likelihood value for the best fit of the multiplicative linear dose-response Poisson model (a parametric model) and the logarithm of the likelihood value for a non-parametric or saturated model (i.e., a model that does not assume a functional form and therefore fits the SMRs perfectly). If the parametric model fits the data adequately, twice the decrease in the logarithm of the likelihood due to the model has an asymptotic chi-square distribution with the number of degrees of freedom being equal to the number of data points being fit (here 6) minus the number of parameters in the parametric model (here 2). The following table shows the values of the logarithm of the likelihood for the best multiplicative linear dose-response Poisson models and the non-parametric models with the corresponding chi-square statistics and significance levels.

Worker Group	Logarithm of the Likelihood Multiplicative Linear Dose-Response Poisson Model	Logarithm of the Likelihood Non-parametric Model	Chi-Square Statistic (4 d.f.)	p-value
All Workers	-66.599	-66.002	1.194	0.3008
Refinery Hired Before 1947	-7.293	-6.081	2.424	0.7241
Non-refinery Hired Before 1947	-50.120	-46.527	7.186	0.1287
Refinery + Non-refinery Hired Before 1947	-57.802	-54.507	6.590	0.1773
Hired After 1946 + Non-refinery Hired Before 1947	-60.870	-57.924	5.890	0.2128

The significance levels (p-values) are all greater than 0.10, indicating that the SMRs are adequately fit by the multiplicative linear dose-response Poisson model.

Goodness of Model Fit to Grimsrud *et al.* (2003) Data:

Model Fit to SIRs Using Maximum Likelihood

The multiplicative linear dose-response Poisson model was fit to the smoking-unadjusted SIR epidemiological data in Grimsrud *et al.* using maximum likelihood estimation. Using the same approach as above to test for goodness-of-fit, the following table lists values of the logarithm of the likelihood for the best multiplicative linear dose-response Poisson model and the non-parametric model with the corresponding chi-square statistics and significance level.

Incidence Rate Basis	Logarithm of the Likelihood Multiplicative Linear Dose-Response Poisson Model	Logarithm of the Likelihood Non-parametric Model	Chi-Square Statistic (2 d.f.)	p-value
Smoking-Unadjusted SIRs	-5.723	-1.178	13.802	0.0010

The significance level (p-value) is less than 0.10, indicating that the SIRs are not adequately fit by the multiplicative linear dose-response Poisson model. The chi-square statistic here had only two degrees of freedom because there are only four SIRs in Grimsrud *et al.* summary statistics and two parameters were estimated in the parametric model.

Models Fit to RRs Using Least Squares

The multiplicative linear dose-response models fit to the smoking-adjusted RR and smoking-unadjusted RR epidemiological data in Grimsrud *et al.* used least squares estimation. The following table lists the models sum of squares and the error sum of squares. These sums of squares are used to calculate an F-ratio that evaluates the amount of variability explained by the model when compared with the variability corresponding to a model that includes the mean rate ratio alone. If the significance level (p-value) of the F-ratio is small, then the multiplicative linear dose-response model fits the data statistically significantly better than the response mean.

Incidence Rate Basis	Model SS (1 d.f.) (MSE(model) = Model SS / 1)	Error SS (2 d.f.) (MSE(error) = Error SS / 2)	F-Statistic (MSE(model) / MSE(error))	p-value
Smoking-Adjusted RRs	0.8066	0.5809	2.7772	0.2375
Smoking-Unadjusted RRs	1.2364	0.8236	3.0024	0.2253

The significance levels are greater than 0.05, indicating that the multiplicative linear dose-response model does not fit the data statistically significantly better than the average response mean.

Although the model fits to the Grimsrud *et al.* data are not statistically significantly satisfactory, the model fits are considered health-protective and, therefore, acceptable for this assessment for several reasons: (1) the model fits to the data are the best linear models (i.e., no other multiplicative linear models fit the data better); (2) the models use data that take into consideration how the incidence rates change with exposures to nickel and are, therefore, statistically preferable to models based on data that do not reflect changes in the incidence rates with exposure levels to nickel; (3) the models used are superior to the simple average relative risk approach used by EPA (1986) in that EPA's approach did not include any regression diagnostic analyses, did not incorporate competing risks, incorrectly used Norwegian background hazard rates instead of the correct US background rates, ignored data regarding changes in the SMRs, SIRs and RRs with exposure levels to nickel, and assumed all exposed workers had identical average cumulative nickel exposures; and (4) use of the models may contribute to greater health-protectiveness than discarding data from one of the two studies considered to have exposure profiles most similar to that expected for Texas since this ultimately results in a more conservative (i.e., higher) URF. Consideration of these factors indicates the models used by the TD are the best available for dose-response analyses of the Grimsrud *et al.* (2003) data, an improvement over the average relative risk model used by USEPA (1986) for this cohort, and are used in the interest of protecting public health.