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Toxic and Essential Trace Element Content of Commonly Administered Pediatric Oral Medications

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Toxic and Essential Trace Element Content of Commonly Administered Pediatric Oral Medications

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OBJECTIVES The aim of this study was to test the hypothesis that commonly administered pediatric oral medications are a significant source of toxic elements. The concentrations of 16 elements were determined in 14 frequently used pediatric oral medications.

METHODS Samples were prepared for analysis by dilution or nitric acid microwave-assisted digestion and analyzed by inductively coupled plasma mass spectrometry. The intake of each element from administration for 1 week of the medication's maximum recommended daily dose to 6-month-olds was calculated and compared to an exposure guideline for that element. Exposure guidelines used for adverse effects were minimal risk levels, oral reference dose, permissible or permitted daily exposure, provisional tolerable weekly intake, and tolerable upper intake concentrations. Exposure guidelines utilized for desired effect were adequate intake and recommended dietary allowance.

RESULTS Intake of the maximum recommended daily dose by 6-month-olds for 1 week would not deliver more than the exposure guideline of any of the elements, with the exceptions of chromium in several medications and zinc in the pediatric electrolyte solution, if it was consumed for 1 week.

CONCLUSIONS Consumed alone, these frequently administered pediatric oral medications would not deliver amounts of toxic elements that exceed established exposure guidelines for adverse effects, nor would most significantly contribute to adequate intake of essential elements.

ABBREVIATIONS ICP-MS, inductively coupled plasma mass spectrometry; US FDA, United States Food and Drug Administration; USP, United States Pharmacopeia

KEYWORDS aluminum; cadmium; lead; maximum allowable concentration; metals (heavy); oral medications; pediatric; recommended dietary allowances; trace elements

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Introduction

Infants are particularly susceptible to metal toxicity as a result of their immature organs. When exposed to toxic metals, infants exhibit increased gastrointestinal absorption, less effective renal excretion, and a less effective blood-brain barrier than are associated with adults.[1] In addition, their low body weight and high food consumption per kilogram of body weight put infants at risk for developing high concentrations of toxic metals.[1] Numerous agencies, including the World Health Organization, the US Environmental Protection Agency, the National Institutes of Health Office of Dietary Supplements, the US Food and Drug Administration (US FDA), and the US Department of Agriculture, have established guidelines for the safe intake of potentially toxic elements. Medications present a potential source of toxic metals to infants. The United States Pharmacopeia (USP) established limits for elemental impurities in USP <232>. In September 2015, the US FDA released Q3D Elemental Impurities Guidance for Industry that states the permitted daily exposure to impurities of some elements in drug products administered by the oral, parenteral, and inhalation routes.[2]

Toxic elements of concern for infant exposure from medications include aluminum, cadmium, and lead. Because they are not essential for humans, these elements present a risk with no potential benefit. Although the gastrointestinal tract provides a significant barrier to oral absorption of many potentially toxic elements, it is not a complete barrier. Oral bioavailability of aluminum is less than 1%; however, elevated plasma aluminum concentrations have been reported[3,4] in healthy infants given aluminum-containing antacids. Target organs of aluminum toxicity are the brain, skeletal system, and bone marrow.[5,6] Toxicity can be manifested as impaired cognitive development and function and in the absence of renal function can be manifested in a lethal encephalopathy, a low-turnover bone disease associated with osteomalacia, and a microcytic anemia. Oral bioavailability of cadmium is estimated to be 1% to 10% and is higher in young animals than in adult animals.[7] Cadmium is a nephrotoxicant and reproductive toxicant with the potential to produce osteomalacia.[7] Absorption of

Table 1. Other Elements Determined in this Study

Reference	Element	Potential Adverse Effects
Elements that are essential micronutrients or beneficial to the human		
11	Barium	Disruption of cardiac rhythm
12	Chromium	Pulmonary and myocardial toxicity
13	Cobalt	Thyroid gland enlargement
14	Copper	Liver damage
15	Magnesium	Diarrhea, nausea, and abdominal cramping
16	Manganese	Neurological deficits
17	Nickel	Gastrointestinal disturbances
18	Selenium	Peripheral anesthesia and pain
19	Vanadium	Diarrhea and hypoglycemia
20	Zinc	Gastrointestinal and hematological effects
Elements lacking evidence of essentiality for the human		
21	Silver	Gray or blue-gray discoloration of the skin, “argyria”
22	Strontium	Bone growth problems
23	Uranium	Nephrotoxicity

water-soluble lead by infants is estimated to be 40% to 50%, whereas it is 10% or less in adults.[8] Lead is a potent neurotoxicant that irreversibly affects central nervous system development, leading to reduced IQ and learning disabilities.[8,9] Oral bioavailability is factored into the risk assessment that generates permissible/permitted daily exposures, evidenced by the different exposure values for the oral and parenteral routes in USP 232 and the FDA’s Q3D Elemental Impurities Guidance for Industry.[2]

There is little information on the content of toxic metals in medications commonly administered to infants. This issue is reviewed in the “Discussion” section. This study addresses the information gap related to the content of toxic metals in medications commonly administered to infants and addresses the hypothesis that commonly administered pediatric oral medications are a significant source of toxic elements. This was accomplished by determining the concentrations of 16 elements, all having the potential to produce toxicity, 6 of which are known to be essential for the human, in 14 frequently used non-prescription and prescription pediatric oral medications. The medications selected for study were representative of the major categories of oral liquids that are frequently administered to infants. The categories were oral multivitamin drops, iron drops, pain and fever medications, fluoride supplements, antibiotics, and pediatric electrolyte solutions.

Elemental concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS), which is the most sensitive and widely used analytical method by which to quantitate elements.[10] This method combines a high-temperature (ICP) source with a mass spectrometer (MS). The ICP source atomizes the sample and then converts the atoms to ions, which are separated and detected by the MS. For a more detailed description, visit http://crustal.usgs.gov/laboratories/icpms/intro.html. The use of ICP-MS provided the opportunity to concurrently quantify numerous elements in addition to aluminum, cadmium, and lead. These are summarized in Table 1.

Materials and Methods

The studied medications, listed in Table 2, were purchased from the Kentucky Clinic Pharmacy (Lexington, KY). National Institute of Standards and Technology traceable multielement standards were purchased from Inorganic Ventures (Christiansburg, VA). Trace metal–grade nitric acid was purchased from Fisher Scientific (Pittsburgh, PA).

Sample Preparation. The procedures used to prepare pharmaceuticals as homogeneous liquids for ICP-MS element quantification are noted below. With the exception of the oral electrolyte solution, each sample was independently prepared in triplicate. A sample aliquot of 0.75 mL was pipetted into a 15-mL metal-free centrifuge tube from VWR International (Radnor, PA) with 0.75 mL of nitric acid. It was open vessel digested in a CEM MARS Xpress microwave following US EPA method 3015A, then diluted to 15 mL with 18.2 mΩ-cm water. Immediately prior to analysis, samples were diluted 5-fold with 18.2 mΩ-cm water, and an internal standard solution from Inorganic Ventures (Christiansburg, VA), containing approximately 1 mg/L each of scandium, germanium, yttrium, rhodium, indium, terbium, and bismuth was added. The oral electrolyte solution was diluted 5- and 10-fold with 18.2 mΩ-cm

Table 2. The Pediatric Oral Medications Studied

Product	Manufacturer	National Drug Code
Pediatric Electrolyte Oral Electrolyte Solution	Leader (distributed by Cardinal Health, Dublin, OH)	37205-0221-08
Q-PAP Infants' Drops Acetaminophen	Qualitest Pharmaceuticals (Huntsville, AL)	0603-0838-73
Children's Māpap Acetaminophen Liquid	Major Pharmaceuticals (Livonia, MI)	0904-1985-20
Infants' Advil Concentrated Drops	Pfizer Inc (Madison, NJ)	0573-0191-20
Children's Ibuprofen Oral Suspension, USP	Major Pharmaceuticals (Livonia, MI)	0904-5577-20
Penicillin V Potassium for Oral Solution, USP	Teva Pharmaceuticals (Sellersville, PA)	0093-4127-74
Amoxicillin for Oral Suspension, USP	Sandoz (Princeton, NJ)	0781-6041-46
Infants' Gas Relief Drops	Leader (distributed by Cardinal Health, Dublin, OH)	37205-119-10
Fer-iron drops	Rugby (Duluth, GA)	0536-0710-80
Tri-vitamin Drops	Rugby (Duluth, GA)	0536-8501-80
Polyvitamin Drops	Rugby (Duluth, GA)	0536-8450-80
Poly-Vita Drops	Major Pharmaceuticals (Livonia, MI)	0904-5099-50
Tri-Vit with Fluoride 0.25-mg Drops	Qualitest Pharmaceuticals (Huntsville, AL)	0603-1785-47
Sodium Fluoride Drops	Sancilio & Company Inc (Riviera Beach, FL)	44946-1032-8

USP, United States Pharmacopoeia

water in triplicate, and both dilutions were analyzed. Samples were analyzed by a 7500cx quadrupole ICP mass spectrophotometer from Agilent Technologies (Santa Clara, CA).

Analysis. Calibration and verification were performed using 2 independent lots of IV-ICPMS-71A multielement standards from Inorganic Ventures. Pre-digestion spike recovery, which measures recovery during the digestion procedure as well as analytical recovery, was determined by adding 50 mcL of the 10 mg/L calibration standard to the sample before digestion. Postdigestion spike recovery, which measures analytical recovery, was determined by adding 10 mcL of 10 mg/L standard to 5 mL of the 5-fold diluted sample.

Care was taken to minimize metal contamination, including use of metal-free centrifuge tubes, trace metal–grade nitric acid, and 18.2 mΩ-cm water. All dilution procedures were conducted in an International Standards Organization class 100 laminar flow hood. The method detection limit was calculated as 3 times the standard deviation of 7 reagent blanks. Analytical results not above the method detection limit were considered to be below the detection limit and were assigned 50% of the method detection limit.

Calculation of Element Amount. The following procedure was used to compare the concentration of each element in the studied medications to exposure guidelines. To determine if the amount of each element in each medication might present a health risk, its intake for 1 week from administration of the medication's

Table 3. Exposure Guidelines for Element Intake

Adequate intake	Established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy
Minimal risk level	Estimate of exposure level posing a minimal risk to humans
Oral reference dose	Obtained from the US EPA Integrated Risk Information System. A daily exposure estimate to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime
Permissible daily exposure	Determined by the USP. It is expressed in mcg/day for the administration of drug products to an average 50-kg person
Permitted daily exposure	Determined by the FDA. It is the maximum acceptable intake of elemental impurity in pharmaceutical products per day
Provisional tolerable weekly intake	An endpoint used for food contaminants, such as heavy metals with cumulative properties, representing permissible human weekly exposure
Recommended dietary allowance	Average daily intake sufficient to meet the needs of 97% to 98% of healthy individuals
Tolerable upper intake level	Maximum daily intake unlikely to cause adverse health effects

EPA, Environmental Protection Agency; FDA, Food and Drug Administration; RDA, recommended daily allowance; USP, United States Pharmacopeia

Table 4. Exposure Guidelines of the Studied Elements

Element	Guideline	Guideline value	Guideline intake*	Reference
Aluminum	Provisional tolerable weekly intake	2 mg/kg	15,200	The Joint Food and Agriculture Organization of the United Nations, World Health Organization Expert Committee on Food Additives, for all Al compounds in food[25]
Barium	Permitted daily exposure	1,400 mcg	9,800	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
	Oral reference dose	0.2 mg/kg/day	10,640	The US EPA Integrated Risk Information System, for chronic oral exposure based on an animal study[26]
Cadmium	Permissible daily exposure	25 mcg/day for a 50-kg person	26.6	USP <232>
		5 mcg	35	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
	Oral reference dose	1 mcg/kg/day	53.2	US EPA Integrated Risk Information System[27]
Chromium	Adequate intake	0.2 mcg/day	1.4	The NIH Office of Dietary Supplements, for zero to 6- mo-old[28]
	Permitted daily exposure	10,700 mcg	74,900	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Cobalt	Permitted daily exposure	50 mcg	350	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Copper	Permissible daily exposure	1000 mcg/day for a 50-kg person	1,064	USP <232>
	Adequate intake	200 mcg/day	1,400	The US Department of Agriculture Food and Nutrition Information Center recommended dietary allowance for zero to 12-month-old [29]
	Permitted daily exposure	3,000 mcg	21,000	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Lead	Permissible daily exposure	5 mcg/day for a 50-kg person	5.32	USP <232>
	Permitted daily exposure	1 mcg	7	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Magnesium	Recommended daily allowance	30 mg for zero to 6-month-old	210,000	The NIH Office of dietary supplements recommended dietary allowance for zero to 6-month-old[15]
Manganese	Tolerable upper intake level	2 mg/day for 1 to 3-yr-old	8,960	No tolerable upper intake level has been established for zero to 12-month-old by the US Department of Agriculture Food and Nutrition Information Center. The value for 1 to 3-yr-old was adjusted for the weight of 6-month-old[29]
Nickel	Permissible daily exposure	500 mcg/day for a 50-kg person	532	USP <232>
	Permitted daily exposure	200 mcg	1,400	The US FDA Q3D Elemental Impurities Guidance for Industry [2]
Selenium	Tolerable upper intake level	45 mcg/day	315	The NIH Office of Dietary Supplements for zero to 6-month-old[30]
	Permitted daily exposure	150 mcg	1,050	The US FDA Q3D Elemental Impurities Guidance for Industry[2]

EPA, Enviormental Protection Agency; FDA, Food and Drug Administration; NIH, National Institutes of Health; US, United States; USP, United States Pharmacopoeia

*as mcg/wk for a 7.6 kg child

Table 4. Exposure Guidelines of the Studied Elements (*cont.*)

Element	Guideline	Guideline value	Guideline intake*	Reference
Silver	Oral reference dose	0.005 mg/kg/day	266	US EPA Integrated Risk Information System oral reference dose[31]
	Permitted daily exposure	150 mcg	1,050	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Strontium	Oral reference dose	0.6 mg/kg/day	31,920	US EPA Integrated Risk Information System[32]
Uranium	Minimal risk level	0.0002 mg/kg/day	10.6	For 15 to 365 day oral exposure[23]
Vanadium	Permissible daily exposure	100 mcg/day for a 50-kg person	106	USP <232>
	Permitted daily exposure	100 mcg	700	The US FDA Q3D Elemental Impurities Guidance for Industry[2]
Zinc	Tolerable upper intake level	4 mg/day	28,000	The US Department of Agriculture Food and Nutrition Information Center, for zero to 6-month-old[29]

EPA, Enviormental Protection Agency; FDA, Food and Drug Administration; NIH, National Institutes of Health; US, United States; USP, United States Pharmacopoeia
*as mcg/wk for a 7.6 kg child

maximum recommended daily dose to 6-month-olds was calculated. Calculations were based on 7.6 kg, the average weight of a 6-month-old.[24] The calculated intake was compared to a guideline for exposure to that element. There is no single source or exposure guideline for all 16 elements determined in this study. Guidelines were obtained from multiple sources. They are described in Table 3. Guideline values for the studied elements are listed in Table 4. Given that there is more than one guideline for some of the tested elements, we compared the intake of that element by a 7.6-kg infant for 1 week to the lowest guideline value.

Results

Table 5 reports the pre- and postdigestion spike recovery results of the 16 studied elements. Spike recovery was variable, as low as 65% to 68% for lead and uranium and as high as 184% for selenium. Deviations from 100% recovery are addressed in the "Discussion" section.

Table 6 shows the exposure guideline intake for each element, selected from the guidelines summarized in Table 4, the concentration of each studied element in each medication, and the percentage of the lowest exposure guideline for 1 week's intake of the pediatric oral medication by a 7.6-kg child. The results provide toxic and essential trace element concentrations in commonly administered pediatric oral medications that pharmacists and others can incorporate into calculations of total element intake. If consumed at the maximum recommended dose for 1 week, which is much longer than its typical period of use, the pediatric electrolyte solution would provide the greatest amount of the greatest number of elements: barium, copper, magnesium, silver, strontium, uranium, and zinc. It would provide 200% of the Institute of Medicine's tolerable upper intake concentration of zinc. Fer-iron drops had the highest concentration of 9 of the elements: aluminum, chromium, cobalt, copper, lead, manganese, nickel, vanadium, and zinc. However, given the small amount of this medication that is administered, it did not always present the greatest percent of the intake guideline. The greatest percent of the intake guideline of aluminum would come from the Fer-iron drops, followed by the penicillin V potassium solution. Both would deliver less than 1% of the weight-adjusted provisional tolerable weekly intake of aluminum.[25] The greatest amount of cadmium would be delivered by the Infant's Advil concentrated drops, followed by the pediatric electrolyte solution, both delivering less than 2% of the USP guideline, adjusted for the weight of a 6-month-old infant. The penicillin V potassium for oral solution product would deliver the greatest percentage of the 6-month-old weight-adjusted USP guideline for lead of 4.4%, followed by the pediatric electrolyte solution that would deliver 2.7% of the guideline. Many of the medications provide adequate intake of the essential micronutrient chromium, 0.2 mcg/day, the guideline used in Table 6, but none approach the FDA's permitted daily exposure for acceptable intake of 10,700 mcg/day. None of the medications provided amounts close to 100% of the recommended daily allowance of magnesium, the greatest being the 4% provided by the pediatric electrolyte solution. Similarly, they do not provide close to 100% of the recommended dietary allowance for zero to 12-months-old of 200 mcg/day copper.[29] The greatest contribution of copper, 3.5%, would be provided by the pediatric electrolyte solution.

Many of the medications contain FD&C color addi-

Table 5. Pre and Postdigestion Spike Recovery Results*

	Predigestion	Postdigestion
Aluminum	95 ± 24	89 ± 5
Barium	106 ± 9	113 ± 2
Cadmium	110 ± 15	120 ± 6
Chromium	94 ± 17	90 ± 2
Cobalt	87 ± 17	90 ± 5
Copper	94 ± 19	115 ± 4
Lead	68 ± 11	72 ± 4
Magnesium	96 ± 7	92 ± 8
Manganese	83 ± 14	90 ± 5
Nickel	101 ± 16	113 ± 2
Selenium	174 ± 51	184 ± 22
Silver	88 ± 13	111 ± 2
Strontium	100 ± 12	110 ± 8
Uranium	65 ± 11	72 ± 4
Vanadium	76 ± 50	89 ± 6
Zinc	103 ± 16	140 ± 17

*Data presented as mean percent ± standard deviation

tives that have maximum allowable concentrations of chromium, lead, and manganese of 50, 10, and ≤ 100 mg/L, respectively,[33] as well as artificial and natural flavors that might contain metals. In the absence of declaration of the amount of FD&C color additives and flavors added, it cannot be determined if FD&C color additives significantly contribute to the measured metal concentrations in these products.

Discussion

The results shown in Table 6 indicate that commonly administered medications given in maximum therapeutic doses to 6-month-olds would generally result in the intake of trace elements well below their adverse effect exposure guidelines, shown in Table 4. These findings suggest there is no concern for element toxicity from these medications alone. The results also show that the medications do not significantly contribute to the required intake for essential elements, with the exception of chromium.

There are reports of concentrations of some of the trace elements that were measured in the present study in medicines given to infants and young children, which can be compared to the present results. The median aluminum concentration in 5% glucose solutions was 5 ng/g.[9] The aluminum concentration has been reported in numerous drugs,[34,35] but in only 3 medications similar to those used in the present study. The median aluminum concentration in electrolyte and flavored electrolyte solutions was 5 ng/g, comparable to the 6.2 mcg/L of the present study.[9] A ferrous sulfate solution contained 130 mcg/L aluminum.[34] The aluminum concentration was reported to be 11 and 36 mcg/L in 2 lots of Poly-vi-sol,[36] compared to 4900 and 3800 mcg/L in 2 generic equivalent products in this study. None of these medications would be expected to deliver more than 1% of aluminum's provisional tolerable weekly intake.[25] Although it has been noted that medications contribute to pediatric lead poisoning,[37] median lead concentrations in 5% glucose, electrolyte, and flavored electrolyte solutions were 0.14, 0.16, and 0.08 ng/g, respectively,[9] and were very low in the present study. Cadmium concentration in these 3 classes of products was 0.01 ng/g.[9]

In addition to commonly used oral medications, other sources can contribute the elements of the present study to their total intake by infants and young children. The US FDA permits aluminum in vaccines as an adjuvant, not to exceed 0.85 to 1.25 mg in an individual dose.[38,39] The aluminum concentration in parenteral nutrition components,[5] infant formula,[40] and foods[41] has been reviewed. Milk-based, cereal-based, and mixed infant formula from Turkey averaged ~7 ng/g lead, whereas cadmium concentrations were ~1, 9, and 5 ng/g, respectively.[42] Calculated daily intake of lead and cadmium from these infant formulae was below their acceptable intake limits. In contrast, 8 of the 63 formulae samples were calculated to deliver more aluminum than the provisional tolerable weekly intake of 2 mg/kg.[25] Several of the infant formulae delivered more than the recommended adequate intake amounts of the essential metals manganese and chromium, but none exceeded the tolerable upper intake concentration of manganese[29] or permitted daily exposure of chromium.[2] The infant formula with the highest cobalt concentration was calculated to deliver slightly more than the permitted daily exposure of cobalt.[2] There was sufficient chromium and zinc contamination of parenteral nutrition components to exceed administration recommendations,[43] but not to exceed the parenteral permitted daily exposure of chromium.[2] The largest total delivered zinc, 0.2 mg/kg/day parenterally, would slightly exceed the tolerable upper oral intake concentration of 4 mg/day for a zero to 6-month-old,[29] for this metal that is ~20% to 30% absorbed in persons with adequate nutritional concentrations.[20]

Extensive PubMed and SciFinder searches did not uncover any further reports of the contents of the 16 elements of the present study in conventional medications intended for infant and pediatric human use.

There are some limitations to this study. As noted in the "Results" section, spike recovery was variable and deviated from 100% for several metals. There was little difference between the pre- and postdigestion spike recoveries, suggesting the primary contributor to recovery deviation was analytical recovery rather than recovery during the digestion procedure. The common

Table 6. Element Exposure Guideline, Medication Element Concentration, and Percentage of Exposure Guideline*

	Aluminum	Barium	Cadmium	Chromium	Cobalt	Copper	Lead	Magnesium	Manganese	Nickel	Selenium	Silver	Strontium	Uranium	Vanadium	Zinc
Exposure guideline as mcg/wk	15,200	9800	26.6	1.4	350	1064	5.3	210,000	8960	530	315	266	31,920	10.6	106	28,000
Pediatric Electrolyte Oral Electrolyte Solution	6.2 0.29	2.5 0.18	0.065 1.7	1.3 660	0.87 0.000	5.3 3.5	0.021 2.7	1200 4.0	2.9 0.23	0.76 1.0	2.7 5.8	0.028 0.072	15 0.33	0.03 2.0	1.7 11	8000 200
QPAP Infants' Drops Acetaminophen	460 0.085	17 0.005	0.73 0.077	22 45	0.87 0.007	2.7 0.007	1.5 0.77	220 0.003	16 0.005	3.0 0.016	24 0.21	0.80 0.0084	8.0 0.0007	1.2 0.31	25 0.66	180 0.018
Children's Māpap Acetaminophen Liquid	650 0.31	3.7 0.003	0.54 0.15	21 110	1.2 0.026	1.7 0.011	1.5 0.96	140 0.005	16 0.013	16 0.22	24 0.54	0.80 0.022	8.0 0.0018	1.2 0.82	25 1.7	180 0.024
Infants' Advil Concentrated Drops Ibuprofen	280 0.064	7.0 0.002	15 1.9	13 32	0.87 0.009	4.4 0.014	1.5 1.9	1200 0.020	0.016 0.006	0.10 0.001	24 0.26	0.80 0.000	10 0.0011	1.2 0.39	25 0.83	260 0.032
Children's Ibuprofen Oral Suspension, USP	490 0.23	16 0.011	0.2 0.053	3.2 16	1.58 0.032	2.2 0.014	1.5 1.9	1600 0.055	16 0.013	1.7 0.023	24 0.52	0.80 0.020	55 0.012	1.2 0.78	25 1.7	200 0.051
Penicillin V Potassium for Oral Solution	620 0.66	23 0.038	0.73 0.44	27 306	0.87 0.040	49 0.75	1.5 4.4	16000 1.2	16 0.029	3.0 0.093	180 8.7	0.80 0.048	150 0.074	1.2 1.8	110 16	87,000 50
Amoxicillin for Oral Suspension	0.18 0. 25	16 0.034	0.54 0.42	20 310	0.87 0.052	3.9 0.076	1.5 5.8	690 0.069	16 0.038	8.1 0.32	24 1.6	0.80 0.063	13 0.0083	1.2 2.3	25 5.0	150 0.11
Infants' Gas Relief Drops	0.064 0.004	110 0.009	0.73 0.023	90 54	0.87 0.002	34 0.026	1.5 0.23	2700 0.011	16 0.002	10 0.016	24 0.062	0.80 0.0025	96 0.002	1.2 0.09	25 0.20	140 0.004
Fer-iron drops	35,000 0.99	27 0.001	8.1 0.13	14,000 4300	560 0.67	750 0.30	23 1.8	10000 0.020	70,000 3.3	7700 6.1	24 0.031	0.43 0.0007	120 0.0015	1.2 0.05	260 1.0	11,000 0.17
Tri-vitamin Drops	11,000 0.53	22 0.002	0.73 0.019	23 11	0.87 0.002	9.2 0.006	1.5 0.19	2100 0.007	8.6 0.001	2.4 0.003	24 0.052	0.80 0.0021	100 0.0023	1.2 0.08	25 0.17	250 0.006
Polyvitamin Drops	4900 0.22	74 0.005	0.73 0.019	24 12	120 0.23	5.7 0.004	1.5 0.19	910 0.003	16 0.001	6.6 0.009	24 0.052	0.80 0.0021	51 0.0011	1.2 0.08	25 0.17	230 0.006
Poly-Vita Drops	3800 0.18	66 0.005	0.2 0.005	19 9.6	130 0.25	3.3 0.002	1.5 0.19	330 0.001	16 0.001	1.8 0.002	24 0.052	0.80 0.0021	15 0.0003	1.2 0.08	25 1.07	260 0.007
Tri-Vit with Fluoride 0.25 mg Drops	64 0.003	9.0 0.001	25 0.66	31 16	18 0.035	45 0.029	1.5 0.01	190 0.006	13 0.001	34 0.045	70 0.15	0.80 0.000	34 0.0007	18 1.2	25 1.17	130 0.003
Sodium Fluoride Drops	64 0.003	19 0.001	0.73 0.019	3.2 1.6	0.87 0.002	2.6 0.002	1.5 0.19	1300 0.004	16 0.001	3.0 0.004	24 0.052	0.80 0.0021	32 0.0007	1.2 0.08	25 0.17	3.5 0.0001

*Element exposure guideline from Table 3; element concentration in the medication in mcg/L; and percentage of the element's exposure guideline based on the maximum medication dose taken for one week by a six month old. Shaded cells indicate all sample replicates were below the detection limit.

confounder for samples with low spike recovery, such as lead and uranium, seemed to be fluoride. Several metals form insoluble fluorides; the ratio between fluorine and the metal needs to be carefully controlled in these cases.

The spike recovery of some metals, notably selenium, was high. This is probably due to a polyatomic contribution from argon chloride, $^{37}Cl^{40}Ar$. In the plasma ion source of the ICP-MS a small percentage of the ions exist as polyatomic species rather than individual atoms. Because an argon plasma was used, polyatomic species containing argon were abundant.[44] In the case of selenium, the monitored m/z ratio (mass/charge ratio, in the case of an ion with a charge of +1, which in this case is >98% of the ions, is equal to the mass) of 77 for ^{77}Se overlaps with the polyatomic species $^{37}Cl^{40}Ar$. Chromium is similarly subject to severe polyatomic interferences. The monitored m/z ratios for chromium of 52 and 53 overlap with $^{12}C^{40}Ar$ and $^{13}C^{40}Ar$.

The recovery deviation results indicate that better quantification, digestion, and analysis methods may need to be optimized for each type of medication based on overall composition. There are no certified reference materials for trace element concentrations in pharmaceuticals that could be used to validate these results, so validation using an independent analytical technique or isotope dilution mass spectrometry would be helpful. Therefore, these results should be considered semiquantitative.

Given that none of the medications were calculated to contribute more than 10% of the guideline value for adverse element exposure, with the exception of 2 observations each for vanadium and zinc, the results do not support the hypothesis that commonly administered pediatric oral medications are sources of dangerous concentrations of the toxic metals and essential trace elements we analyzed. Although it is likely that other marketed generic and name-brand products would have different concentrations of the tested elements, with the exception of vanadium and zinc, they would have to have more than a 10-fold higher concentration to present an adverse element exposure. This could be tested by expanding the present study to include other marketed products. Furthermore, with the exception of chromium, the results show that none of the medications would contribute more than 10% of the guideline value for essential elements.

ARTICLE INFORMATION

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