

Minimal Risk Level Derivation for Cadmium: Acute and Intermediate Duration Exposures

Obaid Faroon^{1,*}, Sam Keith¹, Moiz Mumtaz¹, and Patricia Ruiz¹

¹Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

Abstract

The Agency for Toxic Substances and Disease Registry (ATSDR) lists cadmium as one of its priority hazardous substances. The agency conducted a comprehensive literature review of cadmium and used the information to develop a toxicological profile that identified the full range of health effects associated with exposure to cadmium. It included an assessment that identified screening levels, termed health guidance values or minimal risk levels (MRLs), below which adverse health effects are not expected. In this paper, we describe how MRLs for cadmium are derived. For the acute inhalation MRL, the traditional no observed adverse effect level or lowest observed adverse effect level (NOAEL/LOAEL) approach is used; for the oral intermediate MRL, the benchmark dose (BMD) approach is used. MRLs were developed for the most sensitive route-specific end points, other than mortality and cancer that were sufficiently supported and justified by the data. These included an acute duration (1–14 day exposure) inhalation MRL of 0.03 $\mu\text{g Cd/m}^3$ for alveolar histiocytic infiltration and focal inflammation in alveolar septa and an intermediate duration (15–365 day exposure) oral MRL of 0.5 $\mu\text{g Cd/kg/day}$ for decreased bone mineral density

Corresponding author: Obaid Faroon, Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, Phone: 770-488-3320 Email: Oxs0@cdc.gov

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Introduction

Toxicological profiles are used to help protect people's health. They identify potential adverse health effects caused by exposure to chemicals, particularly priority environmental pollutants. The Agency for Toxic Substances and Disease Registry (ATSDR) develops toxicological profiles by examining, summarizing, and interpreting available toxicological information and epidemiologic evaluations of hazardous substances, such as cadmium. To identify potential harmful effects, dose response curves are constructed to identify the lower bound "no observed adverse effect level" (NOAEL) and the upper bound "lowest observed adverse effect level" (LOAEL) of the chemical of interest. In this paper, we describe how minimum risk levels (MRLs) for cadmium are derived. For the acute inhalation MRL, the traditional NOAEL/LOAEL approach is used; for the oral intermediate MRL, the more recent benchmark dose (BMD) approach is used.

Several federal and state agencies and international bodies use the NOAEL/LOAEL approach for characterizing threshold dose-response relationships for risk assessment. The NOAEL is identified as the highest non-statistically significant dose tested. The LOAEL is the lowest dose tested with statistically significant effect. The NOAEL and LOAEL are used to establish a point of departure and derive health guidance values such as minimal risk levels (MRLs) [1]. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk for adverse non-cancer health effects over a specified duration of exposure. Thus, MRLs are based on the concept that a threshold level of exposure exists, below which no non-cancer health effect is likely to occur. Therefore, an exposure level protective against the most sensitive effect would also be protective against all other effects. ATSDR health assessors and other responders use these substance-specific estimates to identify contaminants and potential health effects that might be of concern at hazardous waste sites. MRLs serve as screening levels; they are not intended to define clean-up or action levels for ATSDR or other agencies.

Uncertainty factors are used with the point of

departure to compensate for data gaps, study duration, species differences, human variability, and other physiological phenomenon [2]. While deriving health guidance values such as the MRLs, further considerations are given to the available mechanistic information, a chemical's mode of action, body burdens, and vulnerabilities of the populations that could influence the dose response curve. If the data are sufficiently robust, ATSDR uses the benchmark dose (BMD) to develop MRLs, considering a wide range of reported health effects at a range of doses. When the requirements of this approach cannot be met, the alternative NOAEL/LOAEL approach is used. However, because of the non-optimal study design and the presence of multiple chemicals and factors where adaptation and compensation interactions occur, this NOAEL/LOAEL approach has limited capacity to assess the biological changes at very low dose levels [1].

A BMD is defined as the statistical lower confidence limit on the dose producing a predetermined level of change in adverse response compared with the response in untreated animals (the benchmark response, or BMR) [3, 4]. The BMD is determined by modeling a dose-response curve in the lower range of doses for which there is a dose-response relationship for biologically observable effects. The BMR is generally set near the lower limit of responses that can be measured directly in animal experiments of typical size. To avoid introducing additional uncertainty or approach the no response level, the BMD method does not extrapolate to doses far below the experimental dose range [3, 4]. Using BMD in place of NOAEL has multiple advantages. BMD is not constrained to using only one experimental dose, as is the NOAEL approach. BMD accounts for variability in the animal response data and can incorporate those response data even from groups other than the experimental study to determine a more accurate estimate of the NOAEL. A BMD can be defined even when all experimentally observed responses would be considered effect-levels (i.e., there is no NOAEL), and thus can avoid application of additional uncertainty factors. BMD analysis data requirements are stringent and hence this approach can be applied to all those chemicals that meet the requirements of the BMD approach.

Cadmium Inhalation Toxicity: Most of the cadmium in the air comes from burning fossil fuels such as coal or oil and incineration of municipal waste. Cadmium concentrations in ambient air have been reported in the ranges of $<0.1 \text{ ng/m}^3$ (remote), $0.1\text{--}5 \text{ ng/m}^3$ (rural), $2\text{--}15 \text{ ng/m}^3$ (urban), and $15\text{--}150 \text{ ng/m}^3$ (industrial). People living near cadmium-emitting industries, such as incinerators, might be exposed to higher level of cadmium than the rest of the population. Solid waste incinerators can discharge cadmium in stack air at concentrations ranging from $20\text{--}2,000 \text{ }\mu\text{g/m}^3$ for traditional incinerators and $10\text{--}40 \text{ }\mu\text{g/m}^3$ for more environmentally friendly advanced incinerators [5, 6].

In the air, cadmium can travel a great distance in the atmosphere, ultimately contaminating areas with no local cadmium inputs. Cadmium was detected at 1,014 of the 1,669 current or former National Priorities List (NPL) hazardous waste sites in 2012. People living near such sites have an increased potential for additional exposure through air, water, and soil [2]. Smoking can greatly increase indoor air concentrations of cadmium, which would otherwise differ little from outdoor air quality [6].

The short-term (acute) effects in humans of breathing cadmium are mainly seen in the lungs and lung epithelial cells [7]. Acute inhalation initially might irritate the upper respiratory tract, although symptoms might be delayed for 4–8 hours. Dyspnea, chest pain, and muscle weakness might also occur. Pulmonary edema, bronchitis, chemical pneumonitis, respiratory failure, and death can occur within days after high level exposure.

Starting in the early 1920s, it became apparent that cadmium fumes were acutely toxic after numerous workers had died after short exposures to presumably high exposures to airborne cadmium oxide [8]. As in metal fume fever, initial symptoms of cadmium fume overexposure were usually mild pulmonary edema that rapidly progressed to severe edema and pneumonitis [9, 10]. Similarly, studies have reported that acute exposure to cadmium can cause lung damage in animals [11-15].

Cadmium Oral Toxicity: The major sources of oral exposure to cadmium in humans are typically food and incidental ingestion from contaminated hands [16,

17]. Very high concentrations of cadmium in food or drinking water can severely irritate the stomach and cause vomiting, diarrhea, and even death [18, 19]. Consuming lower levels over a longer period can result in renal concentrations that can damage the kidneys if sufficiently high. Effects reported in animals include anemia, liver disease, and nerve or brain damage [20-22]. Even lower levels of exposure for extended periods can make bones fragile, so that they are easier to break [23, 24].

An understanding of the adverse health effects in humans from oral exposure to cadmium is primarily based on studies of persons who lived in areas where cadmium levels were elevated and exposure occurred mainly via the diet. Typical levels in leafy vegetables (lettuce, spinach, potatoes, grains, peanuts, soybeans, and sunflower seeds) range from $0.05\text{--}0.12 \text{ mg cadmium/kg}$, compared with $<1 \text{ }\mu\text{g/L}$ in typical surface and groundwater [25, 26]. The EPA maximum contaminant level for cadmium in drinking water is $5 \text{ }\mu\text{g/L}$ [27].

Numerous animal studies have documented the renal, hepatic, musculoskeletal, immunological, neurological, reproductive, and developmental toxicity of cadmium [28-37]. The levels of significant exposure tables and figures in ATSDR's Toxicological Profile for Cadmium [2] present the full set of adverse health effect reported for cadmium.

In this paper, we describe how MRLs for cadmium are derived. For the acute inhalation MRL, the traditional NOAEL/LOAEL approach is used; for the oral intermediate MRL, the BMD approach is used.

Materials and Methods

An exhaustive literature search was conducted to compile the database on the overall toxicity of cadmium (ATSDR, 2012). The studies identified were then categorized by route of exposure and toxicity studied in various organs or systems. Next, the studies that presented dose response data for a given effect were reviewed [2]. Finally, a critical study was selected that best provides all the information needed. That included the dose response for the most sensitive effect caused by cadmium at the lowest dose in humans or animals for a specific route and duration of exposure.

This critical study was used to derive the MRL. The other appropriate studies were used as supporting evidence [1, 38] for the MRL derivation guidance [1]. For the derivation of cadmium acute inhalation and oral intermediate MRLs, NTP [39], Brzoska and Moniuszko-Jakoniuk [35], and [37], Brzoska [40], Brzoska [41] were selected as critical studies because of their experimental design and relevant dose response.

Acute Inhalation MRL Derivation

The critical study selected for deriving the acute duration inhalation MRL was NTP [39]. Fisher F344 rats (five males and five females per group) were exposed to cadmium oxide at concentrations of 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m³, equivalent to 0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m³, for periods of 6.2 hours/day, 5 days/week, for 2 weeks. Cadmium oxide particles had a mean median aerodynamic diameter of 1.5 μm and geometric standard deviation of 1.6–1.8 μm. Each animal was observed twice a day. Weights of the animals and their organs (heart, kidney, liver, lungs, spleen, testis, and thymus) were recorded on the first, eighth, and last days of the study. Histopathological examinations were conducted on a range of tissues (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates). Death occurred only at the highest dose of 8.8 mg Cd/m³, and involved all animals by day 6. Body weight at 2 weeks was reduced by ≤10% compared with controls at the next lower dose of 2.6 mg Cd/m³. Relative and absolute lung weights were significantly increased at 0.26 mg (only in males), 0.88 mg, and 2.6 mg Cd/m³. Histological changes occurred only in the respiratory tract; Table 1 shows the incidence rates. These data were determined to be suitable for deriving the acute inhalation MRL for cadmium.

Intermediate Oral MRL Derivation

The critical study selected for deriving the intermediate oral MRL was Brzoska and Moniuszko-Jakoniuk [35]. The authors exposed 40 3-week old female Wistar rats to drinking water containing concentrations of 0, 1, 5, or 50 mg Cd/L as cadmium chloride, respectively, equivalent to 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day. Body weight

gain and consumption of food and water were not greatly affected. However, sufficient exposure resulted in significantly decreased bone mineral density. Total skeletal bone mineral density was significantly decreased by 3 months exposure to 4 mg Cd/kg/day, 6 months exposure to 0.5 mg Cd/kg/day, and 9 months exposure to 0.2 mg Cd/kg/day. Whole tibia and diaphysis bone mineral densities were significantly decreased after 12 months at ≥0.2 mg Cd/kg/day. Bone mineral density of the proximal and distal ends of the femur decreased after exposure to 0.2 mg Cd/kg/day for 6 months or 0.5 mg Cd/kg/day for 3 months. A 6-month exposure to 0.5 mg Cd/kg/day decreased bone mineral density in all three areas of bone. Exposure to 4 mg Cd/kg/day for 3 months decreased bone mineral density of the femoral proximal, distal, and diaphysis areas. Similarly, lumbar spine bone mineral density was significantly decreased by a 6-month exposure to 0.2 or 0.5 mg Cd/kg/day or a 3-month exposure to 4 mg Cd/kg/day. The area of mineralization was decreased in the lumbar spine at 0.5 mg Cd/kg/day and significantly decreased in both lumbar spine and the femur at 4 mg Cd/kg/day. Tibia weight and length were significantly decreased at 4 mg Cd/kg/day. The mechanical properties of the tibial diaphysis were also affected by cadmium, resulting in alterations in ultimate load, yield load, and displacement at load at ≥0.2 mg Cd/kg/day and altered work to fracture at 4 mg Cd/kg/day. In compression tests of the tibia as a whole, exposure to 0.2 mg Cd/kg/day significantly altered ultimate load and stiffness; exposure to ≥0.5 mg Cd/kg/day affected displacement at yield and work to fracture; and exposure to 4 mg Cd/kg/day resulted in displacement at ultimate load. Multiple regression analysis showed that the bone mechanical properties were weakened primarily through cadmium effects on the organic and non-organic composition of the bone matrix, and the ratio of the ash weight to organic weight. Femur length was decreased after 6 months of exposure to ≥0.2 mg Cd/kg/day, but not at other time points at either 0.2 or 0.5 mg Cd/kg/day. Femur weight was significantly decreased by exposure to 4 mg Cd/kg/day. Exposure to ≥0.2 mg Cd/kg/day resulted in decreased yield load, ultimate load, displacement at ultimate, and work to fracture of the neck, and decreased stiffness in the distal portion. The femoral diaphysis showed significantly altered yield load,

displacement at yield, and stiffness at ≥ 0.2 mg Cd/kg/day. Osteocalcin concentrations were significantly decreased at all doses during the first 6 months, but not the last 6 months. Total and cortical bone alkaline phosphatase levels decreased at 4 mg Cd/kg/day, and trabecular bone alkaline phosphatase decreased at 0.2 mg Cd/kg/day. Exposure to ≥ 0.2 mg Cd/kg/day decreased C-terminal cross-linking telopeptide of type I collagen (CTX) and increased total urinary calcium and calcium fractional excretion.

Results and Discussion

Acute Inhalation MRL Derivation

Because the alveolar histiocytic infiltration incidence data shown in Table 1 did not provide sufficient information on the shape of the dose-response relationship below the 100% response level, those data were considered to be unsuitable for MRL development. Instead, a LOAEL/NOAEL approach was taken. The LOAEL for alveolar histiocytic infiltration and focal inflammation in alveolar septa of 0.088 mg Cd/m³ was identified as the appropriate point of departure for deriving the MRL.

Because exposure was not continuous, the following equation was used to calculate a duration-adjusted LOAEL (LOAEL_{ADJ}):

$$\begin{aligned} \text{LOAEL}_{\text{ADJ}} &= 0.088 \text{ mg Cd/m}^3 \times (\text{the fractional exposure period}) \\ &= 0.088 \text{ mg Cd/m}^3 \times (6.2 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}) \\ &= 0.016 \text{ mg Cd/m}^3 \end{aligned}$$

An equivalent LOAEL concentration for humans (LOAEL_{HEC}) was determined by multiplying the LOAEL_{ADJ} by a regional deposited dose ratio (RDDR). The RDDR is a factor that converts the lung exposure received by the rat to an equivalent human dose using EPA [42] methodology, which directly compares relevant aspects of the respiratory tracts of both species. The RDDR was determined to be 0.617, which was used to calculate the LOAEL_{HEC} using the following EPA equation:

$$\begin{aligned} \text{LOAEL}_{\text{HEC}} &= \text{LOAEL}_{\text{ADJ}} \times \text{RDDR} \\ \text{LOAEL}_{\text{HEC}} &= 0.016 \text{ mg Cd/m}^3 \times 0.617 \\ \text{LOAEL}_{\text{HEC}} &= 0.01 \text{ mg Cd/m}^3 \end{aligned}$$

An uncertainty factor of 300 (10 for use of a LOAEL \times 3 for extrapolation from animals to humans with dosimetric adjustment \times 10 for human variability) was

used in deriving the MRL. These uncertainty factors were justified based on standard factors of 10 each for use of a LOAEL and human variability, and a factor of 3 for dosimetric adjustment to account for extrapolation from the rat to the human for which specific anatomical and physiological comparisons are recognized and used in this assessment. The LOAEL_{HEC} divided by the uncertainty factor of 300 resulted in an acute-duration inhalation MRL of 3×10^{-5} mg Cd/m³ (0.03 μ g Cd/m³).

Other studies found adverse health effects starting at higher doses. Those data were used in our evaluation to lend support to the acute inhalation MRL. Available data and investigations of adverse health effects in humans are limited. Although an MRL could not be developed from the study results, Elinder [43] estimated that exposure for 8 hours to 1–5 mg Cd/m³ would be immediately dangerous to life and health. The primary effect of acute overexposure in humans and in animals is lung damage. Single exposures to either cadmium chloride or cadmium oxide in the range of 1–10 mg Cd/m³ have produced interstitial pneumonitis, diffuse hemorrhagic alveolitis, focal interstitial thickening, and edema, as reported by several authors [11, 12, 44–48]. Repeated exposure to 6.1 mg Cd/m³ for 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats [49]. Mild hypercellularity and increased weight of the lungs were reported at lower concentrations of 0.4–0.5 mg Cd/m³ as cadmium oxide for 2–3 hours (Buckley & Bassett, 1987; Grose et al., 1987) or even lower 0.17 mg Cd/m³ as cadmium chloride for 6 hours/day over 10 days (Klimisch, 1993). At concentrations of 0.19 or 0.88 mg Cd/m³ as cadmium chloride, decreases in humoral immune response were observed in mice exposed for 1–2 hours [50, 51].

Intermediate Oral MRL Derivation

The Brzoska and Moniuszko-Jakoniuk [35], Brzoska and Moniuszko-Jakoniuk [36], Brzoska and Moniuszko-Jakoniuk [37] critical studies provided appropriate data to use the BMD analysis to derive this oral MRL. The lowest dose tested (0.2 mg Cd/kg/day) produced skeletal alterations that included decreased bone mineral density in lumbar spine, femur, and tibia; altered mechanical properties of both femur and tibia; decreased osteocalcin concentrations; decreased trabecular bone alkaline phosphatase concentration; and

Table 1. Histopathologic lesions for male and female rats (F344/N) exposed* to cadmium oxide by inhalation

End point	Sex	Number of rats with end point, by dose (mg Cd/m ³)					
		0	0.088	0.26	0.88	2.6	8.8
Alveolar histiocytic infiltrate and focal inflammation in alveolar septa	Males	0/5	5/5	5/5	5/5	5/5	5/5
	Females	0/5	5/5	5/5	5/5	5/5	5/5
Necrosis of the epithelium lining alveolar ducts	Males	0/5	0/5	5/5	5/5	5/5	5/5
	Females	0/5	0/5	5/5	5/5	5/5	5/5
Tracheobronchiolar lymph node inflammation	Males	0/5	0/3	0/5	5/5	5/5	3/4
	Females	0/4	1/5	1/5	3/5	5/5	3/5
Degeneration of the nasal olfactory epithelium	Males	0/5	0/5	0/5	2/5	5/5	5/5
	Females	0/5	0/5	0/5	4/5	4/5	4/4
Inflammation of the nasal respiratory epithelium	Males	0/5	0/5	0/5	1/5	5/5	3/5
	Females	0/5	0/5	0/5	0/5	4/5	3/4
Metaplasia of the nasal respiratory epithelium	Males	0/5	0/5	0/5	1/5	0/5	5/5
	Females	0/5	0/5	0/5	0/5	4/5	4/4

* 6.2 hours/day, 5 days/week, for 2 weeks.

Table 2. Bone mineral density (mg/cm²) values for the femur and lumbar spine in female rats exposed to cadmium doses from drinking water for 6, 9, or 12 months*

BMD by location and period (months)	Dose (mg Cd/kg/day)			
	0	0.2	0.5	4
Femur [†]				
6	329.7±3.6	317.6±2.7 [‡]	308.5±3.4 [§]	303.4±3.4 [¶]
9	343.8±3.1	328.2±2.9 [§]	322.8±3.0 [¶]	310.4±3.4 [¶]
12	354.3±3.7	338.0±1.9 [§]	330.9±3.1 [§]	318.7±3.4 [¶]
Lumbar spine [†]				
6	272.0±2.4	263.4±2.6 [‡]	258.3±2.7 [§]	249.5±2.9 [¶]
9	282.4±2.3	271.8±1.6 [§]	267.8±1.8 [¶]	259.5±2.7 [¶]
12	286.1±2.3	275.5±1.9 [§]	269.1±1.9 [¶]	257.1±3.0 [¶]

* n=10 rats/dose.

[†] mean±SE; standard errors were transformed to standard deviations for benchmark dose (BMD) modeling via a function in the BMD software.

[‡] Significantly different (p≤0.05) from the control group.

[§] Significantly different (p≤0.01) from the control group.

[¶] Significantly different (p≤0.001) from the control group.

Source: Brzoska and Moniuszko-Jakoniuk [35].

decreased CTX.

Of the adverse effects reported by Brzoska [40], Brzoska [41], bone mineral density was the strongest predictor of femur strength, tibia strength, and fracture risk (Table 2). Therefore, decreased bone mineral density was selected as the critical effect for developing the intermediate duration oral MRL.

The available continuous models in the EPA BMD software (version 1.4.1c) included the linear, polynomial, power, and Hill models. These were fit to the female rat femur and lumbar spine bone mineral density data from 6, 9, and 12 months (Table 2). Table 3 shows the potential points of departure derived from the best-fitting models (linear and Hill). The BMD with its 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control and referred to as the BMDL_{sd1}. The model-fitting procedure for continuous data was followed. 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. Because the linear data were consistent with the assumption of constant variance ($p \geq 0.1$), the other continuous models (polynomial, power, and Hill) were applied to the data. The Hill model was selected for MRL derivation (Table 4). It gave adequate fit to the mean ($p \geq 0.1$) and had the lowest Akaike's information criterion (AIC) value, an inverse estimate of the relative quality of the statistical models used in this assessment. The constant-variance Hill model produced BMD_{sd1} and BMDL_{sd1} values of 0.11 mg Cd/kg/day and 0.05 mg Cd/kg/day, respectively (Figure 1).

Uncertainty Factor used in MRL Derivation

The BMDL_{sd1} of 0.05 mg Cd/kg/day estimated from the 9-months lumbar spine data set was selected as the point of departure for the MRL. An uncertainty factor of 100 (10 for extrapolation from animals to humans \times 10 for human variability) was used to derive the MRL. This MRL is considered to be protective for intermediate duration oral exposure of 15–364 days to cadmium and its compounds.

Although Baranski, Stetkiewicz, Sitarek and al. [52] reported the lowest LOAEL of 0.04 mg Cd/kg/day, it was not selected as the principal study for

derivation of an intermediate-duration MRL. All dose groups in the study showed significantly decreased responses compared to controls, but the study lacked a dose response. Female offspring exposed to each dose (0.04, 0.4, and 4 mg Cd/kg/day) had a significant decrease in exploratory locomotor activity, compared to controls, but no significant differences were found between the cadmium groups, despite the 100-fold difference in doses.

Other studies that reported adverse health effects starting at higher doses lend support to this MRL. Reproductive effects in rats exposed to 8–12 mg Cd/kg/day included necrosis and atrophy of seminiferous tubules and decreased sperm count and motility [33, 53]. Neurological effects in rats exposed to 3.1 mg or 9 mg Cd/kg/day included decreased motor activity [22, 54], whereas 5 mg Cd/kg/day increased their passive avoidance [55]. At approximately 3 mg Cd/kg/day, liver necrosis and anemia occurred [29]. Immunological effects included greater susceptibility to lymphocytic leukemia virus in mice exposed to 1.9 mg Cd/kg/day as cadmium chloride in drinking water for 280 days [56]. Vesiculation of the renal proximal tubules occurred in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks [28]. Decreases in bone strength occurred in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi [57]. Administration to rats by gavage of 0.5 mg Cd/kg/day on gestation days 1–21 resulted in decreased glomerular filtration rates and increased urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium in their 60 day old offspring [30].

Conclusions

In compliance with the Comprehensive Environmental Response, Compensation, and Liability Act, ATSDR conducted a thorough review of peer-reviewed literature regarding cadmium toxicity. The agency identified cadmium as a hazardous substance needing comprehensive assessment, developed a toxicological profile identifying health effects from exposure, and developed MRL health guidance values where data were sufficiently robust. Ideally, the data on cadmium toxicity in humans should be used to derive the MRLs. However, data on the toxicity of cadmium in

Table 3. Summary of benchmark doses (BMDs) and BMD 95% lower confidence limits (BMDLs) from the best fitting models predicting changes in bone mineral density in female rats after cadmium exposure from drinking water.

Exposure Peri- od (months)	Best-fitting model	Number of doses	BMD _{sd1} * (mg Cd/kg/day)	BMDL _{sd1} * (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

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

Table 4. BMD Model predictions for changes in bone mineral density of the lumbar spine in female rats exposed to cadmium (Cd in drinking water for 9 months)

Model*	Variance -value [†]	p-value for the means [‡]	AIC	BMD _{sd1}	BMDL _{sd1}
				(mg Cd/kg/day)	(mg Cd/kg/day)
Linear [‡]	0.36	0.00	211.92	1.93	1.42
Polynomial (1-degree) [‡]	0.36	0.00	211.92	1.93	1.42
Polynomial (2-degree) [‡]	0.36	0.00	211.92	1.93	1.42
Polynomial (3-degree) [‡]	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

* Constant variance assumed for all models.

[†] p-value from the Chi-squared test. Values <0.1 fail to meet conventional goodness-of-fit criteria.

[‡] Restriction = non-positive.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; sd1 = a 1 standard deviation change from the control.

Source: [35].

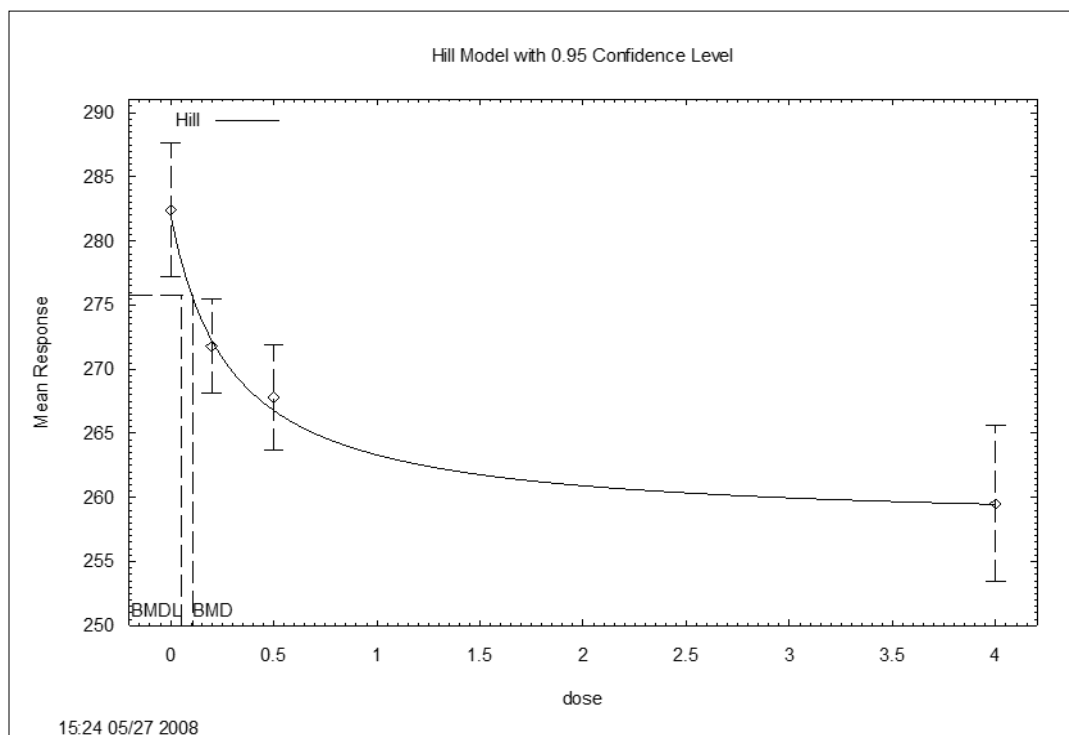


Figure 1. Predicted and observed incidence of changes in lumbar spine bone mineral density in female rats exposed to cadmium in drinking water for 9 months [35]. The benchmark dose (BMD) and BMD 95% lower confidence limits (BMDLs) indicated are associated with a 1 standard deviation change from the control (i.e., BMD_{1sd} , $BMDL_{1sd}$), and are in units of mg Cd/kg/day.

^ Source: ATSDR [2]

MRLs and other health guidance values are not precisely determined levels that present a clear and predictable risk to human health. These values actually represent levels of a potential toxicant that are highly unlikely to pose any threat to human health over a specified duration of daily exposure. MRLs are screening or trigger values used as tools to help determine if further evaluation of a potential exposure scenario is warranted [1].

Several uncertainty factors are used in the MRL derivation process to adjust the actual experimental value to account for differences in susceptibility between the test species and humans, for sensitivity differences within the human population, and to reflect the confidence in the final calculated number and the database supporting that number. Most MRLs

thus contain some degree of uncertainty to compensate for lack of precise toxicological information on the people who might be most sensitive (e.g., infants, the elderly, and those who are nutritionally or immunologically compromised) to the effects of hazardous substances. A conservative protective approach is used to address these uncertainties, consistent with the public health principle of prevention.

Although human data are preferred, relevant human studies often lack the data needed for a quantitative assessment. Consequently, MRLs often are based on results of animal studies, as presented in this paper. In the absence of evidence to the contrary, humans are assumed to be more sensitive than animals

humans are limited and do not lend themselves to the derivation of MRLs. Numerous animal studies have reported a variety of systemic, immunological, neurological, reproductive, and developmental effects. Those studies that found effects on the respiratory and musculoskeletal systems were determined to be appropriate for MRL derivation. In this article, we have provided the rationale and methods for the derivation of two MRLs: an acute-duration inhalation MRL of 0.03 $\mu\text{g Cd}/\text{m}^3$ and intermediate-duration oral MRL of 0.5 $\mu\text{g Cd}/\text{kg}/\text{day}$. To the effects of hazardous substances, and that certain persons might be particularly sensitive. Thus, the resulting MRL might be as much as a hundredfold below levels shown to be nontoxic in laboratory animals. Exposure to a level above the MRL does not mean that adverse health effects will occur. Any MRL can be reevaluated if new and sufficiently supportable data become available. The guidance for MRL derivation is continually evolving to reflect the most current chemical risk assessment methodology and to limit the inherent uncertainties. These methodologies include the use of benchmark dose analysis, the application of computational tools such as physiologically based pharmacokinetic modeling and quantitative structure-activity relationship, and the use of a LOAEL or NOAEL. As we continue to collect pertinent data for risk assessment, those data are expected to represent improvements that in turn reduce the uncertainties in the derived MRLs. Irrespective of the data, some uncertainties will remain, such as biomedical judgement, which will always be associated with the derivation of these health guidance values.

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