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Commentary

Metal Impurities in Food and Drugs

Darrell R. Abernethy,[1] Anthony J. DeStefano,[1,3] Todd L. Cecil,[1] Kahkashan Zaidi,[1] Roger L. Williams,[2] and the USP Metal Impurities Advisory Panel

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Abstract. The major metals of potential health concern found in food, drugs (medicines), and dietary supplements are lead, cadmium, mercury, and arsenic. Other metals, such as chromium, copper, manganese, molybdenum, vanadium, nickel, osmium, rhodium, ruthenium, iridium, palladium, and platinum, may be used or introduced during manufacturing and may be controlled in the final article as impurities. Screening for metals in medicines and dietary supplements rarely indicates the presence of toxic metal impurities at levels of concern. The setting of heavy metal limits is appropriate for medicines and is appropriate for supplements when heavy metals are likely or certain to contaminate a given product. Setting reasonable health-based limits for some of these metals is challenging because of their ubiquity in the environment, limitations of current analytical procedures, and other factors. Taken together, compendial tests for metals in food and drugs present an array of issues that challenge compendial scientists.

KEY WORDS: analysis; impurities; limits; metals; standards; US Pharmacopeia.

INTRODUCTION

The US Pharmacopeial (USP) Convention's Council of Experts has worked for several years to improve approaches in the *United States Pharmacopeia* (*USP*) for metals testing and control. As inorganic impurities, metals are one of three types of impurities (organic, inorganic, and residual solvents) that must be controlled in medicines and their ingredients (1) and, by extension, in certain foods and dietary supplements. The current *USP* test for metals is nonspecific and is insufficiently sensitive to control highly toxic metals at levels that present health concerns. A proposed *USP* compendial revision provides health-based (Permissible Daily Exposure, PDE) criteria for testing metals and establishing health-based limits.

In the current cycle (2005–2010), a Metal Impurities Advisory Panel* to the General Chapters Expert Committee in the Council of Experts working with USP staff has devoted considerable attention to these issues. The Advisory Panel began by evaluating modern instrumental techniques to detect metals of interest and then considered, on the basis of health concerns, which metals should be controlled and the associated control limits. This commentary focuses primarily on the establishment of PDE for lead, cadmium, mercury and arsenic, the broader process of selecting metals for update, and the establishment of health-based limits, along with a brief discussion of instrumental techniques that are capable of detecting or quantifying the metals at the required levels. The evolving standards (*USP* General Chapters describing limits and testing requirements for the selected metals in compendial articles) that will arise from recommendations of the Advisory

USP Metal Impurities Advisory Panel Members: Nancy Lewen (Chair), Timothy L. Shelbourn (Vice Chair), Charles Barton, Courtney M. Callis, Steven J. Dentali, Anna M Fan, Roland Frotschl, Assad Kazeminy, Richard Ko, Gregory C. Turk, Robert Wiens; Government Liaisons: Renee Blosser, FDA, Mamata De, FDA, Bruce A. Fowler, CDC, John F. Kauffman, FDA

**The views expressed in this paper are those of the authors and do not represent official positions of the US Food and Drug Administration, the Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry (CDC/ATSDR), or other US government bodies.

[1] Documentary Standards Division, US Pharmacopeia, Rockville, Maryland 20852-1790, USA.
[2] Chief Executive Officer, US Pharmacopeia, Rockville, Maryland 20852-1790, USA.
[3] To whom correspondence should be addressed. (e-mail: ajd@usp.org)

ABBREVIATIONS: ATSDR, Agency for Toxic Substances and Disease Registry; CDC, Centers for Disease Control and Prevention; cGMP, Current Good Manufacturing Practices; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; GFAAS, Graphite Furnace Atomic Absorption Spectroscopy; IARC, International Agency for Research on Cancer; ICP-OES, Inductively Coupled Plasma–Optical Emission Spectroscopy; ICP-MS, Inductively Coupled Plasma–Mass Spectroscopy; IPCS, International Program on Chemical Safety; IRIS, Integrated Risk Information System; JECFA, Joint Expert Committee on Food Additives; LOAEL, Lowest Observed Adverse Effect Level; MRL, Minimal Risk Level; NA, Not Applicable; ND, Not Determined; NOAEL, No Observed Adverse Effect Level; OEHHA, Office of Environmental Health Hazard Assessment; PDE, Permissible Daily Exposure; RfD, Reference Dose; USP, US Pharmacopeial Convention; WHO, World Health Organization.

Panel to the General Chapters Expert Committee may be reported at a later date. Deliberations of the Advisory Panel regarding metals of concern, limits for these metals, and methodology for their analysis were aided by an Institute of Medicine meeting (2).

THERAPEUTIC VALUE

Metals have been used as medicines through the ages. In 1820, the first *Pharmacopoeia of the United States of America* provided a listing of "simple medicines kept in the shop of the apothecary, but not necessarily prepared by him," including arsenious acid (white arsenic), antimony, bismuth, copper (various salts including copper sulfate or "blue vitriol"), iron, mercury, lead (various salts including lead subcarbonate or "white lead"), tin, silver, gold, and zinc (3).

In 1941 *The Pharmacological Basis of Therapeutics, 1st Edition,* included a series of arsenicals, antimony, mercurials, bismuth, zinc, copper, silver, gold, chromium, iron, magnesium, and selenium, all with designated therapeutic indications for various diseases (4). This textbook described in some detail the toxicities of these metal-containing drugs and included several instances in which the margin between therapeutic effect and toxicity is deemed insufficient to justify the use of certain metals.

At the present time, metals that are approved for therapeutic use in the US include aluminum, arsenic, bismuth, copper, iron, lithium, manganese, magnesium, and selenium (5).

METAL TOXICITY

A number of sources provide information about the toxicity of metals based on animal and human data and may be considered for use by regulatory and public health authorities. In addition to the published scientific literature, they include the following:

- Agency for Toxic Substances and Disease Registry (ATSDR) of the US Department of Health and Human Services (http://www.atsdr.cdc.gov/, accessed June 16, 2009)
- Integrated Risk Information System (IRIS) of the US Environmental Protection Agency (http://cfpub.epa.gov/ncea/iris/index.cfm, accessed June 16, 2009)
- World Health Organization (WHO) International Program on Chemical Safety (IPCS) (http://www.who.int/ipcs/en/, accessed June 16, 2009)
- Joint Expert Committee on Food Additives (JECFA) of the WHO and the Food and Agriculture Organization (http://www.who.int/ipcs/food/jecfa/en/, accessed June 16, 2009).
- State of California Office of Environmental Health Hazard Assessment (OEHHA) (http://oehha.ca.gov/, accessed June 16, 2009)—reproductive/developmental toxicity and carcinogenicity information for articles marketed in California (relative to Proposition 65)

Chemical-specific assessments that address the most current issues are also published by federal and state agencies.

The types of toxicity considered include acute, subchronic, and chronic, and the major concerns are related to neurotoxicity, nephrotoxicity, hepatic toxicity, cardiovascular effects, reproductive/developmental toxicity, neurodevelopmental toxicity, immunotoxicity, and carcinogenicity. In general, exposure limits for environmental media or dietary items are established for chronic or long-term exposure because of the anticipated long-term exposures or intakes. Such limits also will be protective for short-term exposures using standard risk-assessment methodology. Special situations may require limits for shorter-term exposures. Speciation of a metal can be important for toxicity characterization.

In the Institute of Medicine Meeting (2), there was a clear consensus that the most toxic and environmentally ubiquitous metals to focus on with respect to control in pharmaceutical ingredients were mercury, lead, cadmium, and arsenic. To this list were added the metal catalysts considered to be the most important by the European Medicines Agency (EMEA), less iron and zinc, which are essential minerals (6). An extensive review of the toxicity of these catalysts is presented in the EMEA Guideline. A brief discussion of the toxicity of these four most toxic metals follows.

Neurotoxicity

Chronic lead exposure, even at very low levels, has been associated with decreased intelligence quotient in children (7). Methyl mercury poisoning from eating contaminated fish in Japan and contaminated bread in Iraq resulted in parathesis, loss of gait coordination, slurred speech, sensory deficits, mental disturbances, and neurodevelopmental effects (8,9). More recent studies in fish-eating populations conducted in the Seychelles Islands, the Faroe Islands, and New Zealand showed that in utero exposure was associated with neuropsychological effects in the offspring (Environmental Protection Agency (EPA), 2001, http://www.epa.gov/ncea/iris/subst/0073.htm, accessed December 02, 2009). Combined exposure to methyl mercury and lead could certainly occur, but it is unknown if the toxicity is additive, synergistic, or targeted to unique cellular targets and unrelated. Methyl mercury is not an issue for medicines, where the typical form of mercury is mercuric but is present in some dietary supplements, such as fish oil.

Nephrotoxicity

Lead, cadmium, and mercury are nephrotoxic (10–12). Again, it is unclear how toxicity to combined exposures would manifest. When an individual is exposed to more than one metal that has the same or similar organ toxicity, present risk assessment models assume the toxins are additive in their effects, although this is based on limited data (13). In the case of chronic co-exposure to arsenic and cadmium, at least additive nephrotoxicity has been reported (14). At present, data are insufficient to support establishing science-based limits for specific articles based on combined multiple metal exposures with similar toxicities. Thus, at present, the metal limits will be treated individually.

Populations at Increased Risk

Metals as developmental neurotoxins are of particular concern during brain and nervous system development. Exposure of the prepartum mother and of the child during the neonatal and early childhood periods to lead as a prototype neurotoxic metal presents increased risk by comparison to exposure at later ages (7). For nephrotoxic metals,

individuals with pre-existing renal dysfunction are more susceptible than those with normal renal function (13,15). Similarly, individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (16,17). The limits described in Table I are set for healthy adults with a 50-kg body weight. For medicines or dietary supplements that are likely to be used in vulnerable patient groups, acceptable limits may be lower.

Selection of Metals for Update and Development of Health-Based Limits

An assessment of acceptable exposure for metals in food and drugs requires careful evaluation of the following:

1. Human (preferred if good-quality data are available) and animal toxicity data associated with exposure to the metal
2. Likelihood of presence of the metal in the article to be tested
3. Level and pattern of use or consumption of the article or product
4. Level of exposure to the metal
5. Other sources of exposure to the metal
6. Other factors that may affect toxicity (e.g., co-exposure to other metals)
7. Data quality and individual variability
8. Special populations at increased risk for toxicity.

These considerations and other factors form the basis for a risk-based approach for the selection of metals that should be controlled and their control limits. For example, if a metal catalyst was used during drug substance synthesis, some amount of the metal may be present in the drug ingredient, but concerns may be mitigated if the catalyst was not used during manufacture. Equipment used in the manufacture of the ingredients or the final product is another source of metal contamination. For pharmacopeial purposes, this source of contamination is considered a cGMP issue that is controlled by process validation. Some metals, such as lead, mercury, cadmium, and arsenic, are ubiquitous in the environment in appreciable quantities. These may add to the total exposure when consumers use drugs or consume dietary supplements that may contain the same metals and other metals of concern (18–21). Still, some dietary supplements and many drugs have been evaluated repeatedly over time, and no significant levels of metals of interest have been found (22,23).

At times, risk evaluation is complicated by the necessity to identify the species of the metal that is likely to be present. In the case of arsenic, mercury, and chromium, the metal species determines its toxicity (24). The International Union of Pure and Applied Chemistry definition of chemical species is "a specific form of an element defined as to isotopic composition, electronic or oxidation state, and/or complex or molecular structure." Inorganic arsenicals (As^{+3}, As^{+5}) are highly toxic, methyl arsenates are of limited toxicity, and

Table I. Limits of Metals for Pharmaceuticals

Metal	Oral Daily Dose PDE (μg/day)	Oral Component Limit (μg/g)[a]	Parenteral Component Limit (μg/g)[a]	Detection Limit, ICP–OES, (μg/g)[b,c]	Detection Limit, GFAAS, (μg/g)[b,c]	Detection Limit, ICP-MS, (μg/g)[c,d]
High Toxicity						
Arsenic (inorganic)	15	1.5	0.15	3.5	0.1	0.01
Cadmium	25	2.5	0.25	0.06	0.0008	0.002
Lead	10	1	0.1	2	0.04	0.003
Mercury (Hg^{+2})	15	1.5	0.15	3	0.6	0.001
Intermediate Toxicity						
Chromium III	250	25	2.5	0.3	0.05	0.02
Molybdenum	250	25	2.5	0.12	0.006	0.002
Nickel	250	25	2.5	0.6	0.05	0.02
Palladium	100	10	1.0	4	0.05	ND
Platinum	100	10	1.0	2	0.02	0.003
Osmium[e]	100 (Combination not to exceed)	10 (Combination not to exceed)	1.0 (Combination not to exceed)	2	NA	0.001[f]
Rhodium[e]				2	0.01	ND
Ruthenium[e]				5	1	ND
Iridium[e]				2	0.05	ND
Vanadium	250	25	2.5	0.78	0.1	0.004
Low Toxicity						
Copper	2500	250	25	0.2	0.001	0.01
Manganese	2500	250	25	0.05	0.005	0.02

[a] Assumes 10-g oral or parenteral dose
[b] Dean JA, ed. Lange's Handbook of Chemistry, 15th ed. New York: McGraw-Hill; 1999:7.29–7.33.
[c] All limits are Limits of Detection (3σ) corrected for a 1 g/100 mL dilution.
[d] Fernandez-Turiel JL, *et al.* Strategy for water analysis using ICP-MS. J Anal Chem. 2000;368:601–06.
[e] The sum of these four metals should not exceed the limits specified in this row.
[f] Tyutyunnik OA, Koshcheeva IYa, Orlova VA, Shumskaya TV, Gorbacheva SA. Determination of osmium traces in natural samples. J Anal Chem. 2004;59(9):885–88.

organic arsenicals such as arsenobetaine are nontoxic (25). In contrast, methyl mercury is highly toxic, Hg^{+2} is less toxic, and Hg^{+1} and metallic Hg^{0} have very limited toxicity (24). Chromium toxicity similarly depends on species: Cr^{+6} is highly toxic and carcinogenic, but Cr^{+3} is an essential trace element (26). Unless preparatory separations for these species are undertaken, the analytical method will simply detect total metal content, which may be unrelated to potential toxicity (27).

Plant-derived (botanical) dietary supplements may accumulate metals from the soil where they are grown or from other environmental sources, such as air or water. Similarly, animal- or mineral-based dietary supplements may contain metals associated with their local environments (Table II). Taking into account metals likely to be used as catalysts in manufacturing (6) and adding highly toxic metals that are ubiquitous in the environment (lead, mercury, cadmium, and arsenic) and other similarly distributed metals (35,36) allows categorization of metals based on health concern (Table I).

Development of Health-based Limits for Pharmaceuticals

The sources of toxicity noted above were used to develop a consensus oral permissible daily exposure (oral PDE) for each metal of interest in pharmaceutical products. In particular, the PDEs for the 12 medium- and low-toxicity metals in Table I are adopted from those presented in the recent EMEA guideline on the presence of residual metal catalysts in pharmaceuticals (6).

For arsenic, both the International Agency for Research on Cancer (IARC) and EPA classify inorganic arsenic as carcinogenic to humans (37,38). EPA Reference Dose (RfD) for chronic oral exposures, 0.3 μg/kg/day, is based on a no-observed-adverse-effect level (NOAEL) of 0.8 μg/kg/day and a lowest-observed-adverse-effect level (LOAEL) of 14 μg/kg/day for hyperpigmentation, keratosis, and possible vascular complications in a human population in Taiwan consuming arsenic-contaminated drinking water. Using the oral RfD of 0.3 μg/kg/day, an oral PDE of 15 μg/day based on a 50-kg person is derived.

For cadmium, the major effect is kidney damage producing tubular proteinuria. A concentration of 200 μg Cd/g wet human renal cortex is the highest renal level not associated with significant proteinuria (39). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) that results in 200 μg Cd/g wet human renal cortex (39). The toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 5 and 10 μg/kg/day from water and food, respectively. Thus, based on an estimated NOAEL of 5 μg/kg/day for Cd in drinking water and an uncertainty factor of 10, an RfD of 0.5 μg/kg/day (water) was calculated. An equivalent RfD for Cd in food is 1 μg/kg/day. Both values reflect incorporation of an uncertainty factor of 10. ATSDR determined that the adverse effect levels for renal effects were similar to those observed for skeletal effects, but the renal effects database was stronger and, therefore, was used for derivation of a chronic-duration oral Minimal Risk Level (MRL). Data were derived from select environmental studies worldwide that examined the relationship of urinary cadmium and the prevalence of elevated levels of biomarkers of renal function. The 95% lower confidence limit of urinary cadmium dose corresponding to the probability of exceeding the risk of low molecular weight proteinuria has been estimated as 0.5 μg/g creatinine, assuming accumulation over a 55-year period. This value corresponds to an intake of 0.33 μg/kg/day in females. Applying a safety factor of 3 for human variability, ATSDR has set the MRL at 0.1 μg/kg/day. Using the ATSDR MRL as the oral PDE yields a PDE of 5 μg/day.

The EPA has not developed an RfD for lead because it appears that lead is a nonthreshold toxicant, and it is not appropriate to develop RfDs for these types of toxicants. Instead, the EPA has developed the Integrated Exposure Uptake Biokinetic Model. In 1994, the FDA adopted an allowable level for lead at 5 ppb as a bottled water quality standard regulation (59 FR 26933). Assuming an average consumption of 2 L/day of the bottled water, the oral PDE is 10 μg/day for a 50-kg person.

With regard to mercury, as discussed above, the presence of methyl mercury in pharmaceutical products is extremely unlikely. Therefore, the EPA recommended RfD for mercuric chloride—0.3 μg/kg/day or 15 μg/day for a 50-kg person—is used as the oral PDE. The RfD was based on formation of mercuric-mercury–induced autoimmune glomerulonephritis in rats (EPA, last revised 1995, searched 2009, http://www.epa.gov/ncea/iris/subst/0692.htm). Because for oral products a 10-gram daily dose is assumed, the

Table II. Toxic Metal Impurities in Dietary Supplements

Mineral	Contaminating Metal Impurity	Levels of Metal Impurity	Reference
Calcium (bone meal, dolomite, fossil oyster shells)	Lead	0.6–190 ppm	(28)
Zinc	Lead	More than 1 μg/daily dose	(29)
Women's and children's vitamins	Lead	Median exposure 0.576 μg/daily dose	(30)
Tums chewable tablets	Lead	2.67 μg/daily dose	(29)
Vitamin Shoppe multivitamins Especially for Women	Lead	15.3 μg/daily dose	(31)
Botanical/other natural ingredient	**Contaminating metal impurity**	**Levels of metal impurity**	**Reference**
Panax pseudoginseng	Lead	48.6 ppm	(32)
Licorice extract	Arsenic	0.5 ppm	(33)
Ginkgo	Lead	12.5 μg/daily dose	(34)
Ginseng	Lead	9.2 μg/daily dose	(34)
St. John's Wort	Lead	5.8 μg/daily dose	(34)
Shark cartilage	Lead	1.4 ppm	(32)

maximum permissible metal concentration on a per-gram basis (μg/g) is one-tenth of the oral PDE. To account for the limited bioavailability of many metals after oral ingestion, for pharmaceuticals that are administered parenterally, a safety factor of 10 (the oral-route concentration is divided by 10) is applied to the metal PDE and is reflected as a factor of 10-fold decrease in concentration relative to the corresponding oral concentration in Table I.

The table, including elements and PDE, is subject to change as usage patterns change or as new toxicity data become available. For pharmaceuticals, high-toxicity metals that are ubiquitous in the environment must be verifiably absent above the limits noted in Table I. This could be established by determination of levels in ingredients that make up the product or by determination of levels in the product after manufacture. For metal catalysts, a specific catalyst must be verifiably absent above the limits noted when the catalyst was used in the manufacturing process. Metals of low toxicity not listed in Table I should be controlled in the context of current Good Manufacturing Practices (cGMP). A separate table will be reported in future communications to accommodate the elements and exposures associated with dietary supplements.

TESTING FOR METALS

Current Approaches

The first appearance of a pharmacopeial test for metals occurred in *USP VIII* (1905) and was titled "Time-Limit Test for Heavy Metals" (40). This was a nonspecific sulfide-precipitation method and was put forward as a screen for antimony, arsenic, cadmium, copper, iron, lead, and zinc. This test was modified in *USP XII* (1942) with the addition of a lead standard comparison solution (41). With various modifications, the test procedure remains official in *USP*'s General Chapter *Heavy Metals* <231> (42). It also can be required in dietary supplement food articles that indicate conformance to a *USP* monograph. Variants of this test are also the current standard in the *European Pharmacopoeia 6.0* Chapter 2.4.8 "Heavy Metals" (43), the *Japanese Pharmacopoeia XV* Chapter 1.07 "Heavy Metals Limit Test" (44), and the *International Pharmacopoeia* 4th Edition Chapter 2.2.3 "Limit Test for Heavy Metals" (45).

The nonspecific metals limit test in <231> has been criticized for 1) the large sample size required for analysis, 2) the lack of element-specific information, 3) the use of a visual comparison to the black precipitate of lead sulfide reference material, 4) the low recovery of essentially all the elements and lead standard during sample preparation if the sample is insoluble and requires heating or digestion, and 5) the safety and other issues associated with the generation of hydrogen sulfide in a laboratory setting. In the last decade and more, USP has issued calls to revise the metals test procedure described in <231> (46–48).

Modern Instrumental Methods

Many procedures have been developed for selective detection and quantification of metal species. Some procedures use excitation and emission phenomena to detect metals in intact material, such as X-ray fluorescence and neutron activation analysis. Other procedures separate the metals from the organic matrix. These procedures require an initial atomization and ionization process. This process is accomplished using flame, furnace, plasma, laser, or spark techniques. Once ionized, the metals are quantified using optical emission, chromatographic techniques, or mass spectrometry. These procedures are all options for the research laboratory, but in the manufacturing environment operating under cGMP, the list of possibilities is more limited. Because of the constraints with methods of sufficient sensitivity and selectivity for toxicologically based metal limits, analysts may find that electrothermal atomic absorption spectrometry, inductively coupled plasma–optical emission spectrometry (ICP-OES), and inductively coupled plasma–mass spectrometry (ICP-MS) are the most suitable procedures (47,48). The choice of analytical procedure depends on the solubility of the drug ingredient or dietary supplement and other components of the material (matrix). To provide guidance about the range of sensitivities of ICP-OES, ICP-MS, and graphite furnace atomic absorption spectrometry (GFAAS), Table I lists the approximate limits of detection for each element by each method.

CONCLUSION

The PDE and approaches described in this paper represent a substantial revision of the current pharmacopeial approaches to metals testing. Modern instrumental procedures offer the possibility of detecting all metals at levels below those corresponding to the listed PDE. Evolving standards for levels of metals in compendial drug products therefore must be clear about the choice of metals and specified PDE to avoid unnecessary testing. The risk-based approach presented in this communication provides a way forward. Evolution of the considerations of the Advisory Panel into compendial standards for *USP–NF* is in progress (see www.usp.org/hottopics/metals.html for periodic reports). The standards will be applied to drugs in *USP* and excipients in *NF,* as well as dietary supplements labeled to indicate conformance to *USP* standards.

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