A Reassessment of Regulatory Reference Values and Background Exposure Levels for Heavy Metals in the Human Diet

Candace Wong[1,2] and Imad Saab[1]
[1]ILSI North America Food and Chemical Safety Committee
[2]University of Rochester, Department of Environmental Medicine, Toxicology Program

Introduction

- Heavy metals such as arsenic, cadmium, lead, mercury, and chromium are metals of concern for food ingredients and products because exposures to high levels can cause adverse health effects
- Heavy metals can arise from the environment or from contamination from anthropogenic sources
- The overall objective of this study was to better understand the current state of human exposure to heavy metals from consumption

The objectives for this study:

1. Identify current regulatory reference values for heavy metals
2. Evaluate changes in reference values over time
3. Compare reference values set by different agencies by examining key pivotal studies used
4. Review current total background level exposure from food and water
5. Incorporate the new background levels and reference values into the new JIFSAN-hosted Heavy Metal Screening Tool

Methods

Definitions

- **Reference Value**: the calculated daily maximum safe exposure levels via food and water based on lifetime intake without significant adverse health effects
- **Background-Exposure Level**: the combined level of heavy metal consumed from food and water on a daily basis

Methods

- Reference values were analyzed across multiple agencies including the United States Environmental Protection Agency (EPA), Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), and the Agency for Toxic Substances and Disease Registry (ATSDR)
- For consistency, values in this study were expressed as µg/kg bw/day and converted as necessary using the EPA Exposure Factors Handbook (EPA 2011).
- Background-Exposure Level
  - Food Background Exposure Level –a literature search for publications utilizing consumption databases combined with chemical residue studies to determine intake of a particular metal from food ingestion were used
  - Water Background Exposure Level – taken as the regulated Maximum Contaminate Level (MCL) set by the EPA for public drinking water nationwide. For metals such as lead, further considerations were taken into account, including the median lead level of water municipalities across 15 major cities in the U.S.

Heavy Metal Reference Values By Agency Over Time

Metals/Metalloids	Reference Value	Agency and Year
Inorganic Arsenic	0.3 µg/kg/day 2.14 µg/kg/day 0.3 µg/kg/day	EPA 1991 JECFA 1998 ATSDR 2007
Cadmium	1 µg/kg/day 0.83 µg/kg/day 0.36 µg/kg/day 0.1 µg/kg/day	EPA 1989 JECFA 2010 EFSA 2011 ATSDR 2012
Lead	Young Children: 0.26 µg/kg/day* Older Children and Adults: 0.16 µg/kg/day**	FDA 2018
Methylmercury	0.3 µg/kg/day 0.1 µg/kg/day 0.23 µg/kg/day 0.19 µg/kg/day	ASTSDR 1999 EPA 2001 JECFA 2007 EFSA 2012
Chromium (III)	1500 ug/kg/day 300 µg/kg/day	EPA 1999 EFSA 2014
Chromium (VI)	3 µg/kg/day 0.9 µg/kg/day 2.2 µg/kg/day	EPA 1998 ATSDR 2012 Health Canada 2018

Table 1. Differences in reference values by agency over time. *Assuming a 11.4 kg 1 year old **Assuming an 80 kg adult

Reference Values - Pivotal Studies

Metal/ Metalloid	Reference Value	Pivotal Study	Endpoint	POD Value	Uncertainty Factor
Inorganic Arsenic	0.3 µg/kg/day (EPA 1991)	Contaminated well water (Tseng 1968, Tseng 1977)	Skin lesions, hyperkeratosis and hyperpigmentation	NOAEL = 0.0008 mg/kg/day	3 – uncertainty in NOAEL for sensitive individuals
Cadmium	1 µg/kg/day (EPA 1989)	US EPA 1985 Drinking Water Criteria Document on Cadmium	Protienuria	NOAEL = 0.01 mg/kg/day	10
Lead	0.26 µg/kg/day Young Children 0.16 µg/kg/day Older Children and Adults (FDA 2018)	CDC Blood Lead Level (BLL)	The CDC BLL is based on the 97.5th percentile of blood lead level distribution in children	CDC BLL = 5 µg/dL; 0.16 µg/dL per 1 µg Pb/day conversion factor for children; 0.04 µg/dL per 1 µg Pb/day for women of childbearing age	10
Methylmercury	0.1 µg/kg/day (EPA 2001)	Mother-infant pairs in Faroe Islands (Grandjean 1997)	Neurophysical effects in offspring at 7 years old	1.3 µg/kg/day daily ingested maternal value to reach cord blood Hg concentration	Composite of 10 – uncertainty in cord blood estimates and pharmacodynamic variability and uncertainty
Chromium (III)	1500 µg/kg/day (EPA 1999)	Rats fed Cr_2O_3 bread (Ivankkovic & Preussman 1975)	Histological changes	NOAEL = 1,468 mg/kg/day	Composite 1000 – interspecies/ interhuman variability, database deficiencies
Chromium (VI)	3 µg/kg/day (EPA 1998)	Rats ingesting K_2CrO_4 water (Mackenzie 1958)	Pathologic changes in tissue	NOAEL = 2.5 mg/kg/day	Composite 900 – interspecies/ interhuman variability, less than lifetime exposure duration, concerns based on human studies

Table 2. Pivotal studies used to derive current U.S. regulatory reference values. Pivotal studies include studies that are critical to the calculation of a final regulatory standard or level, or to the quantified costs, benefits, risks, and other impacts on which a final regulation is based.

Total Background Levels of Heavy Metals

Metal/Metalloid	Food Intake Study	Food Intake Background Level	Water Intake Level*	Total Dietary Background Level
Inorganic Arsenic	Xue 2010	0.02 µg/kg/day	0.16 µg/kg/day	0.18 µg/kg/day
Cadmium	JECFA 2013	0.18 µg/kg/day	0.08 µg/kg/day	0.26 µg/kg/day
Lead	Spungen 2019 (children 1-3 yrs)	0.11 µg/kg/day Children	0.13 µg/kg/day Children^#	0.24 µg/kg/day
	JECFA 2011 (Adult)	0.03 µg/kg/day Adult	0.075 µg/kg/day Adults^##	0.11 µg/kg/day
Methylmercury	Xue 2012	0.02 µg/kg/day	0.03 µg/kg/day	0.05 µg/kg/day
Total Chromium	Moschandreas 2002	0.47 µg/kg/day	1.5 µg/kg/day	1.97 µg/kg/day

Table 3. Total background exposure level based on a combination of heavy metal exposure from food and water intake
*Water intake levels based on current EPA Maximum Contaminant Levels unless noted
^Median lead levels across 15 major U.S. cities derived from recent municipal water quality reports
Assuming an 11.4 kg 1-year old consuming 0.3 L of water
Assuming an 80 kg adult consuming 1.2 L of water

Comparison of Heavy Metal Reference Values

Heavy Metal/Metalloid	Current Reference Value*	Tran 2015 Reference Value
Inorganic Arsenic	0.3 µg/kg/day	0.3 µg/kg/day
Cadmium	1 µg/kg/day	0.83 µg/kg/day
Lead	0.26 µg/kg/day Children (11.4 kg 1 yr old)	6 µg/day (0-6y) 15 µg/day (7y+)
	0.16 µg/kg/day Adult (80 kg)	25 µg/day (pregnant/lactating) 75 µg/day (adults)
Mercury	0.1 µg/kg/day (MeHg)	0.57 µg/kg/day (inorganic Hg)
Chromium (III)	1500 µg/kg/day	250 µg/day
Chromium (VI)	3 µg/kg/day	0.9 µg/kg/day

Table 4. Comparison of reference values of heavy metals found in this study compared to then current values by Tran 2015 used in the Metal Dietary Screening Tool. *Reported in this work

Comparison of Heavy Metal Background Values

Heavy Metal/Metalloid	Current Background Value*	Tran 2015 Background Value
Inorganic Arsenic	0.18 µg/kg/day	0.285 µg/kg BW/day Default: 95% combined food + water (5% for tool use)
Cadmium	0.26 µg/kg/day	0.36 µg/kg/day
Lead	0.24 µg/kg/day Children	Total background assumed 50% of PTTI for vulnerable population; 1/3 of PTDI for adults
	0.11 µg/kg/day Adults	Total background assumed 50% of PTTI for vulnerable population; 1/3 of PTDI for adults
Mercury	0.05 µg/kg/day	0.127 µg/kg/day
Chromium (VI)	1.97 µg/kg/day	1.7 µg/kg/day Water contribution only, no food

Table 5. Comparison of background-exposure levels of heavy metals found in this study compared to then current values by Tran 2015 used in the Metal Dietary Screening Tool. *Reported in this work

Heavy Metal Screening Tool (HMST)

- The Heavy Metal Screening Tool (HMST) can be used as an aid for rapid risk assessments of heavy metals in food ingredients and food products
- Heavy metals included in the tool: arsenic, cadmium, lead, and mercury
- Utilizes updated reference values and background-exposure level results from this study, along with updated food consumption databases [Food Commodity Intake Survey (FCIS), National Health and Nutrition Examination Survey (NHANES), and Total Dietary Study (TDS) Foods] to provide information regarding consumption distribution and max allowable levels (ppm)
- Reference values incorporated into the HMST are derived from US regulatory agencies with background-exposure levels corresponding with appropriate age-matched values
- The new version is now web-based, making it more interactive and user-friendly
- The tool is hosted by the International Life Sciences Institute (ILSI) North America and Joint Institute for Food Safety and Applied Nutrition (JIFSAN) and will be available for public use in the near future

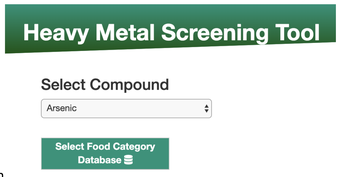

Figure 1. Heavy Metal Screening Tool – Step 1: Heavy metal selection

Summary & Conclusions

- Most heavy metals of concern are below their respective safe reference values
  - Arsenic, cadmium, and mercury background-exposure levels from food and water were found to be well below current safe US regulatory reference values
- Special consideration should be given for lead, especially in young children where the background-exposure level from food and water is nearly that of its reference value
- Chromium (III) and chromium (VI) were not considered to be a significant concern in foods, and thus, were not included as part of the Heavy Metal Screening Tool
- References values and background-exposure levels for heavy metals differ from those reported by Tran (2015), demonstrating the need for periodical updates
- Over time, reference values can change as new studies are published and scientific bodies re-assess and revise their recommended guidelines. Total dietary backgrounds can also shift with time as consumption trends and residue levels in food and water change.

Acknowledgements

I would like to acknowledge and thank the ILSI North America Staff, JIFSAN staff, as well as the Food Chemical Safety Fellowship Subcommittee of ILSI North America for their guidance and support throughout this project.

References:

- EPA. (2011). Exposure Factors Handbook. The United States Environmental Protection Agency. Washington, DC. (September). https://doi.org/EPA/600/R-090/052F
- Tran, N. L., Barraj, L. M., Scrafford, C., Bi, X., & Troxell, T. (2015). Partitioning of Dietary Metal Intake-A Metal Dietary Exposure Screening Tool. Risk Analysis, 35(5), 872–881. https://doi.org/10.1111/risa.12322