

NICKEL REFERENCE EXPOSURE LEVELS (REVISED DRAFT)

Air Toxicology and Epidemiology Branch
Office of Environmental Health Hazard
Assessment
August, 2011



Revisions Summary

- New Acute REL based on Graham et al. (1978) supported by Adkins et al. (1979): Immunotoxicity.
- New 8-Hr REL based on NTP 1994c Lung lesions (NiSO₄)
- New introductory section on Physical and Chemical Properties Affecting Toxicity (particle size, density, solubility).
- New Table on solubility and solubility products of Ni compounds.
- Expanded section on uses and sources including new table on environmental airborne nickel.
- New section on air pollution studies of nickel as a species of PM.
- Revised sections on epigenetics (animal and human data) and nickel-induced cardiovascular effects (animal and human data).
- New section on mechanism of lung injury.
- New Toxicity Summary Table (Appendix)



Revisions Summary (cont.)

- Revised and extended rationale for deposition–based DAF for cRELS.
- Added particle size information throughout the text.
- Added newer articles to table on genetox and additional rationale for inclusion in noncancer assessments(DNA damage and cardiovascular effects, other noncancer effects, Cooke et al. , 2006)
- Added 48 new references supporting revisions.
- Reorganized the document moving and combining text for improved intelligibility (e.g., Immunotoxicity now a separate section).

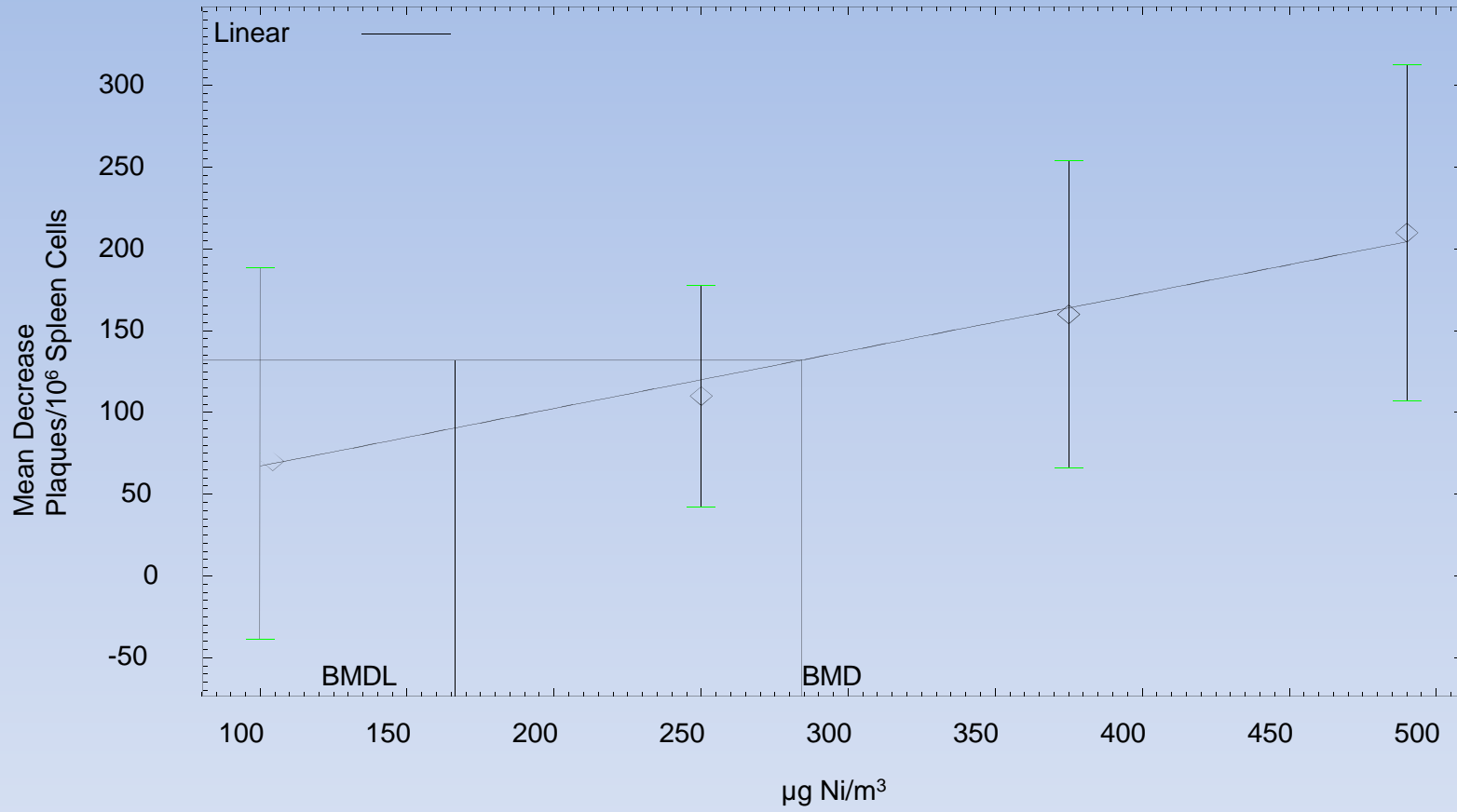


Acute Toxicity in Animals

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



Linear Model with 0.95 Confidence Level



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Acute REL

- Study: Graham et al. (1978). Depressed antibody response
- Exposure: 100 to 490 $\mu\text{g Ni/m}^3$ (2hr)
- LOAEL = 250 $\mu\text{g Ni/m}^3$
- NOAEL = 100 $\mu\text{g Ni/m}^3$ (questionable value)
- BMDL = 165 $\mu\text{g Ni/m}^3$ (-100 plaques/1E6 cells)
- BMDL = 233 $\mu\text{g Ni/m}^3$ (1 hr adjustment)
- BMDL UF = $\sqrt{10}$ (modeled dose response for NOAEL equiv.)
- Interspecies UF = 10 (default)
- Intraspecies UF = 30 ($\sqrt{10}$ PD x 10PK)
- Cumulative UF = 1000
- aREL = $233/1000 = 0.2 \mu\text{g Ni/m}^3$

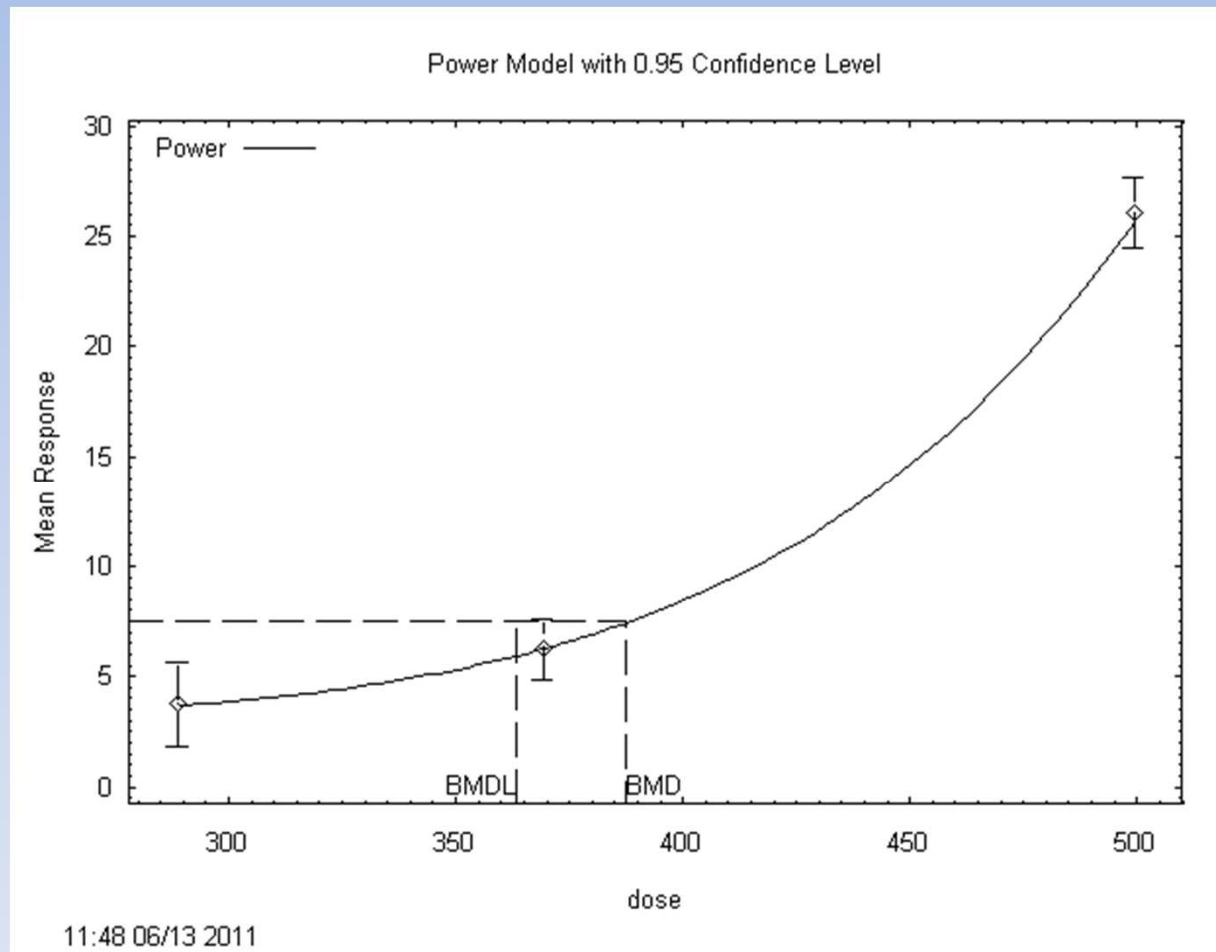


Acute REL Supporting Study

- Study: Adkins et al. (1979). Increased mortality in Ni-treated mice after experimental *Streptococcus pyogenes* infection.
- Exposure: 289 to 499 $\mu\text{g Ni}/\text{m}^3$ (NiCl_2 aerosol $<1.4 \mu\text{m}$, 2hr)
- LOAEL = 499 $\mu\text{g Ni}/\text{m}^3$
- NOAEL = 369 $\mu\text{g Ni}/\text{m}^3$ (questionable value)
- BMDL = 365 $\mu\text{g Ni}/\text{m}^3$ (for a doubling of mortality increase)
- BMDL = 730 $\mu\text{g Ni}/\text{m}^3$ (1 hr adjustment of BMDL)
- BMDL UF = $\sqrt{10}$ (modeled dose response for NOAEL equiv.)
- Interspecies UF = 10 (default)
- Intraspecies UF = 30 ($\sqrt{10}$ PD x 10PK)
- Cumulative UF = 1000
- aREL = $730/1000 = 0.7 \mu\text{g Ni}/\text{m}^3$



Adkins et al. (1979) Increase in Mortality % vs. Ni $\mu\text{g}/\text{m}^3$ 2 hr



8-Hour REL

- Study: NTP (1994c) supported by Graham et al. 1978.
- Study Population: Male and female rats
- Exposure: Inhalation of NiSO₄ aerosol 6hr/day, 5 days/week for 16 d to 2 years (13 week data used)
- Effect: Lung lesions e.g., alveolar proteinosis
- NOAEL = 30 µg Ni/m³
- NOAEL = 5.7 µg Ni/m³ (human equivalent continuous value)
- Interspecies UF = √10
- Intraspecies UF = 30 (10 PD x √10 PK)
- Cumulative UF = 100
- 8-Hr REL = 5.7/300 = 0.019 = 0.06 µg Ni/m³



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 NiSO₄•6H₂O/m³ (0,0.03, 0.06, 0.11 mg Ni/m³), 6hr/d x 5d/wk x 104 wk
- Critical Effects: Pathological changes on lung, lymph nodes and nasal epithelium
- LOAEL = 60 µg Ni/m³
- NOAEL = 30 µg Ni/m³
- BMDL = 30.5 µg Ni/m³
- Average experimental concentration = 5.4 µg Ni/m³
- Human equivalent Concentration = 1.4 µg Ni/m³ (MPPD2)



cREL Ni and Ni compounds except NiO (Cont.)

- Interspecies UF = $\sqrt{10}$
- Intraspecies UF = 30 (10PD x $\sqrt{10}$ PK)
- Cumulative UF = 100
- cREL = $1.4/100 = 0.014 \mu\text{g Ni/m}^3$



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/m³) 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/m³
- BMDL = 117 µg/m³ (5%, alveolar proteinosis)
- Average Experimental Concentration = 20.9 µg Ni/m³



cREL NiO (Cont.)

- Human Equivalent Concentration = $2.0 \mu\text{g Ni/m}^3$ (from Hsieh et al., 1999)
- Interspecies UF = $\sqrt{10}$
- Intraspecies UF = 30 (10 PD x $\sqrt{10}$ PK)
- Cumulative UF = 100
- cREL = $2.0/100 = 0.02 \mu\text{g Ni/m}^3$



Oral Chronic REL

- Study: NiPERA (2000a,b)
- Study Population : Rats (Sprague-Dawley)
- Exposure: Aqueous gavage with NiSO₄
- 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



Overall RELs Summary

- Acute REL = 0.2 $\mu\text{g Ni/m}^3$ Immunotoxicity
- 8-Hr REL = 0.06 $\mu\text{g Ni/m}^3$ Pneumotoxicity
- Chronic REL = 0.014 $\mu\text{g Ni/m}^3$ Lesions in lung, lymph nodes and nasal epithelium, alveolar proteinosis (Ni and Ni compounds except NiO)
- Chronic REL (NiO) = 0.02 $\mu\text{g Ni/m}^3$ Alveolar proteinosis
- Oral REL = 11 $\mu\text{g/kg-d}$ Perinatal mortality (Same as basis for drinking water PHG)

