MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 106
Species: Human

Minimal Risk Level: 0.1 [X] µg Cd/kg/day [ ] 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: ATSDR conducted 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 (Buchet et al. 1990; Järup et al. 2000; Jin et al. 2004c; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; Wu et al. 2001). The studies were selected based on the following qualitative criteria: (1) the study measured an urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off value for β2-microglobulin of ≥1,000 µg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000–10,000 µg/g creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in glomerular filtration rate. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as µg/g creatinine) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed above. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10}, the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved. For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic

Dose and end point used for MRL derivation: Aggregate UCD_{10} estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Table A-4. The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 µg/g creatinine was considered as the point of departure for the MRL.

Table A-4. Estimates of the UCD_{10} and Cadmium Intake from Environmental Exposure Dose-Response Studies

	UCD_{10}[a] (µg Cd/g creatinine)	Cadmium intake[b] (µg/kg/day)	
		Females	Males
Europe (n=4)[c]			
Mean	1.34	0.97	2.24
Median	—	—	—
95% CI	0.50, 2.18	0.33, 1.75	0.70, 3.94
Japan (n=4)[d]			
Mean	5.23	4.59	10.1
Median	—	—	—
95% CI	4.24, 6.21	3.67, 5.49	8.07, 12.0
China (n=3)[e]			
Mean	9.55	8.60	18.8
Median	—	—	—
95% CI	2.96, 16.1	2.48, 14.7	5.51, 31.9
All (n=11)			
Mean	4.99	4.37	9.58
Median	4.20	3.63	7.99
95% CI	1.44, 6.60	1.06, 5.86	2.45, 12.8

[a]Estimates of urinary cadmium level corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (UCD_{10}).
[b]UCD was transformed into estimates of chronic cadmium intake that would result in the UCD at age 55 using a modification (Choudhury et al. 2001; Diamond et al. 2003) of the Kjellström and Nordberg (1978) model.
[c]Dose-response function data from Buchet et al. (1990), Suwazono et al. (2006), and Järup et al. (2000); dose response data from males and females in the Buchet et al. (1990) study were treated separately.
[d]Dose-response function data from Kobayashi et al. (2006) and Shimizu et al. (2006); dose response data from males and females were treated separately.
[e]Dose-response function data from Jin et al. (2004c) and Wu et al. (2001); dose response data from males and females in the Jin et al. (2004c) study were treated separately.

UCD = urinary cadmium dose

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

The $UCDL_{10}$ of 0.5 µg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as µg/kg/day) that would result in the $UCDL_{10}$ at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake). The dose transformations were achieved by simulation using a modification of the Kjellström and Nordberg (1978) model. The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males

and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, μg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

where K is the age-specific renal cadmium burden (μg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974)

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}); and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, \textit{adult females}$$
$$LBM = BW \cdot 0.88, \textit{adult males}$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

Dose units expressed as cadmium intake (μg/kg/day), urinary cadmium excretion (μg/g creatinine), or kidney tissue cadmium (μg/g cortex) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake (μg/kg/day) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 μg/g creatinine (UCD_{10} and $UCDL_{10}$) are 0.97 and 0.33 μg/kg/day in females and 2.24 and 0.70 μg/kg/day in males.

Uncertainty Factors used in MRL derivation:

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

The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of human studies, and thus, an uncertainty factor of 3 was used.

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? No.

Other additional studies or pertinent information that lend support to this MRL: The results of numerous studies of environmentally exposed populations provide strong evidence that the kidney, and possibly bone, is the most sensitive target of toxicity following chronic exposure to cadmium. Most of the studies have focused on subclinical alterations of kidney function, as measured by the urinary excretion of several biomarkers including low molecular weight proteins (β2-microglobulin, pHC, retinol binding protein), intracellular tubular enzymes (NAG), amino acids, high molecular weight proteins (albumin), and electrolytes (potassium, sodium, calcium). Significant associations between urinary cadmium levels and an increased prevalence of abnormal levels of these biomarkers have been found in populations living in areas with moderate or high cadmium pollution or low cadmium pollution (Bandara et al. 2010; Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Ferraro et al. 2010; Hayano et al. 1996; Honda et al. 2010; Horiguchi et al. 2004, 2010; Hwangbo et al. 2011; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a, 2009b; Monzawa et al. 1998; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). Increases in the prevalence of abnormal biomarker levels appear to be the most sensitive indicator of cadmium toxicity and alterations have been observed at urinary cadmium levels ranging from 1 μg/g creatinine (Järup et al. 2000) to 9.51 μg/g creatinine (Jin et al. 2004a).

Several studies have examined the possible association between exposure to cadmium and bone effects. Significant associations between urinary cadmium levels and an increased risk of bone fractures at urinary cadmium levels of ≥0.7 μg/g creatinine (Alfvén et al. 2004; Staessen et al. 1999; Wang et al. 2003), increased risk of osteoporosis at urinary cadmium levels of ≥1.5 μg/g creatinine (Alfvén et al. 2000; Jin et al. 2004b; Wang et al. 2003), and decreased bone mineral density at urinary cadmium levels of ≥0.6 μg/g creatinine (Engström et al. 2009; Nordberg et al. 2002; Schutte et al. 2008; Trzcinka-Ochocka et al. 2010).

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Three approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study identified the lowest adverse effect level; the investigators estimated that a urinary cadmium level of 1 μg/g creatinine would be associated with a 10% increase in the prevalence of abnormal pHC levels above background prevalence (approximately a 10% added risk). The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 μg/g creatinine. For the second approach, eight published benchmark dose analyses were evaluated (Jin et al. 2004b; Kobayashi et al. 2006, 2008a; Shimizu et al. 2006; Suwazono et al. 2006, 2011b, 2011c; Uno et al. 2005). The lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria

ranged from 0.7 µg/g creatinine (Uno et al. 2005) to 9.9 µg/g creatinine (Kobayashi et al. 2006). The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Using individual dose-response functions from each study, estimates of the internal cadmium dose corresponding to probabilities of 10% excess risk of low molecular weight proteinuria were calculated. The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 µg/g creatinine was considered as a potential point of departure for the MRL.

The points of departure selected using the three different approaches are similar: 0.5 µg/g creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 µg/g creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 µg/g creatinine from the dose-response analysis. The third approach was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

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