APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] μg Cd/m^3

Reference: NTP. 1995. Cadmium oxide administered by inhalation to F344/N rats and B6C3F1 mice. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Experimental design: Groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) 6.2 hours/day, 5 days/week for 2 weeks. The mean MMAD of the cadmium oxide particles was 1.5 μm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1 and 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates).

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

Dose and end point used for MRL derivation: The LOAEL of 0.088 mg Cd/m^3 was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the incidence data for alveolar histiocytic infiltration do not provide sufficient information about the shape of the dose-response relationship below the 100% response level.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The $LOAEL_{HEC}$ was calculated using the equations below.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR$$

The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$$LOAEL_{ADJ} = 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$
$$LOAEL_{ADJ} = 0.016 \text{ mg Cd/m}^3$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed 0.088 mg Cd/m^3, the reported MMAD of 1.5 μm and the midpoint of the reported range of geometric standard deviations (1.7)

$$LOAEL_{HEC} = 0.016 \text{ mg Cd/m}^3 \times 0.617$$
$$LOAEL_{HEC} = 0.01 \text{ mg Cd/m}^3$$

Was a conversion used from intermittent to continuous exposure? Yes (see above)

Other additional studies or pertinent information that lend support to this MRL: The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m^3 would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m^3 as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). At lower concentrations of 0.4–0.5 mg Cd/m^3 as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m^3 as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m^3 as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m^3 (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m^3as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m^3

as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m^3 as cadmium oxide for 2 hours (Rusch et al. 1986).

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