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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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Chapter 1 Summary Table

Table 1 provides a summary of health- and welfare-based values from an acute and chronic evaluation of respirable (particle size less than 10 micrometers (< 10 µm)) nickel and inorganic nickel compounds. Table 2 provides summary information on nickel and nickel compounds physical/chemical data.

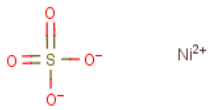
Table 1. Health- and Welfare-Based Values

Short-Term Values	Concentrations	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 ReV (HQ = 1.0)	1.1 µg/m^3 [b]	
$^{acute}ESL_{odor}$	---	No data found
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentrations**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	0.036 µg/m^3 **Long-Term ESL for Air Permit Reviews**	**Critical Effect(s):** Pulmonary fibrosis and chronic active lung inflammation in rats
chronic ReV (HQ = 1.0)	0.12 µg/m^3 [b]	
$^{chronic}ESL_{linear(c)}$	0.059 µg/m^3 [a, b, c]	**Critical Effect(s):** Lung cancer in industrial workers
$^{Chronic}ESL_{veg}$	---	No data found

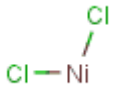
[a] Since compound is a respiratory sensitizer, exceedance of the short-term or long-term ESL during the air permit review should be discouraged to protect against sensitization.
[b] Value that may be used for ambient air monitoring data.
[c] Unit risk factor (URF) = 1.7 x 10^{-4} per µg/m^3

Abbreviations used: **HQ**, hazard quotient; **µg/m^3**, micrograms per cubic meter; **h**, hour; **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 effect; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL

Table 2. 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	0.293 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 2. Chemical and Physical Properties (Continued)			
Parameter	**Value**	**Value**	**Reference**
Name of Chemical	Nickel Chloride	Nickel Oxide	ATSDR 2005
Molecular Formula	$NiCl_2$	NO	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)	0.642 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 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).

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). 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 are railroad equipment facilities, electric utilities, and petroleum refineries. These sources represented close to 90% of the nickel emissions in Texas in 2005. The 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). 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 (^{acute}ESL) 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 ^{acute}ESL 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).*

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 2. 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) is the most sensitive effect 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, including a significant number of occupational asthmatics, following exposure to aerosolized nickel sulfate. 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.

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 $\mu g/m^3$ for 30 minutes (min), for which 67 $\mu g/m^3$ 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 (FEV_1) was determined before and after the exposure during 24-hours (h). A greater than 15% decrease in FEV_1 which is often a result of significant bronchoconstriction considered a positive response. Nickel inhalation in this study induced significant bronchoconstriction in six of the asthmatic subjects. 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 $\mu g\ Ni/m^3$ based on positive bronchial provocation tests (greater than a 15% decrease in FEV_1) in six of seven asthmatics.

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 (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 immunosuppresion 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.

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 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).

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 more specific dose metrics 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. When MOA information is lacking regarding whether both concentration and duration play a role in the effect observed in the key study, it is conservative to adjust the 30-min exposure duration value to a 1-h exposure duration value (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) did not provide the MMAD or σ_g. However, as Graham *et al.* (1978) is not the key study, study-specific information on these parameters 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 1.80 and 1.60, respectively, are available from other studies for use as surrogates. Therefore, the TD used input terms from several studies (Graham *et al.* 1978; Serita 1999; Ishihara *et al.* 2002) for the RDDR model run for the supporting study. The input and output terms are presented in Figure 1.

Figure 1. RDDR Model Run Output for Nickel Chloride Data

Regional deposited dose ratios

MMAD = 1.80
Sigma g = 1.60

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
mouse	25	28.4	3.000	0.483	3.500	0.091	0.050	0.094
human	70000	13800.0	200.000	0.308	3200.000	0.079	54.000	0.268
RATIO	0.000	0.002	0.015	1.571	0.001	1.155	0.001	0.352
RDDR			0.215		2.170		0.782	

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
mouse	0.050	0.186	0.051	0.669	25	0.669
human	54.320	0.125	54.340	0.655	70000	0.655
RATIO	0.001	1.482	0.001	1.021	0.000	1.021
RDDR	1.185		2.252		5.973	

V. 2.3

The RDDR of the total respiratory tract was selected as the appropriate output to use to develop a POD_{HEC} for the following reasons:

- the particle diameter in the toxicity study was small enough that one would expect particle deposition in all regions of the human respiratory system (extrathoracic, tracheobronchial, pulmonary, and thoracic regions);
- the particles could be absorbed along the entire tract based on water solubility; and
- 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.

To derive the POD_{HEC}, the RDDR for the total respiratory tract was multiplied by the POD_{ADJ} from the Graham *et al.* (1978) study:

$$POD_{HEC} = POD_{ADJ} \times RDDR$$
$$= 100\ \mu g\ Ni\ /m^3 \times 2.252$$
$$= 225.2\ \mu g\ Ni\ /m^3$$

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 intrahuman variability (UF_H) because the study population included a significant number of occupational asthmatics, which are considered a sensitive subpopulation;
- 10 for extrapolation from a LOAEL to a NOAEL (UF_L) because 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); and
- 3 for 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).

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

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}:

supporting acute ReV $= POD_{HEC} / (UF_A \times UF_H \times UF_D)$
$= 225.2\ \mu g\ Ni/m^3 / (3 \times 10 \times 3)$
$= 2.25\ \mu g\ Ni/m^3$

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 3).

Table 3. Derivation of the Acute ReV and ^{acute}ESL	
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 0.3 mg/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	3
Database Quality	Medium
Acute ReV (HQ = 1)	**1.1 µg/m^3**
^{acute}ESL (HQ = 0.3)	**0.33 µg/m^3**

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 2.3 µg Ni/m^3 based on the Graham *et al.* (1978) animal study. The supporting animal-based acute ReV is 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 not available.

3.2.2 Vegetation Effects

Data 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 (Tables 1 & 3). For evaluation of air monitoring data, the acute ReV of 1.1 µg/m^3 will be used. 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 (TCEQ 2006).

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). 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/or lung 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; 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).*

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 2.

4.1.1.2 Key and Supporting Studies

4.1.1.2.1 Human Studies

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

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 $^{chronic}ESL_{nonlinear(nc)}$.

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 B6C3F$_1$ 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 and eight minutes 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. In all three nickel studies (NTP 1996a, 1996b, 1996c), mice were less susceptible to proliferative and fibrotic lung lesions than rats exposed to the same compound. In rats, the respective equivalent of 0.03 mg Ni/m^3 (0.12 mg/m^3 nickel sulfate hexahydrate) is considered the NOAEL, which is lower than the NOAEL for mice (0.06 mg Ni/m^3). *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 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 is not fully known to inform the choice of the most appropriate dose metric. Regardless, data on other more specific dose metrics are not available for NTP (1996c). Therefore, the exposure concentration of nickel from the key study was used as the default dose metric.

4.1.4 POD

A NOAEL of 0.03 mg Ni/m^3 from the NTP (1996c) study for lung fibrosis and chronic inflammation in rats was selected by the TD for use as the POD. The data were not amenable to standard benchmark concentration modeling.

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:

$$POD_{ADJ} = POD \times D/24 \times F/7$$

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

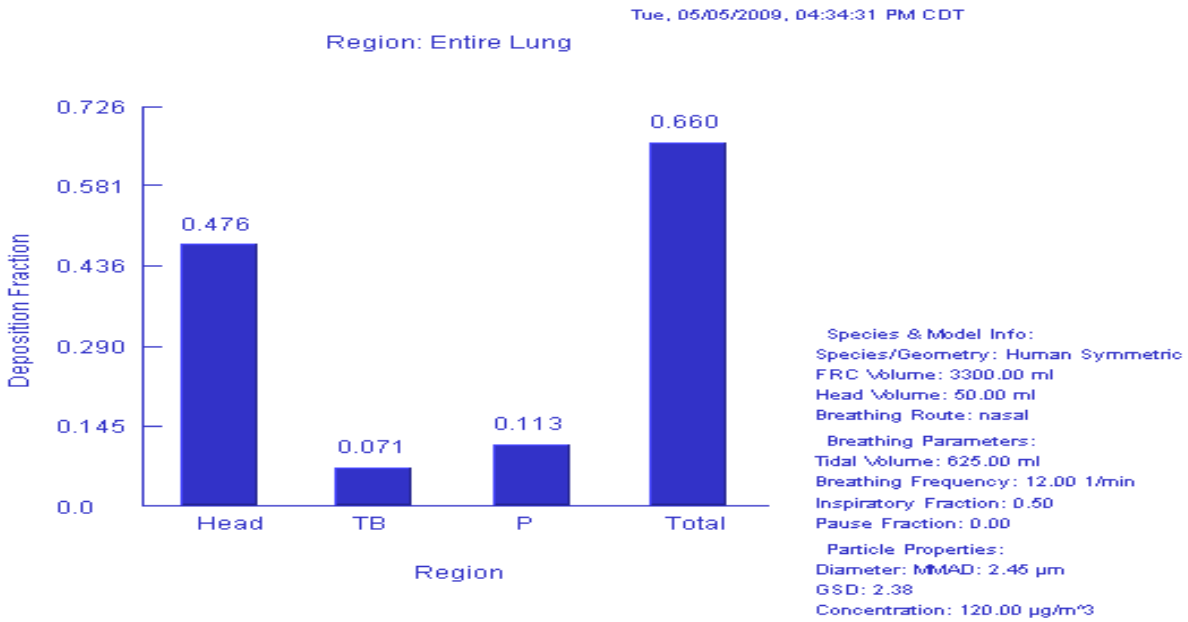
$$POD_{ADJ} = 0.0053571 \text{ mg Ni/m}^3$$

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

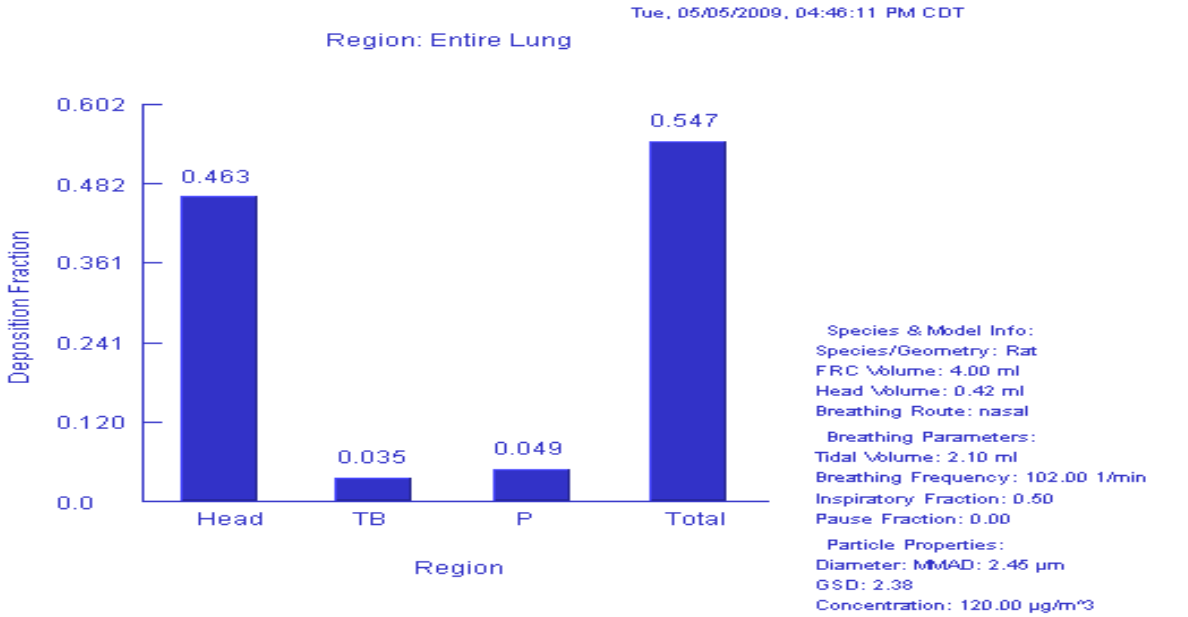
4.1.5.2 Default Dosimetry Adjustment from Animal-to-Human Exposure

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 2004) to derive a deposition fraction that is used in the regional deposited dose ratio (RDDR), which is an appropriate model for rats. 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 target region for divalent nickel was considered to be the pulmonary region. All remaining values used were default. 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:

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

$$RDDR\ (pulmonary) = \frac{137.3\ mL/min}{13{,}800\ mL/min} \times \frac{0.049}{0.113} \times \frac{54\ m^2}{0.34\ m^2} = 0.68521$$

where: RDDR = Regional Depositional Dose Ratio
V_E = Minute ventilation
DF = Depositional fraction in the respiratory tract target region
NF = Normalizing factor
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 0.68521 for the pulmonary region was multiplied by the nickel equivalent POD_{ADJ} from the NTP (1996c) study:

POD_{HEC} = POD_{ADJ} x RDDR
= 0.0053571 mg Ni/m^3 x 0.68521
= 0.0036707 mg Ni/m^3

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

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:

chronic ReV $= POD_{HEC} / (UF_A \times UF_H \times UF_D)$
$= 0.0036707$ mg Ni/m^3/ (3 x 10 x 1)
$= 0.00012236$ mg Ni/m^3
$= 0.12236$ µg Ni/m^3

4.1.6.2 Critical Effect

As indicated in Section 4.1.1.2, available animal data indicate that pulmonary fibrosis and chronic active inflammation 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 selected these specific 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 0.12236 µg Ni/m^3 was rounded to two significant figures at the end of all calculations which yields a chronic ReV of 0.12 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 0.036 µg Ni/m^3 (Table 4).

Table 4. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$	
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	Pulmonary fibrosis and chronic active lung inflammation
POD (original study NOAEL)	0.03 mg Ni/m^3 (NOAEL)
Exposure Duration	6h/day, 5 days/week for 2 years
POD_{ADJ}	5.3571 µg Ni/m^3
POD_{HEC}	0.12236 µg Ni/m^3
Total uncertainty factors (UFs)	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Incomplete Database UF	1
Database Quality	High
Chronic ReV (HQ = 1)	**0.12 µg/m^3**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**0.036 µg/m^3**

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). The chronic ReV falls between the CalEPA chronic REL of 0.05 µg Ni/m^3 and the ATSDR MRL of 0.9 µg Ni/m^3.

4.2 Carcinogenic Potential

4.2.1 Weight of Evidence (WOE) from Epidemiological 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 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.

See Section 3.2.1.7 of ATSDR (2005) for a discussion of the inhalation animal studies which have examined the potential of various forms of nickel (i.e., nickel subsulfide, nickel oxide, and nickel sulfate) to increase lung tumors. In general, only chronic inhalation exposure to nickel subsulfide and nickel oxide resulted in lung tumors (adenocarcinomas, squamous cell carcinomas, and fibrosarcoma) in Fisher 344 rats, but no significant alteration in tumor incidences were observed in mice. Considering available study data for both inhalation and other exposure routes (e.g., intraperitoneal, intrapleural, intramuscular, subcutaneous), the ICNCM (1990) indicates there is: sufficient data in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides, and crystalline nickel sulfides; and limited animal evidence for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts (e.g., nickel sulfate), nickel arsenides, nickel antimonide, nickel selenides, and nickel telluride; and inadequate animal carcinogenic evidence for nickel trioxide, amorphous nickel sulfide, and nickel titanate.

4.2.2 WOE Classifications

It is not known with exact 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 that there is also sufficient evidence in humans that nickel sulfate (soluble nickel) is carcinogenic. 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 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) (funded by the Nickel Producers Environmental Research Association) 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). IARC is reassessing the carcinogenicity of soluble and insoluble nickel in 2009 (Goodman et al. 2009).

USEPA has classified nickel refinery dust and nickel subsulfide as Group A human carcinogens (IRIS 2005). 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 (IRIS 2003). The URFs were derived in 1986.

The Department of Health and Human Services (NTP 2002) has classified metallic nickel as reasonably anticipated to be a human carcinogen, and nickel compounds as known human carcinogens (ATSDR 2005). ACGIH currently classifies insolublw nickel subsulfide and nickel oxide as confirmed human carcinogens (A1), metallic nickel as not suspected as a human carcinogen (A5), and and soluble nickel chloride and nickel sulfate as not classifiable as a human carcinogen (A4) (Goodman et al. 2009). According to guidance in the new cancer guidelines (USEPA 2005a), the TD considers nickel compounds as a group to be “Carcinogenic to Humans” via inhalation.

4.2.3 Carcinogenic MOA

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, HIF-1 transcription factor) epigenetic factors (ATSDR 2005). While *in vitro* and *in vivo* studies in mammals indicate that nickel is genotoxic, it has a low mutagenic potential. Nickel-induced DNA damage has resulted in the formation of chromosomal aberrations, which could result in deletion of senescence or tumor suppressor genes. Additionally, certain nickel compounds have been shown to promote cell proliferation, which may increase the likelihood of converting a repairable DNA lesion into a non-repairable mutation. Nickel ions may inhibit DNA repair, although the mechanism is unclear (ATSDR 2005). Nickel can bind to biological macromolecules (e.g., proteins), 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. The binding of nickel ions with heterochromatin may result in a number of alterations (e.g., DNA hypermethylation, gene silencing) that can disrupt gene expression. For example, DNA methylation may result in genes no longer being expressed due to incorporation into heterochromatin. Gene expression may also be altered by activated transcription factors. Hypoxia-inducible transcription factor HIF-1α, for example, is induced by exposure to both soluble and insoluble nickel compounds. 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 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 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). In regard to nongenotoxic effects as possible MOAs, 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 hypoacetylation of histones. 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). For example, interference with iron homeostasis outside the nucleus can lead to the induction of the HIF-1 transcription factor, which can affect the expression of many genes, particularly those related to angiogenesis (important for tumor promotion). Nickel-induced signal transduction effects can be equally elicited by both soluble and insoluble nickel (Goodman et al. 2009).

See Section 3.5.2 of ATSDR (2005) and Goodman et al. (2009) for additional available information on possible MOAs. As the available relevant data are somewhat 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. 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).

Per ATSDR (2005), there are no nickel refining or mining operations in the United States. According to the Toxics Release Inventory (TRI) (USEPA 2005), Texas does not have any nickel refineries, and twelve other facility types emitted over 97% of the total nickel emissions in Texas (Table 5). Available information 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), and would therefore be low in sulfidic nickel (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, 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)).

Generally, the major nickel species in ambient air is a soluble form, nickel sulfate (e.g., oil- and coal-fired electric utility units) (Schaumlöffel 2005). Additionally, the emissions profile from Texas facilities (low in sulfidic nickel) 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 lower levels of sulfidic nickel (Section 4.2.5 *Epidemiological Studies Used to Develop URFs*).

Table 5. 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

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 6), and other available epidemiological studies, was provided by Seilkop and Oller (2003). Workers in two of these studies (Clydach, Wales and Copper Cliff, Ontario) were exposed to relatively high levels of sulfidic nickel (Seilkop and Oller 2003). 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 sulfidic nickel (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 significantly different than the emissions profile of facilities in Texas.

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 6), so exposure profiles 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 ($^{chronic}ESL_{linear(c)}$). The Grimsrud et al. (2002) case-control study was not used for the carcinogenic assessment as use of Grimsrud et al. (2003) results in a more robust dose-response analysis. The Grimsrud et al. (2003) cohort is more reliable because it includes greater than seven times more workers than the Grimsrud et al. (2002) case-control study. In addition, the Grimsrud et al. (2003) reports standardized incidence ratios (SIRs) and relative risks (RRs), which are more appropriate for dose-response model fitting than the odds ratios presented by Grimsrud et al. (2002). Enterline and Marsh (1982) report appropriate data to estimate the carcinogenic potency of nickel, including standardized mortality ratios (SMRs).

Table 6. Summary of Epidemiological Studies with Adequate Dose-Response Data (Seilkop and Oller 2003)

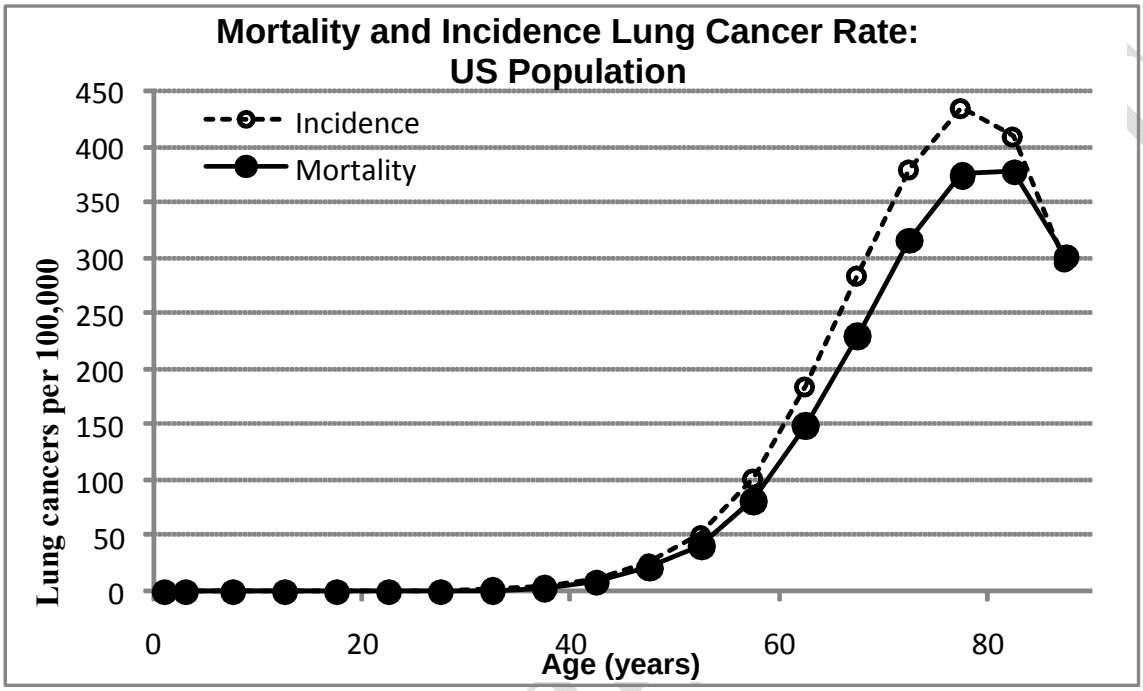
Occupational Location and Exposure Period	Number of Workers	Lung cancer p value	Nickel Species	Typical Exposure Concentration ($mg\ Ni/m^3$)
Clydach, Wales refinery before 1930 (1902-1930 [b])	1348	394 SMR [a] $p < 0.001$	Sulfidic Oxidic Soluble Metallic	> 10 > 10 > 1 > 0.5
Clydach, Wales refinery after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

[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.

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. The respiratory cancer data from Enterline and Marsh (1982) are a reasonable surrogate for lung cancer 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 is 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 are sufficiently similar as to be comparable for purposes of this assessment; see Figure 3).

Figure 3. Lung Cancer Mortality vs Incidence



[a] Based on US lung cancer rates (Appendix A)

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 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). For example, because the TD is using total nickel, the conclusions of Goodman et al. (2009) that soluble nickel is not a complete carcinogen but may be carcinogenic in the presence of insoluble nickel compounds do not have significant implications for the TD's carcinogenic evaluation of Grimsrud et al. (2003), which showed the strongest association for soluble nickel. The TD is not using soluble nickel alone as the dose metric for this study (i.e., not treating soluble nickel as a complete carcinogen) but is using total nickel as the dose metric for the carcinogenic assessment, which also includes insoluble sulfidic, oxidic, and metallic forms. The TD considers use of total nickel as the most reasonable dose metric for the carcinogenic assessment considering the uncertainty regarding the most culpable carcinogenic form(s), the potential interaction of nickel forms (i.e., the potential role of mixtures) in nickel-induced carcinogenicity, and the generally

robust association between total nickel and increased respiratory cancer risk in nickel epidemiological studies.

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 this study 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 used 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:

$$\text{URF} = \text{background rate for lung cancer} \times \frac{(\text{relative risk} - 1)}{\text{average lifetime exposure level}}$$

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 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; and (3) the significant uncertainty associated with attempting to attribute cancer risk to a particular form or forms of nickel.

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 rate ratios (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 relative to that in the unexposed. 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 7 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 calculate 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.

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 7 below.

Table 7. Lung Cancer Rate Ratios from Grimsrud et al. (2003)

Total Nickel Cumulative Exposure (mg/m^3-years)	Midpoint of Exposure Range (mg/m^3-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 (lung cancer in this case) that are otherwise comparable to cases and that may have been unexposed or exposed to the chemical of interest (various levels and forms of nickel in this case). 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 somewhat of 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:

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

which is equivalent to

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

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 9 below. 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 9. 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 8 below. 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 8. Lung Cancer Rate Standardized Incidence Ratio (SIR) from Grimsrud et al. (2003)

Total Nickel Cumulative Exposure (mg/m^3-years)	Midpoint of Exposure Range (mg/m^3-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 9.

Table 9. 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]	**5.44E-05**	1.74E-04 [c]
Smoking-Unadjusted RRs	4.91E-05	-7.85E-05 [b]	6.48E-05	2.08E-04 [c]
Estimates based on the standardized incidence ratios using Poisson regression				
Smoking-Unadjusted SIRs	1.58E-05	2.33E-05 [d]	**4.92E-05**	7.51E-05 [e]

[a] Excess relative risk estimates are per μg/m^3-years.
[b] 95%LCL = β - (2.920 x SE) for a t-distribution with 2 degrees of freedom.
[c] 95%UCL = β + (2.920 x SE) for a t-distribution with 2 degrees of freedom.
[d] 95%LCL = β - (1.645 x SE) for a standard normal distribution.
[e] 95%UCL = β + (1.645 x SE) for a standard normal distribution.

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:

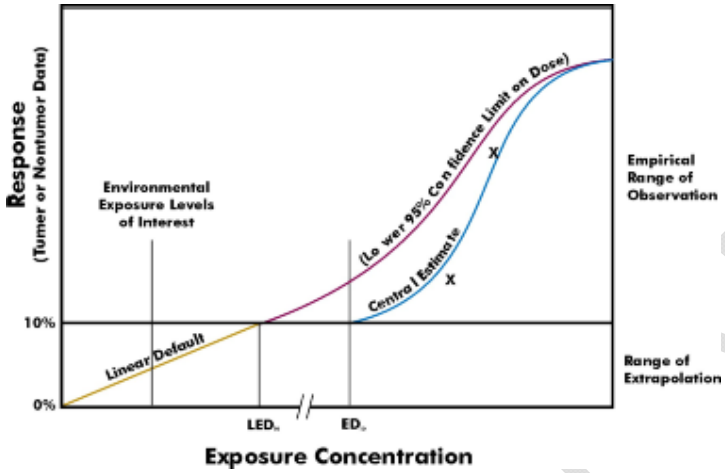
$$Concentration_{HEC} = Concentration_{OC} \times (VE_{ho}/VE_{h}) \times (days\ per\ week_{oc}/days\ per\ week_{res})$$

where: $Concentration_{HEC}$ = human equivalent concentration applicable to the general public (μg/m^3)
$Concentration_{OC}$ = occupational exposure concentration (μg/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 or a URF estimated using a low POD are approximately equal.

Table 10 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 9, 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 10. 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-4/ 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);
- As incidence data were available and utilized as opposed to mortality data, use of the URF (MLE) based on the central estimate β was preferred over use of the β (95%UCL), consistent with TCEQ (2006);
- As smoking is an important confounder for lung cancer incidence, the URF of 2.83E-04 per $\mu g/m^3$ based on smoking-adjusted RRs (value shaded in Table 10) 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 $\mu g/m^3$ based on available SIRs (value shaded in Table 10) 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), while there is a 3.2 fold difference between the URFs calculated using the RR-based β and β (95%UCL)). 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 $\mu g/m^3$ (smoking-adjusted RR-based β) and 2.56E-04 per $\mu g/m^3$ (SIR-based β) (values shaded in Table 10) 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 $\mu g/m^3$) 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 $\mu g/m^3$). 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 6). 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. 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 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 11 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 somewhat of 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 Table 10 data as:

- 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 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 11. 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 in Enterline and Marsh (1982).
[b] mg/m^3-months was converted to $\mu g/m^3$-years for calculating the β by multiplying by 1,000 μg/mg x 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 for β for respiratory cancer (Appendix B). 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 12 below.

Table 12. β Values and SE Based on Respiratory Cancer Mortality from Enterline and Marsh (1982)

Worker Group	SE	β (95% LCL) [a, b]	B (MLE) [a]	β (95% UCL) [a, c]
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 x SE).
[c] 95%UCL = β + (1.645 x SE).

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 13 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 13 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 13 below. Since the β (95% LCL) values were negative (Table 12), suggesting zero excess risk, calculation of a URF and an air concentration at 1 in 100,000 excess risk was not possible.

Table 13. 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 12), suggesting zero excess risk, calculation of a URF and an 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)

As the TD cannot exclude the possibility of some nickel subsulfide exposure due to emissions from facilities in Texas, the preferred β value is that based on the dataset for all workers combined (as opposed to just non-refinery workers or workers hired after 1946 + non-refinery workers), which includes workers

exposed to nickel subsulfide. Additionally, the dataset for all workers is the most robust for development of the β. The TD considers the respiratory cancer mortality data from Enterline and Marsh (1982) as a reasonable surrogate for lung cancer mortality since more than 93% of the observed (65 of 69) and expected (57.71 of 61.47) respiratory cancers were lung cancers, and considers lung cancer mortality as reasonably predictive of 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 make 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 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). As incidence for lung cancer is reasonably predictive of mortality, the URFs based on Grimsrud et al. (2003) and Enterline and Marsh (1982) may be appropriately combined for the final URF.

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 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 14 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), increasing the weight for the URF associated with that β, which is the appropriate effect as confidence is somewhat increased for URFs with β values that have relatively lesser variance. The overall weight for a URF (see the last column of Table 14) 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) x 100 = overall weight % for a given URF). The resulting pooled URF of 2.59E-04 per μg/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 μg/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 14, 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 somewhat 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 14. 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 / SE^2 [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 10.
[b] See Table 13.
[c] See Appendix C.
[d] See Table 3 in Enterline and Marsh (1982).
[e] See Tables 9 and 12 for the values of the SE of β.
[f] Weighting factor = total person-years x $1/SE^2$.
[g] Overall weight of URF (%) = (weighting factor/sum of weighting factors) x 100.
[h] combined URF = 0.1293×2.83E-04 + 0.8707×2.56E-04
[i] SE of β for combined URF = $[(0.1293\times4.10E\text{-}05)^2 + (0.8707\times1.58E\text{-}05)^2]^{1/2}$.

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 14) and the overall weight percents (expressed in decimal form) from the last column of Table 14:

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.*

4.3 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 = 0.12 µg/m^3
- $^{chronic}ESL_{nonlinear(nc)}$ = 0.036 µg/m^3
- $^{chronic}ESL_{linear(c)}$ = 0.059 µg/m^3

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ of 0.036 µg/m^3 (Table 1). 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 µg/m^3 is lower than the chronic ReV of 0.12 µg/m^3, although both values may be used for the evaluation of air data as well as

the URF of 1.7E-04 per µg/m^3. The $^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

Chapter 5 References

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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 http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_09.pdf

[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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December 17, 2007

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.

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

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

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

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

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

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

or, equivalently,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

where

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

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

$$\frac{\partial^2 LL}{\partial\alpha^2} = \sum -O_j/\alpha^2$$

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

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

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

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

The determinant for the matrix is

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

and the variance of the maximum likelihood estimate of α is

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

while the variance of the maximum likelihood estimate of β is

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

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

References

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

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

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).

	Person-years	Expected no.
0	10,649.8	9.295
0.01-0.41	49,843.9	24.458
0.42-1.99	42,174.8	24.672
2.0+	51,284.4	45.036

In table 8 (the Poisson regressions), the person-years above correspond to columns 3 and 4 (unadjusted Rate ratios). Some individuals were excluded from the adjusted analysis because data on smoking were missing, and the number of person-years and observed cases are consequently slightly lower (data not given).

STATA OUTPUT

```
.
.       * Four continuous log-linear models (water-soluble, sulfidic, oxidic, and metallic Ni)
. xi: clogit caco solnikum sulfnikum oxinikum metnikum i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -201.99184
Iteration 1:   log likelihood = -201.51839
Iteration 2:   log likelihood = -201.51651
Iteration 3:   log likelihood = -201.51651

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(8)      =     112.75
                                                  Prob > chi2     =     0.0000
Log likelihood = -201.51651                       Pseudo R2       =     0.2186

------------------------------------------------------------------------------
       caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
    solnikum |   1.221155   .0685275     3.56   0.000     1.093966    1.363131
   sulfnikum |   .9550564     .15775    -0.28   0.781     .6909284    1.320155
    oxinikum |   .9900191   .0206013    -0.48   0.630     .9504536    1.031232
    metnikum |   .9096616   .0850913    -1.01   0.311     .7572809    1.092705
_Itobday0x~1 |   3.669987   2.062629     2.31   0.021     1.219739    11.04236
_Itobday0x~2 |   12.34608   6.902956     4.50   0.000     4.126715    36.93635
_Itobday0x~3 |   18.68211   10.36357     5.28   0.000     6.298496     55.4134
_Itobday0x~4 |   33.00594    19.6001     5.89   0.000     10.30667    105.6978
------------------------------------------------------------------------------

.
.       * 6-category total nickel cumulated variable
. pctile nitottmp=totnikum if caco==0 & totnikum>0, nq(5)

. xtile nitot6c=totnikum if totnikum>0, cut(nitottmp)

. replace nitot6c=0 if totnikum==0
(62 real changes made)

. sort caco

. 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

-------------------------------------------------------------------------------------------------------------------------------
-> caco = 1

                          totnikum
-------------------------------------------------------------
      Percentiles      Smallest
 1%           0              0
 5%     .0115342             0
10%     .1642885             0       Obs                 213
25%      .755141             0       Sum of Wgt.         213

50%     2.596603                      Mean            7.95775
                        Largest       Std. Dev.      13.46399
75%     8.928002       58.46352
90%     20.19308       69.50865       Variance        181.279
95%      38.3337       69.94364       Skewness       2.950439
99%     69.50865       81.88099       Kurtosis       12.51074


. table nitot6c, c(mean totnikum p50 totnikum min totnikum max totnikum)

-------------------------------------------------------------------------------
totnikum  |
categoriz |
ed by     |
nitottmp  | mean(totnikum)   med(totnikum)   min(totnikum)   max(totnikum)
----------+--------------------------------------------------------------------
        0 |              0               0               0               0
        1 |      .14786827       .15328768       .00901639       .35205742
        2 |       .7909581       .77367122       .35210534       1.3954925
        3 |      2.1069292       1.9979898       1.4070411        3.073837
        4 |      5.2831784       4.8682517       3.0750959       8.8237532
        5 |      26.982036       17.473296       8.8277261       101.37143
-------------------------------------------------------------------------------

. sort caco

. by caco: tab nitot6c

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

   totnikum |
categorized |
by nitottmp |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |         53       10.10       10.10
          1 |         95       18.10       28.19
          2 |         94       17.90       46.10
          3 |         94       17.90       64.00
          4 |         95       18.10       82.10
          5 |         94       17.90      100.00
------------+-----------------------------------
      Total |        525      100.00

-------------------------------------------------------------------------------------------------------------------------------
-> caco = 1

   totnikum |
categorized |
by nitottmp |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |          9        4.23        4.23
          1 |         25       11.74       15.96
          2 |         39       18.31       34.27
          3 |         42       19.72       53.99
          4 |         44       20.66       74.65
          5 |         54       25.35      100.00
------------+-----------------------------------
```

```
      Total |        213      100.00

. xi: clogit caco i.nitot6c i.tobday0x1020, gr(set) or
i.nitot6c         _Initot6c_0-5       (naturally coded; _Initot6c_0 omitted)
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -205.46843
Iteration 1:   log likelihood = -205.28076
Iteration 2:   log likelihood = -205.28044
Iteration 3:   log likelihood = -205.28044

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(9)      =     105.22
                                                  Prob > chi2     =     0.0000
Log likelihood = -205.28044                       Pseudo R2       =     0.2040

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 _Initot6c_1 |   1.302338   .6256102     0.55   0.582     .5079582    3.339023
 _Initot6c_2 |   2.244108   1.046193     1.73   0.083      .899948      5.5959
 _Initot6c_3 |   2.351057   1.076797     1.87   0.062     .9580941    5.769232
 _Initot6c_4 |   2.443339   1.097816     1.99   0.047     1.012815    5.894365
 _Initot6c_5 |    3.20676   1.448795     2.58   0.010     1.322814    7.773816
_Itobday0x~1 |   3.942954   2.203385     2.46   0.014     1.318733    11.78926
_Itobday0x~2 |   11.80507   6.506123     4.48   0.000      4.00817     34.7689
_Itobday0x~3 |     17.322    9.39015     5.26   0.000     5.986415    50.12209
_Itobday0x~4 |   32.18765   18.71558     5.97   0.000     10.29807    100.6057
------------------------------------------------------------------------------

. lrtest, saving(0)

. estimates store full

. xi: clogit caco i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -211.89093
Iteration 1:   log likelihood = -211.78507
Iteration 2:   log likelihood = -211.78499
Iteration 3:   log likelihood = -211.78499

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(4)      =      92.21
                                                  Prob > chi2     =     0.0000
Log likelihood = -211.78499                       Pseudo R2       =     0.1788

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Itobday0x~1 |   3.815237   2.117391     2.41   0.016      1.28564    11.32201
_Itobday0x~2 |   11.68693   6.440199     4.46   0.000     3.968603    34.41625
_Itobday0x~3 |   17.66794   9.576931     5.30   0.000     6.106482    51.11882
_Itobday0x~4 |   29.81461    17.2679     5.86   0.000     9.581504    92.77361
------------------------------------------------------------------------------

. lrtest, using(0)
You ran lrtest using the old syntax.  Click here to learn about the new syntax.


Likelihood-ratio test                                 LR chi2(5)  =     13.01
(Assumption: . nested in LRTEST_0)                    Prob > chi2 =    0.0233

.
.         * A single total nickel variable
. xi: clogit caco totnikum i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -211.47024
Iteration 1:   log likelihood =  -211.2437
Iteration 2:   log likelihood = -211.24343
Iteration 3:   log likelihood = -211.24343

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(5)      =      93.30
                                                  Prob > chi2     =     0.0000
Log likelihood = -211.24343                       Pseudo R2       =     0.1809

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    totnikum |   1.006645   .0063247     1.05   0.292     .9943252    1.019118
_Itobday0x~1 |   3.830728   2.131338     2.41   0.016     1.287331    11.39915
_Itobday0x~2 |   11.79045   6.517103     4.46   0.000     3.990556    34.83591
_Itobday0x~3 |   17.95308   9.763234     5.31   0.000     6.183565    52.12414
_Itobday0x~4 |   30.68485   17.85746     5.88   0.000      9.80744    96.00463
```

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

. lrtest, saving(0)

. xi: clogit caco i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -211.89093
Iteration 1:   log likelihood = -211.78507
Iteration 2:   log likelihood = -211.78499
Iteration 3:   log likelihood = -211.78499

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(4)      =      92.21
                                                  Prob > chi2     =     0.0000
Log likelihood = -211.78499                       Pseudo R2       =     0.1788

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Itobday0x~1 |   3.815237   2.117391     2.41   0.016      1.28564    11.32201
_Itobday0x~2 |   11.68693   6.440199     4.46   0.000     3.968603    34.41625
_Itobday0x~3 |   17.66794   9.576931     5.30   0.000     6.106482    51.11882
_Itobday0x~4 |   29.81461    17.2679     5.86   0.000     9.581504    92.77361
------------------------------------------------------------------------------

. lrtest, using(0)
You ran lrtest using the old syntax.  Click here to learn about the new syntax.

Likelihood-ratio test                                 LR chi2(1)  =      1.08
(Assumption: . nested in LRTEST_0)                    Prob > chi2 =    0.2980

. xi: clogit caco totnikum, gr(set) or

Iteration 0:   log likelihood = -257.96096
Iteration 1:   log likelihood = -257.74525
Iteration 2:   log likelihood = -257.74521
Iteration 3:   log likelihood = -257.74521

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(1)      =       0.29
                                                  Prob > chi2     =     0.5887
Log likelihood = -257.74521                       Pseudo R2       =     0.0006

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    totnikum |   1.003041   .0055952     0.54   0.586     .9921344    1.014068
------------------------------------------------------------------------------

.
.         * A single log-transformed total nickel variable
. gen lntotni=ln(totnikum+1)

. xi: clogit caco lntotni i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -208.37396
Iteration 1:   log likelihood = -208.21929
Iteration 2:   log likelihood = -208.21913
Iteration 3:   log likelihood = -208.21913

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(5)      =      99.34
                                                  Prob > chi2     =     0.0000
Log likelihood = -208.21913                       Pseudo R2       =     0.1926

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     lntotni |   1.234228   .0975286     2.66   0.008     1.057142    1.440977
_Itobday0x~1 |   3.826454   2.136224     2.40   0.016      1.28112    11.42887
_Itobday0x~2 |   12.00606   6.626613     4.50   0.000     4.069948    35.41701
_Itobday0x~3 |   17.85004   9.687922     5.31   0.000     6.161101     51.7154
_Itobday0x~4 |   31.42643    18.2943     5.92   0.000     10.04117    98.35711
------------------------------------------------------------------------------

. lrtest, saving(0)

. xi: clogit caco i.tobday0x1020, gr(set) or
i.tobday0x1020    _Itobday0x1_0-4     (naturally coded; _Itobday0x1_0 omitted)

Iteration 0:   log likelihood = -211.89093
Iteration 1:   log likelihood = -211.78507
Iteration 2:   log likelihood = -211.78499
Iteration 3:   log likelihood = -211.78499
```

```
Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(4)      =      92.21
                                                  Prob > chi2     =     0.0000
Log likelihood = -211.78499                       Pseudo R2       =     0.1788

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Itobday0x~1 |   3.815237   2.117391     2.41   0.016      1.28564    11.32201
_Itobday0x~2 |   11.68693   6.440199     4.46   0.000     3.968603    34.41625
_Itobday0x~3 |   17.66794   9.576931     5.30   0.000     6.106482    51.11882
_Itobday0x~4 |   29.81461    17.2679     5.86   0.000     9.581504    92.77361
------------------------------------------------------------------------------

. lrtest, using(0)
You ran lrtest using the old syntax.  Click here to learn about the new syntax.


Likelihood-ratio test                                 LR chi2(1)  =      7.13
(Assumption: . nested in LRTEST_0)                    Prob > chi2 =    0.0076

. xi: clogit caco lntotni, gr(set) or

Iteration 0:   log likelihood = -255.11708
Iteration 1:   log likelihood = -254.95312
Iteration 2:   log likelihood = -254.95312

Conditional (fixed-effects) logistic regression   Number of obs   =        738
                                                  LR chi2(1)      =       5.88
                                                  Prob > chi2     =     0.0153
Log likelihood = -254.95312                       Pseudo R2       =     0.0114

------------------------------------------------------------------------------
        caco | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     lntotni |   1.188089   .0844462     2.42   0.015     1.033589    1.365684
------------------------------------------------------------------------------

.
end of do-file
```

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.

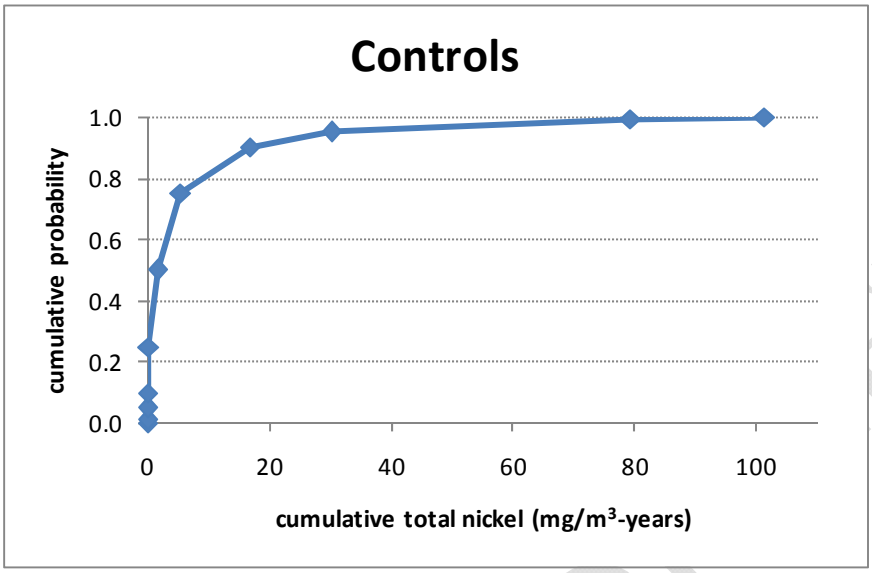
Estimation Based on Definition of Expected Value

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:

$$E[X] = [(0.0+0.0)/2]\times 0.10 + [(0.2492623+0.0)/2]\times 0.15 + [(1.605923+0.2492623)/2]\times 0.25 + [(5.509768+1.605923)/2]\times 0.25 + [(16.80044+5.509768)/2]\times 0.15 + [(30.23084+16.80044)/2]\times 0.05 + [(79.30529+30.23084)/2]\times 0.04 + [(101.3714+79.30529)/2]\times 0.01$$

$$E[X] = 7.083208$$

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:

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

$$E[X|X>2] = 14.2958.$$

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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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."

3

BEIR IV:

Derivation of Formulas:
(Using notation in BEIR report)

i = 1, 2, ..., T

i = index for the years for a person's life

year i is the year from the person's (i-1)-th birthday
to his (or her) i-th birthday

i=1 refers to the year from birth to the 1st birthday
i=1 = age 0
...
i=7 refers to the year from the 6-th birthday to the 7-th birthday
i=7 = age 6

4

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i -1

q(7) = probability of reaching a person 's 7-th birthday
given that he reached his 6 -th birthday

$q(7) = P(\text{Death} \geq 7 \mid \text{Death} \geq 6)$

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i -1

$q(i) = \exp[- h(i)^*]$

1 - q(i) = probability of death in year i
conditional on the person surviving through year i -1

3
4

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

5

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

$S(1,i) \times [\ 1 - q(i)\ ]$ = probability of surviving up to year i and then dying (from any cause) in year i

6

3

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

S(1,i) = probability of surviving up to year i

$S(1,i) \times [1 - q(i)]$ = probability of surviving up to year i and
then dying (from any cause) in year i

$h(i)/h(i)^*$ = proportion of deaths in year i due to the response

$[h(i)/h(i)^*] \times S(1,i) \times [1 - q(i)]$ = probability of surviving i-1 years
and dying of response in year i

4

BEIR IV: Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i
conditional on the person not having the response
through year i-1

$S(1,i) = q(1) \times q(2) \times ... \times q(i -1)$

$S(1,i) \times [1 - q(i)]$ = probability of surviving up to year i and
then dying (from any cause) in year i

$h(i)/h(i)^*$ = proportion of deaths in year i due to the response

$[h(i)/h(i)^*] \times S(1,i) \times [1 - q(i)]$ = probability of surviving i-1 years
and dying of response in year i

$R_0 = \sum_{i=1,...,T} [h(i)/h(i)^*] \times S(1,i) \times [1 - q(i)]$
= probability of a response mortality in the first T years of life
(i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

5

3

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

4

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

3

BEIR IV: Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year i due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

exp { - h(i)* - h(i) × [f(i) - 1] } = probability with exposure of surviving year i conditional on person surviving thru year i-1

q(i) × exp { - h(i) × [f(i) - 1] } = probability with exposure of surviving year i conditional on person surviving thru year i-1

4

BEIR IV: Derivation of Formulas: Risk with exposure

q(i) = probability of surviving year i without exposure
when all causes of death are acting conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i); f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

exp { - h(i)* - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

q(i) × exp { - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

$q(1) \times \exp\{ - h(1) \times [f(1) - 1] \} \times \ldots \times q(i-1) \times \exp\{ - h(i-1) \times [f(i-1) - 1] \}$
$= S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ - h(k) \times [f(k) - 1] \})$
= probability of surviving up to year i with exposure

$S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k) - 1] \}) \times (1 - q(i) \times \exp\{-h(i) \times [f(i) - 1] \})$
= probability with exposure of surviving up to year i
and then dying (from any cause) in year i

5

3

BEIR IV: Derivation of Formulas: Risk with exposure

q(i) = probability of surviving year i without exposure
when all causes of death are acting conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) mortality rate in year i without exposure
conditional on the person not having the response through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards model for the effect of exposure of the form h(i) × f(i); f(i) = [1 + e(i)] if multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) mortality rate in year i with exposure
conditional on the person not having the response through year i-1

h(i) × [f(i) - 1] = increase in response mortality rate in year due to exposure

h(i)* + h(i) × [f(i) - 1] = mortality rate due to all causes in year i with exposure
conditional on the person surviving through year i-1

exp { -h(i)* - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

q(i) × exp { - h(i) × [f(i) - 1] } = probability with exposure of surviving year i
conditional on person surviving thru year i-1

$q(1) \times \exp\{ - h(1) \times [f(1) - 1] \} \times \ldots \times q(i-1) \times \exp\{ - h(i-1) \times [f(i-1) - 1] \}$
$= S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ - h(k) \times [f(k) - 1] \})$= probability of surviving up to year i with exposure

$S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k) - 1] \}) \times (1 - q(i) \times \exp\{-h(i) \times [f(i) - 1] \})$
= probability with exposure of surviving up to year i and then dying (from any cause) in year i
$\{ h(i) \times f(i) \} / \{ h(i)^* + h(i) \times [f(i) - 1] \}$
= proportion of deaths in year i due to the response with exposure
$(\{h(i) \times f(i)\}/\{h(i)^* + h(i) \times [f(i)-1]\}) \times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k)-1]\}) \times (1-q(i) \times \exp\{-h(i) \times [f(i)-1] \})$
= probability of surviving i-1 years and dying of response in year i with exposure

4

BEIR IV: Derivation of Formulas: Risk with exposure

$(\{h(i) \times f(i)\}/\{h(i)^* + h(i) \times [f(i)-1]\})$
$\times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k)-1]\})$
$\times (1-q(i) \times \exp\{-h(i) \times [f(i)-1] \})$
= probability of surviving i-1 years
and dying of response in year i with exposure

$R_{exposure} = \sum_{i=1,\ldots,T}$
$(\{h(i) \times f(i)\} / \{h(i)^* + h(i) \times [f(i)-1] \})$
$\times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$
$\times (1 - q(i) \times \exp \{ - h(i) \times [f(i) - 1] \})$

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) with exposure (with exposure in addition to the background exposure)

BEIR IV: Risks

$R_0 = \sum_{i=1,...,T} [\, h(i)/h(i)^* \,] \times S(1,i) \times [1 - q(i)\,]$

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) at dose 0 (no exposure in addition to background exposure)

$R_{exposure} = \sum_{i=1,...,T} (\{h(i) \times f(i)\} / \{h(i)^* + h(i) \times [\, f(i)-1 \,] \}) \times S(1,i) \times \exp(- \sum_{k=1,...,i-1} \{ -h(k) \times [\, f(k)-1 \,] \}) \times (1 - q(i) \times \exp \{ - h(i) \times [\, f(i) - 1 \,] \})$

= probability of a response mortality in the first T years of life (i.e., up to the T-th birthday, age T) with exposure (with exposure in addition to the background exposure)

Added Risk = $R_{exposure} - R_0$

Extra Risk = $(R_{exposure} - R_0) / (1 - R_0)$

Excess Risk = either Added Risk or Extra Risk

The Second Presentation: 3.1 Issues in Quantitative Epidemiology: Calculating Excess Risk: When Specified Response is Incidence

Calculating Excess Risk using Actuarial Method or Life Table Method. The following derivation for the situation in which the specified response is incidence (not death) "parallels" the derivation in BEIR IV; however, the derivation and result are necessarily different for incidence than for mortality.

"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."

3

Derivation of Formulas:
(Using notation in BEIR report)

i = 1, 2, ..., T

i = index for the years for a person's life

year i is the year from the person's (i-1)-th birthday
to his (or her) i-th birthday

i=1 refers to the year from birth to the 1st birthday
i=1 = age 0
...
i=7 refers to the year from the 6-th birthday to the 7-th birthday
i=7 = age 6

4

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

q(7) = probability of reaching a person's 7-th birthday
given that he reached his 6-th birthday

$q(7) = P(\text{Death} \geq 7 \mid \text{Death} \geq 6)$

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

$q(i) = \exp[- h(i)^*]$ -- definition of hazard rate

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

3

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

Note that h(i) is NOT part of h(i)*,
because h(i) refers to incidence and h(i)* refers to death.

4

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

q(i) = exp[- h(i)*]

1 - q(i) = probability of death in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

qr(i) = exp[- h(i)] = probability of no response in year i
conditional on the person not responding through year i-1

1 -qr(i) = probability of response (incidence) in year i
conditional on the person not responding through year i-1

5

3

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i
conditional on the person not having the response
through year i-1

qr(i) =probability of no response (incidence) in year i
conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:

$SR(1,i) = qr(1) \times qr(2) \times ... \times qr(i-1)$ with $SR(1,1) = 1.0$.

4

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:

$S(1,i) = q(1) \times q(2) \times ... \times q(i-1)$ with $S(1,1) = 1.0$.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:

$SR(1,i) = qr(1) \times qr(2) \times ... \times qr(i-1)$ with $SR(1,1) = 1.0$.

$S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$ = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

3

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:
SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

S(1,i) × SR(1,i) ×[1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

A person is "observed" in year i if that person either dies in year i or has the specified response (incidence) in year i.

h(i)/ [h(i)* + h(i)] = proportion of observations (deaths plus incidences) in year i due to the response

{ h(i)/ [h(i)* + h(i)] } × S(1,i) × SR(1,i) × [1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then having the response (incidence) in year i

4

Derivation of Formulas:

i = 1, 2, ..., T

q(i) = probability of surviving year i when all causes of death are acting conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i conditional on the person not having the response through year i-1

qr(i) =probability of no response (incidence) in year i conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year:
SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

S(1,i) × SR(1,i) ×[1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then dying (from any cause) or having the response in year i

h(i)/ [h(i)* + h(i)] = proportion of observations (deaths plus incidences) in year i due to the response

{ h(i)/ [h(i)* + h(i)] } × S(1,i) × SR(1,i) × [1 - q(i) × qr(i)] = probability of surviving to year i, not responding before year i, and then having the response (incidence) in year i

$R_0 = \sum_{i=1,...,T} \{ h(i) / [h(i)^* + h(i)] \} \times S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$
= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) at dose 0 (no exposure in addition to background exposure)

5

3

Derivation of Formulas:

Background Risk of an Incidence:

$R_0 = \sum_{i=1,...,T} \{ h(i) / [h(i)^* + \mathbf{h(i)}] \} \times S(1,i) \times \mathbf{SR(1,i)} \times [1 - q(i) \times \mathbf{qr(i)}]$
= probability of a response (incidence) in the first T years of life
(i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

Contrast with the form of the calculation for the
Background Risk of a Mortality
and that h(i) refers to mortality here and incidence above:

$R_0 = \sum_{i=1,...,T} [h(i) / h(i)^*] \times S(1,i) \times [1 - q(i)]$
= probability of a response mortality in the first T years of
life (i.e., up to the T-th birthday, age T) at dose 0
(no exposure in addition to background exposure)

4

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = exp [- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp [- h(i)] = probability of no response in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form $h(i) \times f(i)$
f(i) = [1 + e(i)] if the multiplier is a linear function

$h(i) \times f(i)$ = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response
through year i-1

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = exp [- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp [- h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response through year i-1

A person is "observed" in year i if that person either dies in year i or has the specified response (incidence) in year i.

h(i)* + h(i) × f(i) = observation rate due to all causes in year i with exposure
conditional on the person not dying or having the response through year i-1

3

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = = exp[- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

f(i) = proportional effect (multipler) in year i assuming a proportional hazards
model for the effect of exposure of the form h(i) × f(i)
f(i) = [1 + e(i)] if the multiplier is a linear function

h(i) × f(i) = response (e.g., lung cancer) incidence rate in year i with exposure
conditional on the person not having the response through year i-1

h(i)* + h(i) × f(i) = observation rate due to all causes in year i with exposure
conditional on the person not dying or having the response through year i-1

exp { - h(i)* - h(i) × f(i) } = q(i) × exp { - h(i) × f(i) }
= q(i) × exp{ - h(i) - h(i) × [f(i) - 1] } = q(i) × qr(i) × exp {- h(i) × [f(i)-1] }
probability with exposure of not dying and not
responding in year i conditional on not dying and not responding thru year i-1

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = = exp[- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year: SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

q(i) × qr(i) × exp {- h(i) × [f(i)-1] } = probability with exposure of not dying and not responding in year i conditional on not dying and not responding thru year i-1

$q(1)\times qr(1)\times\exp\{-h(1)\times[\,f(1)-1\,]\,\}\times\ldots\times q(i-1)\times qr(i-1)\times\exp\{-h(i-1)\times[\,f(i-1)-1\,]\,\}$
$= S(1,i)\times SR(1,i)\times\exp\left(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[\,f(k)-1\,]\,\}\right)$
= probability with exposure of not dying and not responding up to year i

$S(1,i)\times SR(1,i)\times\exp\left(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[f(k)-1]\}\right)\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}]$
= probability with exposure of not dying and not responding up to year i
and then dying (from any cause) or having the response in year i

3

Derivation of Formulas: Risk with exposure

i=1, 2, ..., T

q(i) = = exp[- h(i)*] = probability of surviving year i without exposure
when all causes of death are acting
conditional on the person surviving through year i-1

h(i)* = mortality rate due to all causes in year i without exposure
conditional on the person surviving through year i-1

h(i) = response (e.g., lung cancer) incidence rate in year i without exposure
conditional on the person not having the response through year i-1

qr(i) = exp[-h(i)] = probability of no response (incidence) in year i without exposure
conditional on the person not responding through year i-1

S(1,i) = probability of surviving up to year i is the product of surviving each prior year:
S(1,i) = q(1) × q(2) × ... × q(i-1) with S(1,1) = 1.0.

SR(1,i) = probability of no response up to year i is the product of no response in each prior year: SR(1,i) = qr(1) × qr(2) × ... × qr(i-1) with SR(1,1) = 1.0.

q(i) × qr(i) × exp {- h(i) × [f(i)-1] } = probability with exposure of not dying and not responding in year i conditional on not dying and not responding thru year i-1

$S(1,i)\times SR(1,i)\times\exp(-\sum k=1,\ldots,i-1\{-h(k)\times[\,f(k)-1\,]\,\})\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}\,]$
= probability with exposure of not dying and not responding up to year i
and then dying (from any cause) or having the response in year i

$\{\,h(i)\times f(i)\,\}\,/\,\{\,h(i)^{*}+h(i)\times f(i)\,\}$ = proportion of observations (deaths plus incidences) in year i due to the response with exposure

$(\{h(i)\times f(i)\}/\{h(i)^{*}+h(i)\times f(i)\})\times S(1,i)\times SR(1,i)\times\exp\left(-\sum_{k=1,\ldots,i-1}\{-h(k)\times[f(k)-1]\}\right)$
$\times[1-q(i)\times qr(i)\times\exp\{-h(i)\times[\,f(i)-1]\}]$ = probability with exposure of not dying and not responding up to year i and then having the response in year i

4

3

Derivation of Formulas: Risk with exposure

$$(\{ h(i) \times f(i) \} / \{ h(i)^* + h(i) \times f(i) \})$$
$$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{-h(k) \times [f(k)-1]\})$$
$$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$$

= probability of not dying and not responding in i-1 years and then having the response in year i with exposure

$$R_{exposure} = \sum_{i=1,\ldots,T}$$
$$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times f(i) \})$$
$$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$$

= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) with exposure (with exposure in addition to the background exposure)

4

Derivation of Formulas:

Risk of an Incidence with exposure:

$$R_{exposure} = \sum_{i=1,\ldots,T}$$
$$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times \mathbf{f(i)} \})$$
$$\times S(1,i) \times \mathbf{SR(1,i)} \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times [1 - q(i) \times \mathbf{qr(i)} \times \exp \{ -h(i) \times [f(i)-1] \}])$$

Contrast with the <u>form</u> of the calculation for the Risk of a Mortality with exposure and that h(i) refers to mortality here and incidence above:

$$R_{exposure} = \sum_{i=1,\ldots,T} (\{h(i) \times f(i)\} / \{h(i)^* + h(i) \times [f(i)-1] \})$$
$$\times S(1,i) \times \exp(- \sum_{k=1,\ldots,i-1} \{ -h(k) \times [f(k)-1] \})$$
$$\times (1 - q(i) \times \exp \{ - h(i) \times [f(i) - 1] \})$$

3

Risks

$R_0 = \sum_{i=1,...,T} \{ h(i) / [h(i)^* + h(i)] \} \times S(1,i) \times SR(1,i) \times [1 - q(i) \times qr(i)]$
= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T)
at dose 0 (no exposure in addition to background exposure)

$R_{exposure} = \sum_{i=1,...,T}$

$(\{h(i) \times f(i)\} / \{ h(i)^* + h(i) \times f(i) \})$
$\times S(1,i) \times SR(1,i) \times \exp(- \sum_{k=1,...,i-1} \{ -h(k) \times [f(k)-1] \})$
$\times [1 - q(i) \times qr(i) \times \exp \{ -h(i) \times [f(i)-1] \}]$

= probability of a response (incidence) in the first T years of life (i.e., up to the T-th birthday, age T) with exposure
(with exposure in addition to the background exposure)

Added Risk = $R_{exposure} - R_0$

Extra Risk = $(R_{exposure} - R_0) / (1 - R_0)$

Excess Risk = either Added Risk or Extra Risk

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6