APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

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).

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

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).

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

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 [X] Intermediate [ ] Chronic
Graph Key: 33
Species: Rat

Minimal Risk Level: 0.5 [X] µg Cd/kg/day [ ] ppm

Reference: Brzóska MM, Moniuszko-Jakoniuk J. 2005d. Disorders in bone metabolism of female rats chronically exposed to cadmium. Toxicol Appl Pharmacol 202(1):68-83.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005a. Bone mineral density, chemical composition and biomechanical properties of the tibia of female rats exposed to cadmium since weaning up to skeletal maturity. Food Chem Toxicol 43(10):1507-1519.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005c. Weakness in the mechanical properties of the femur of growing female rats exposed to cadmium. Arch Toxicol 79(5):277-288.

Experimental design: Groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

Effect noted in study and corresponding doses: No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and

displacement at load were observed at ≥0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of the ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥0.2 mg Cd/kg/day; however, decreases in length were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femoral neck and distal, decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥0.2 mg Cd/kg/day.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] $BMDL_{sd1}$

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures.

Available continuous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to data (Table A-1) for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The BMD and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike's information criterion (AIC) for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the benchmark dose software (BMDS) to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and non-constant variance are negative, then the data set is considered not to be suitable for BMD modeling.

Table A-1. Data Sets for Changes in Mineral Bone Density of the Femur and Lumbar Spine in Female Rats Exposed to Cadmium in Drinking Water for 6, 9, or 12 Months

	Dose (mg Cd/kg/day)			
Dataset[a]	0	0.2	0.5	4
Femur[b]				
6 month	329.7±3.6	317.6±2.7[c]	308.5±3.4[d]	303.4±3.4[e]
9 month	343.8±3.1	328.2±2.9[d]	322.8±3.0[e]	310.4±3.4[e]
12 month	354.3±3.7	338.0±1.9[d]	330.9±3.1[d]	318.7±3.4[e]
Lumbar spine[b]				
6 month	272.0±2.4	263.4±2.6[c]	258.3±2.7[d]	249.5±2.9[e]
9 month	282.4±2.3	271.8±1.6[d]	267.8±1.8[e]	259.5±2.7[e]
12 month	286.1±2.3	275.5±1.9[d]	269.1±1.9[e]	257.1±3.0[e]

[a]n=10.
[b]mean±SE; standard errors were transformed to standard deviations for benchmark dose modeling via a function in the BMD software.
[c]Significantly different (p≤0.05) from the control group.
[d]Significantly different (p≤0.01) from the control group.
[e]Significantly different (p≤0.001) from the control group.

Source: Brzóska and Moniuszko-Jakoniuk 2005d

The potential points of departures derived from the best fitting models for each dataset are summarized in Table A-2.

Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models Predicting Changes in Bone Mineral Density in Female Rats After Cadmium Exposure From Drinking Water

Exposure Period (months)	Best-fitting model	Number of doses	BMD_{sd1}[a] (mg Cd/kg/day)	$BMDL_{sd1}$[a] (mg Cd/kg/day)
Femur				
6	Linear	3	0.24	0.17
9	Hill	4	0.11	0.05
12	Hill	4	0.09	0.05
Lumbar spine				
6	Hill	4	0.19	0.08
9	Hill	4	0.11	0.05
12	Hill	4	0.12	0.07

[a]BMDs and BMDLs from continuous data are associated with a 1 standard deviation change from the control.

The $BMDL_{sd1}$ of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone.

For the 9-month lumbar spine data set, the simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model that provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-3). Using the constant-variance Hill model, the BMD_{sd1} and $BMDL_{sd1}$ are 0.11 mg/kg and 0.05 mg Cd/kg/day, respectively (Figure A-1).

Table A-3. Model Predictions for Changes in Bone Mineral Density of the Lumbar Spine in Female Rats Exposed to Cd in Drinking Water for 9 Months

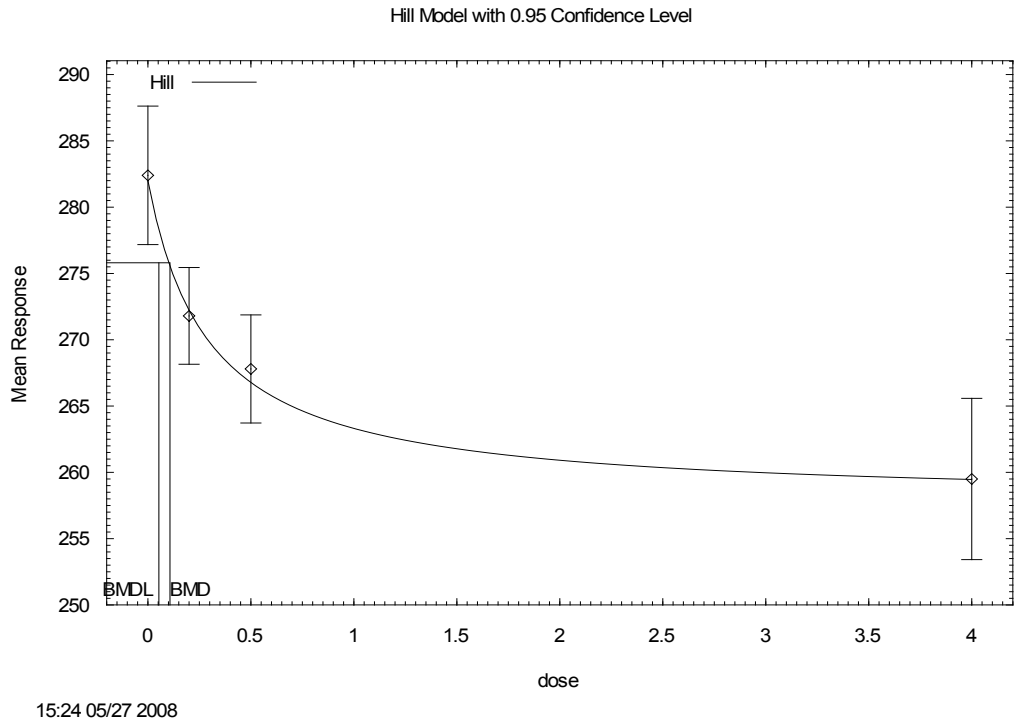
Model[a]	Variance p-value[b]	p-Value for the means[b]	AIC	BMD_{sd1} (mg Cd/kg/day)	$BMDL_{sd1}$ (mg Cd/kg/day)
Linear[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (1-degree)[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (2-degree)[c]	0.36	0.00	211.92	1.93	1.42
Polynomial (3-degree)[c]	0.36	0.00	211.92	1.93	1.42
Power	0.36	0.00	211.92	1.93	1.42
Hill	**0.36**	**0.60**	**197.21**	**0.11**	**0.05**

[a]Constant variance assumed for all models.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Restriction = non-positive.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test; Std1 = a 1 standard deviation change from the control.

Source: Brzóska and Moniuszko-Jakoniuk 2005d

Figure A-1. Predicted and Observed Incidence of Changes in Lumbar Spine Bone Mineral Density in Female Rats Exposed to Cadmium in Drinking Water for 9 Months (Brzóska and Moniuszko-Jakoniuk 2005d)*



*BMDs and BMDLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg Cd/kg/day.

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Investigators estimated doses based on body weight and water consumption.

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? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c, 2010); similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989).

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F_2 and F_3 generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥1.5 mg Cd/kg/day

(Kelman et al. 1978; Baranski 1987; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were poorly reported and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

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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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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

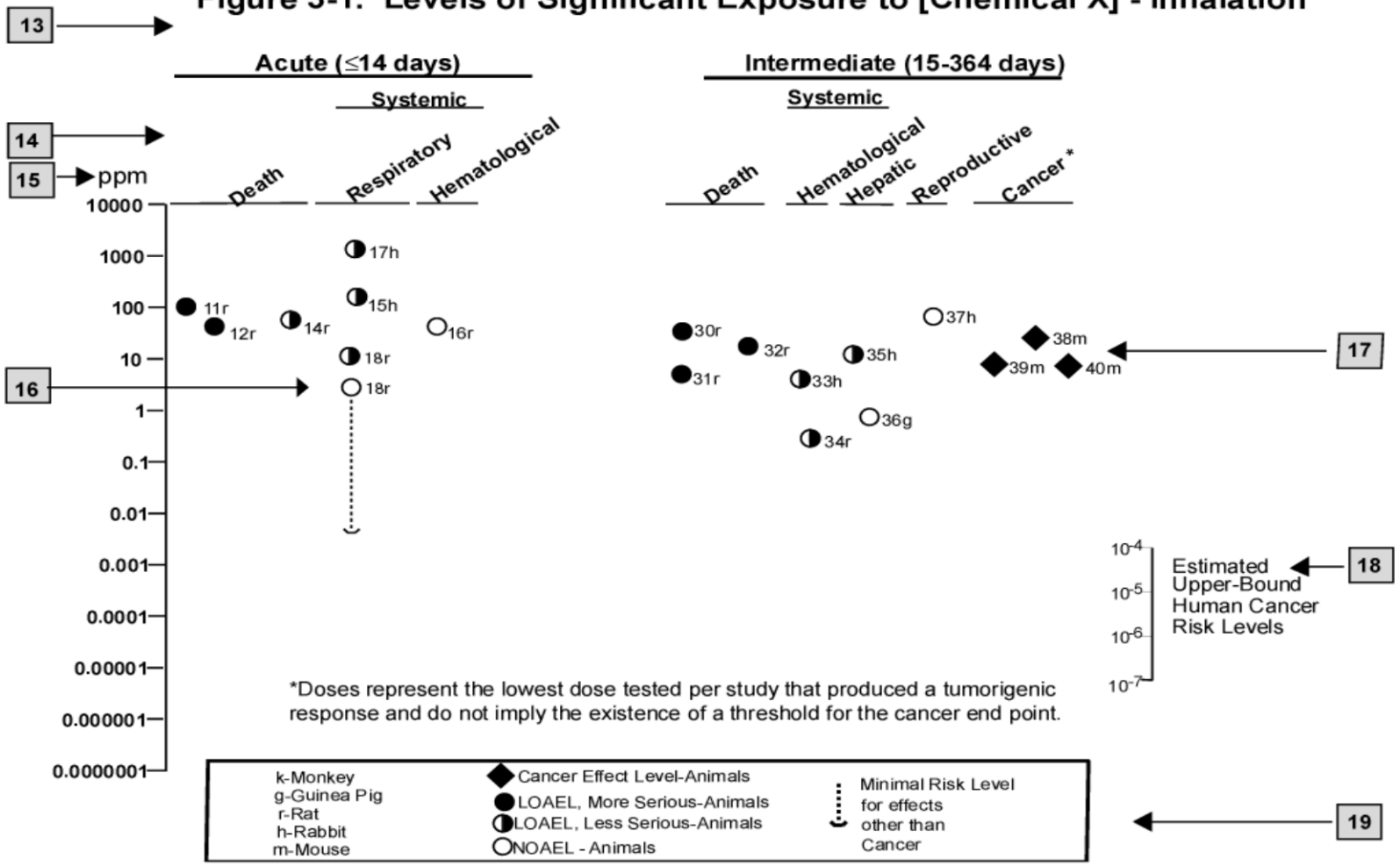
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

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