NICKEL REFERENCE EXPOSURE LEVELS (DRAFT)

Air Toxicology and Epidemiology Branch
Office of Environmental Health Hazard Assessment

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Authority

- The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the **Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)).**

- Consideration of possible differential effects on the health of infants, children and other sensitive subpopulations is mandated by the **Children's Environmental Health Protection Act (Senate Bill 25, Escutia, chapter 731, statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*).**

Summary

- **Nickel (II) causes a variety of non-carcinogenic toxic effects including occupational contact dermatitis, occupational asthma, and reproductive toxicity in humans.**
- **Studies in experimental animals exhibit immune suppression, nephrotoxicity, pneumotoxicity, perinatal mortality and altered gene expression.**
- **The most sensitive effects appear to be in the lung and immune system.**

Nickel as a Toxic Air Contaminant

- High potential exposure to nickel and nickel compounds:
  - Widespread occurrence.
  - Numerous uses.
- Effects leading to differential impacts on infants and children:
  - Adverse impacts on the respiratory and immune systems including asthma (see Sections 5,6,8 and 9).
  - Increased perinatal mortality and reduced birth weight observed in animals studies of reproductive toxicity (see Section 7.2).
- **OEHHA therefore recommends that nickel be identified as a toxic air contaminant which may disproportionately impact children, pursuant to Health and Safety Code, Section 39669.5(c).**

Ni(II) sources

- **Air**: The annual statewide average ambient air concentration of nickel for 2002 was 4.5 ± 4.1 SD ng Ni/m^3 (CARB, 2008).
- **Soil:** Soils concentrations throughout the U.S. ranged from <5 to 700 ppm, with a geometric mean of 13.0 ± 2.31. (U.S. Geological Survey)
- **Drinking water:** generally contains nickel at concentrations ranging from 0.55 to 25 µg Ni/L**.**
- **Food:** The mean and median concentrations of nickel in combined dietary solids and liquids were 47 and 43 µg Ni/kg, respectively.

Toxicokinetics

- **Oral absorption** 0.5 to 40 % based on water solubility, vehicle (water or food), fasted or fed.
- **Inhalation:** 50% of soluble $NiCl_2$ cleared from lungs in 3 days. Insoluble forms cleared much more slowly, e.g., NiO $T_{1/2}$'s in lung of 12 and 21 mo depending on particle size**.**
- **Distribution** in all tissues dependent on water solubility and dose. For $NiSO_4$,

  kidney > testes > brain > spleen > heart > liver.

Toxicokinetics (Cont.)

- **Excretion:** Most nickel absorbed from diet and environmental media is rapidly excreted in urine.
  - First order elimination half lives :
    6 and 50 hr in rats, 8 and 83 hr in rabbits.
- **Excretion:** Sweat and milk possible excretion routes in humans.
- **Models:** Biokinetic, PBPK, Lung Deposition-Clearance, Keratinocyte- Cytokine Response, Tracheobronchial Epithelial Cell.

Acute Toxicity in Humans

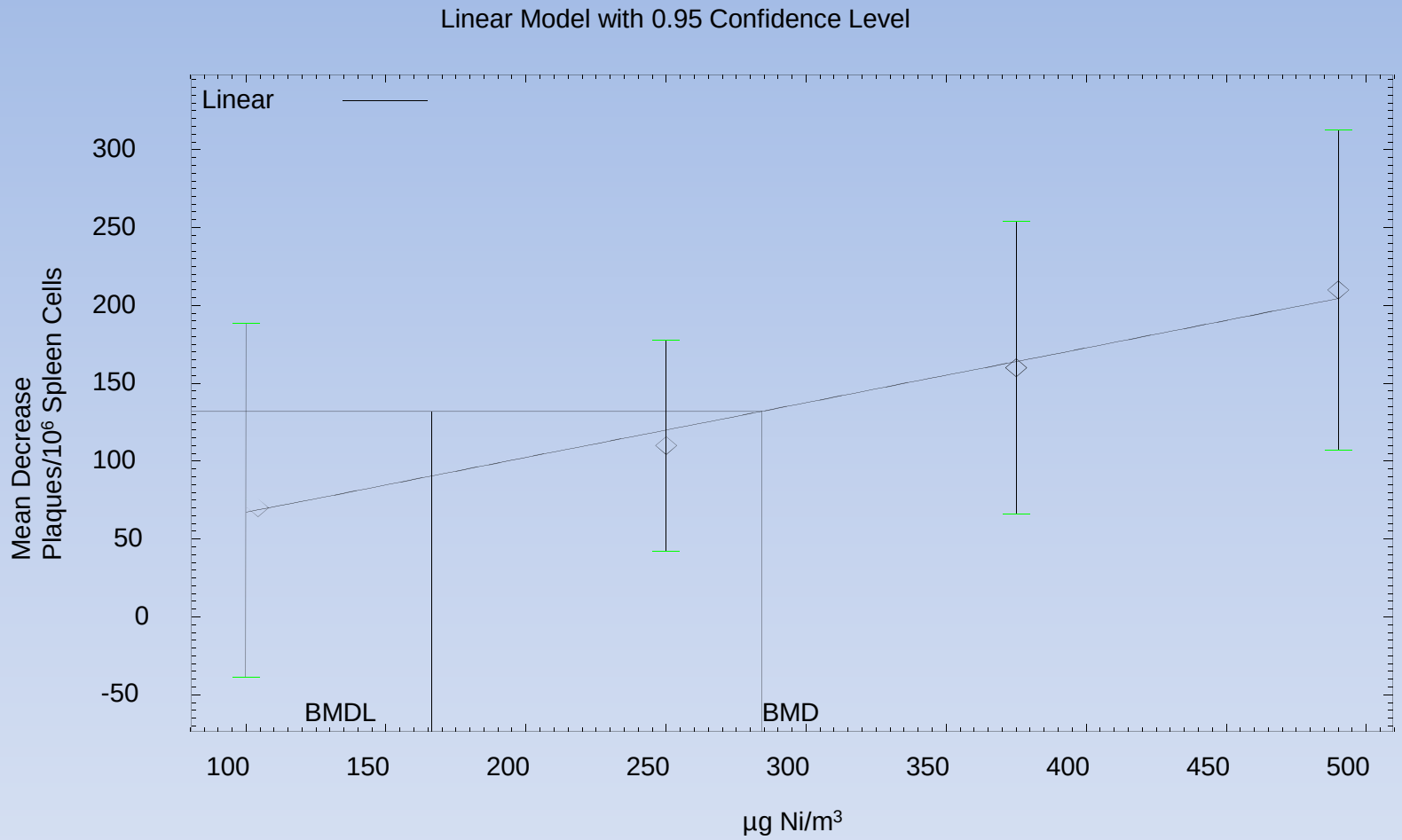
- **32 Workers consumed 0.5 to 2.5 g Ni(II) as chloride and sulfate in drinking water.**
  - 20 had nausea, vomiting, abdominal discomfort, giddiness, lassitude, headache, cough and shortness of breath, for a few hours to several days (Sunderman et al., 1988).
- **7 metal plating workers with occupational asthma tested for lung function with 30 min exposure to 0.3 mg/m^3 $NiSO_4$.**
  - 6/7 had significantly decreased FEV_1 (>15%) (Cirla et al., 1985).

Acute Toxicity in Animals

- **Water soluble Ni(II) compounds** more acutely toxic than water insoluble by oral route
- **$NiSO_4$ and Ni acetate** single dose oral LD_{50}'s ranged from 39 to 141 mg/kg in rats and mice.
- **NiO and Ni_3S_2**
  - single oral LD_{50}'s > 3000 mg/kg in rats and mice.
  - Subacute inhalation exposure (6hr/d x 5d/wk, 12 days) to 5 or 10 mg Ni_3S_2/m^3 caused lung pathology, mortality at higher dose in mice and rats.

Acute Toxicity in Animals (Cont.)

- **Immunotoxicity in mice (Graham et al., 1975, 1978).** Six-week old mice exposed to 0 to 490 µg/m^3 $NiCl_2$ (≤ 3 µm) for two hours. Exposed animals gave significant decrease in antibody-forming cells after antigen challenge. LOAEL = 250 µg Ni/m^3, NOAEL ≈ 100 µg Ni/m^3, BMDL = 164.6 µg Ni/m^3 (-100 plaques/1E6 cells)


Linear Model with 0.95 Confidence Level
Linear
Mean Decrease Plaques/10^6 Spleen Cells
300
250
200
150
100
50
0
-50
BMDL
BMD
100
150
200
250
300
350
400
450
500
µg Ni/m3
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Reproductive & Developmental Toxicity in Animals

- Two generation reproduction study in rats (0, 0.22, 0.56, 1.12, or 2.23 mg Ni/kg-d) by $NiSO_4$ aqueous gavage (min. of 70 days of treatment, NiPERA 2000b).
  - Dose related increases in perinatal mortality.
  - LOAEL = 2.23 mg Ni/kg-d
  - NOAEL = 1.12 mg Ni/kg-d
- Spermatotoxicity in mice (Pandey & Srivastava, 2000). Male mice orally administered (0, 5, 10, 20 mg $NiSO_4$ or $NiCl_2$/kg-d) x 5d/wk x 35 d.
  - Significant decreases in sperm count at 20 and motility at 10 and 20 mg/kg-d.
  - Increases in abnormal sperm shapes at 10 and 20 mg/kg-d.
  - $BMDL_{1SD}$ = 2.91 mg/kg-d for sperm motility ($NiSO_4$) and 0.46 ($NiSO_4$) and 0.34 ($NiCl_2$) mg/kg-d for sperm abnormality.

Reproductive & Developmental Toxicity in Humans

- Spontaneous abortion (SA) case-control study of Vaktsjold et al., 2008b) in female nickel refinery workers.
  - Odds ratios for association between Ni exposure and SA was 1.38 (95% C.I. 1.04-1.84) (unadjusted) and 1.14 (95% C.I. 0.95-1.37) (adjusted). Possibly a weak excess risk.
- Semen quality in 57 workers exposed to nickel and chromium and 57 unexposed controls (Danadevi et al., 2003) .
  - Sperm concentration reduced in exposed group 14.5E6/mL vs. 62.8E6/mL .
  - Reduction in rapid linear sperm motility and increase in sperm tail defects correlation with increased blood nickel in exposed workers. Negative correlation with blood Cr.

Chronic Toxicity Human Studies

- Lung radiographic abnormalities (pulmonary fibrosis, PF) in workers exposed to airborne nickel (Berge & Skyberg, 2003).
  - OR for PF and soluble Ni was 4.34 (95% C.I. 1.75-10.77) (unadjusted) and 2.24 (95% C.I. 0.82- 6.16) (adjusted for age, smoking, asbestos, sulfidic Ni).
  - Sulfidic Ni PF OR was 5.06 (1.70-15.09) (unadjusted) and 2.04 (0.54-7.70) (adjusted).
  - $BMDL_{01}$ = 0.35 soluble and 0.19 sulfidic (mg Ni/m^3)yr.
- Results indicate dose-response for cumulative Ni exposure and PF. Mean and median exposure periods were 21.8 and 21.9 yr, respectively.

Chronic Toxicity in Animal Studies

- Oller et al., (2008) inhaled Ni metal in rats (0, 0.1, 0.4, or 1.0 mg Ni/m^3, MMAD = 1.8µm) 6hr/d x 5d/wk x 24 mo. No NOAEL.
  - Respiratory lesions: alveolar proteinosis , alveolar histiocytosis, chronic inflammation, bronchiolar-alveolar hyperplasia and bronchial lymph node infiltrate.
- NTP (1994c) chronic study of $NiSO_4.6H_2O$ in rats. Exposures 0, 0.03, 0.06, or 0.11 mg Ni/m^3, as above.
  - Lung inflammatory lesions, macrophage hyperplasia, and nasal epithelial atrophy seen at 0.06 mg Ni/m^3 and above.
  - LOAEL = 60 µg/m^3, NOAEL = 30 µg/m^3, $BMDL_{05}$ = 30.5 µg/m^3.

Chronic Toxicity in Animal Studies

- NTP(1994a) chronic study of NiO in mice exposed to (0, 1.0, 2.0, or 4.0 mg Ni/m^3) 6hr/d x 5d/wk x 24 mo.
  - Lung lesions similar to other studies. Bronchial lymph-node hyperplasia evident in all Ni-exposed animals.
  - NOAEL not observed, LOAEL 1.0 mg/m^3, $BMDL_{05}$ = 117 µg Ni/m^3 (alveolar proteinosis).

Acute REL

- Study: Cirla et al. (1985) 7 metal plating volunteers with occupational asthma
- Exposure: 0.3 mg $NiSO_4 \bullet 6H2O/m^3$ (67 µg Ni/m^3) for 30 minutes
- LOAEL = 67 µg Ni/m^3 (30 min) for FEV1
- NOAEL = Not observed
- LOAEL = 33 µg Ni/m^3 (1 hr adjustment)
- LOAEL UF = 10
- Intraspecies UF = √10
- Cumulative UF = 30
- aREL = 33/30 = 1.1 µg Ni/m^3

8-Hour REL

- Study: Graham et al. (1978) Supported by NTP 1994c
- Study Population: Female mice
- Exposure: Inhalation of 100 to 490 µg $NiCl_2/m^3$ for 2 hours
- Effect: Depressed antibody response to sheep red blood cells
- LOAEL = 250 µg Ni/m^3
- BMDL = 165 µg Ni/m^3 (for ~100 plaques/million cells)
- NOAEL = 100 µg Ni/m^3 (questionable)
- BMDL = 82 µg Ni/m^3 (extrapolated to 8 hours)
- LOAEL UF = √10 for BMR analysis
- Interspecies UF = 10
- Intraspecies UF = 30 (10 PD x √10 PK)
- Cumulative UF = 1000
- 8-Hr REL = 82/1000 = 0.08 µg Ni/m^3

Chronic REL Ni and Ni Compounds Except NiO

- Study: NTP 1994c
- Study Population: Male and female rats
- Exposure: Discontinuous inhalation 0, 0.12, 0.25, or 0.5 mg $NiSO_4 \bullet 6H2O/m^3$ (0,0.03, 0.06, 0.11 mg Ni/m^3), 6hr/d x 5d/wk x 104 wk
- Critical Effects: Pathological changes on lung, lymph nodes and nasal epithelium
- LOAEL = 60 µg Ni/m^3
- NOAEL = 30 µg Ni/m^3
- BMDL = 30.5 µg Ni/m^3
- Average experimental concentration = 5.4 µg Ni/m^3
- Human equivalent Concentration = 1.4 µg Ni/m^3 (MPPD2)

cREL Ni and Ni compounds except NiO (Cont.)

- Interspecies UF = √10
- Intraspecies UF = 30 (10PD x √10PK)
- Cumulative UF = 100
- cREL = 1.4/100 = 0.014 µg Ni/m^3

Chronic REL NiO

- Study: NTP 1994a
- Study Population: Male and female mice (57-69/group)
- Exposure: Discontinuous inhalation (0, 1.0, 2.0, 4.0 mg Ni/m^3) 6hr/d x 5d/wk x 104 wk
- Critical Effects: Pathological changes in the lung including pulmonary inflammation and alveolar proteinosis
- LOAEL = 1.0 mg Ni/m^3
- BMDL = 117 µg/m^3 (5%, alveolar proteinosis)
- Average Experimental Concentration = 20.9 µg Ni/m^3

cREL NiO (Cont.)

- Human Equivalent Concentration = 2.0 µg Ni/m^3 (from Hsieh et al., 1999)
- Interspecies UF = √10
- Intraspecies UF = 30 (10 PD x √10PK)
- Cumulative UF = 100
- cREL = 2.0/100 = 0.02 µg Ni/m^3

Oral Chronic REL

- Study: NiPERA (2000a,b)
- Study Population : Rats (Sprague-Dawley)
- Exposure: Aqueous gavage with $NiSO_4$
- Critical Effects: Perinatal mortality in two generation study
- LOAEL = 2.23 mg Ni/kg-d
- NOAEL = 1.12 mg Ni/kg-d
- Average exposure = 1.1 mg/kg-d
- Human equivalent = 1.1 mg/kg-d

Oral cREL (Cont.)

- LOAEL UF = 1
- Interspecies UF = 10
- Intraspecies UF = 10
- Cumulative UF = 100
- Oral cREL = 1.1/100 = 0.011 mg Ni/kg-d

Overall RELs Summary

- Acute REL = 1.1 µg Ni/m^3 FEV_1 decrease
- 8-Hr REL = 0.08 µg Ni/m^3 Immunotoxicity
- Chronic REL = 0.014 µg Ni/m^3 Lesions in lung, lymph nodes and nasal epithelium, alveolar proteinosis (Ni and Ni compounds except NiO)
- Chronic REL (NiO) = 0.02 µg Ni/m^3 Alveolar proteinosis
- Oral REL = 11 µg/kg-d Perinatal mortality (Same as basis for drinking water PHG)

NiPERA Letter to SRP, April 19, 2011

- Dosimetry Adjustment: OEHHA calculates the HEC based solely on the ratio of *deposition fractions* in humans and rats. A more precise calculation can be made based on the ratio of *deposited doses*.
- OEHHA : DAF ($NiSO_4$) = (Fr)a/(Fr)h = (0.089/0.348) = 0.264
- NiPERA: RDDRr ($NiSO_4$) = (SA)h/(SA)a x (Ve)a/(Ve)h x (Fr)a/(Fr)h = (54/0.34)(214.2/13,800)(0.089/0.348) = 0.554
- RDDRr normalization factors are default adult values not child whereas human Fr is mean of all age-specific values.
- All child values show higher fractional depositions than adult. Child range = 0.32 to 0.4 vs. 0.25 for adult.

NiPERA Letter to SRP (Cont.)

- Alternative approach with MPPD2 Model. Compare retention of particles for comparable periods of age in deposition/clearance simulations: 3mo (2weeks); 3yr(6 mo); 9yr(1yr), 14 yr(1yr), 21Yr(2yr), Adult rat (90d). Exposure of 120 µg/m3 x 6 hr/d x 5d/wk x weeks above. Metric: Specific Retention(SR) µg NiSO4/d/m2 alveolar surface area.
- Preliminary SR values: 3mo = 2.10; 3 yr = 1.12; 9yr = 0.91; 14yr = 0.86; 21yr = 0.29; Rat = 0.33.
- DAF = (SR)a/(SR)h x (Fr)a/Fr)h = 0.465 x 0.264 = 0.12

Chemical Forms of Ni(II)

- Ni, nickel metal
- NiO, nickel oxide
- $NiCl_2$, nickel chloride
- $NiSO_4 \cdot 6H_2O$, nickel sulfate hexahydrate
- Ni_3S_2 , nickel subsulfide
- NiS, nickel sulfide
- Ni, NiO, Ni_3S_2 are insoluble in water
- $NiSO_4 \bullet 6H_2O$, $NiCl_2$ are soluble in water

Uses and Exposure Sources

- About 40 % of nickel used in stainless steel, permanent magnets, and alloys
- About 20% used as $NiSO_4$ and $Ni(OH)_2$ in electroplating, batteries, dyes, catalysts
- Most common airborne exposures to nickel compounds are to insoluble nickel compounds
  - elemental nickel, nickel sulfide, nickel oxides from dusts and fumes