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: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 63
Species: Human

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] µg Cd/m^3

Reference: Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Suwazono Y, Sand S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Experimental design: As detailed in the chronic oral MRL worksheet, a meta-analysis of select environmental exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of renal function in environmentally exposed populations was conducted; for the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). The meta-analysis was used to establish a point of departure for the urinary cadmium-response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) were used to predict cadmium air concentrations.

Dose and end point used for MRL derivation: Analysis of the available environmental exposure studies and occupational exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of β2-microglobulin proteinuria (UCD_{10}). The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European environmental exposure studies (Buchet et al. 1990; Järup et al. 2000; Suwazono et al. 2006); the UCD_{10} values from the occupational exposure studies were 7.50 µg/g creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 µg/g creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). The UCD_{10} from the environmental exposure studies was selected as the basis of the MRL. The 95% lower confidence limit on this value ($UCDL_{10}$) of 0.5 µg/g creatinine was used as the point of departure for the MRL.

[ ] NOAEL [ ] LOAEL [X] $UCDL_{10}$

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

Inhalation exposures (μg/m^3) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucocilliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Kjellström-Nordberg pharmacokinetic model (1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

An airborne cadmium concentration of 1.8–2.4 μg/m^3 as cadmium oxide or 1.2–1.4 μg/m^3 as cadmium sulfide would result in a urinary cadmium level of 0.5 μg/g creatinine, assuming that the air was the only source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in nonsmoking males and females in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively (0.32 μg/kg/day for males and females combined) (Choudhury et al. 2001).

Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (AMAD=1 μm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 μg/m^3 and a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.5 μg/g creatinine.

Uncertainty Factors and Modifying Factors used in MRL derivation:

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

The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990).

[X] modifying factor of 3

The modifying factor of 3 was used to account for the lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys.

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: Not applicable.

Was a conversion used from intermittent to continuous exposure? The pharmacokinetic model assumes continuous exposure.

Other additional studies or pertinent information that lend support to this MRL: Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations include an increase in residual volume in workers exposed to air concentrations of cadmium

fumes ranging from 0.008 (in 1990) to 1.53 mg/m^3 (in 1975) (mean urinary cadmium level in the workers was 4.3 µg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m^3 (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m^3 (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as N-acetyl-β-glucosaminidase (NAG), amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate. The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β2-microglobulin, retinol binding protein, and human complex-forming glycoprotein [pHC]) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Significant alterations in the prevalence of low molecular weight proteinuria among cadmium workers has been observed at urinary cadmium levels of 1.5 µg/g creatinine and higher (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994).

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