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Bioaccessibility of As, Cd, Cu, Ni, Pb, and Sb in Toys and Low-Cost Jewelry

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ABSTRACT: Children can be exposed to toxic elements in toys and jewelry following ingestion. As, Cd, Cu, Ni, Pb, and Sb bioavailability was assessed (n = 24) via the in vitro gastrointestinal protocol (IVG), the physiologically based extraction test (PBET), and the European Toy Safety Standard protocol (EN 71-3), and health risks were characterized. Cd, Cu, Ni, and Pb were mobilized from 19 metallic toys and jewelry (MJ) and one crayon set. Bioaccessible Cd, Ni, or Pb exceeded EU migratable concentration limits in four to six MJ, depending on the protocol. Using two-phase (gastric + intestinal) IVG or PBET might be preferable over EN 71-3 since they better represent gastrointestinal physiology. Bioaccessible and total metal concentrations were different and not always correlated, indicating that bioaccessibility measurement may provide more accurate risk characterization. More information on impacts of multiple factors affecting metals mobilization from toys and jewelry is needed before recommending specific tests. Hazard index (HI) for Cd, Ni, or Pb were >1 for all six MJ exceeding the EU limits. For infants (6−12 mo old), 10 MJ had HI > 1 for Cd, Cu, Ni, or Pb (up to 75 for Cd and 43 for Pb). Research on prolonged exposure to MJ and comprehensive risk characterization for toys and jewelry exposure is recommended.

INTRODUCTION

Children are particularly sensitive to contaminant exposure due to their physiological and developmental properties and are exposed to toxic substances including metals via multiple pathways, i.e., food, air, water, and soil.[1−3] For children <6 years old, object mouthing is a common behavior and mouthing frequency and duration are especially high for infants (6−12 mo) and toddlers (1−3 y).[4−6] According to Farmakakis et al.,[7] toys were the most frequent cause of medical emergency situations due to aspiration or ingestion of inedible foreign bodies in Greek children, followed by coins and jewelry.

In the past, children's exposure to lead (Pb) via the ingestion of low-cost jewelry resulted in cases with serious acute or chronic adverse effects, including death.[8−10] Recent studies also show contamination with other toxic elements in various toys and especially in jewelry (with cadmium (Cd), and to a lesser extent copper (Cu), nickel (Ni), arsenic (As), and antimony (Sb)),[11] in plastic toys, and in modeling clay (with As, Cd, and Sb).[12] Toys and jewelry sold in North America may contain high levels of metals mainly due to lack of regulations for certain contaminants and inadequate enforcement of current ones.[13−15] Sources, presence, toxic effects, and mobilization potential of various contaminants in toys and low-cost jewelry have been already discussed in the reviews of Becker et al.[13] and Guney and Zagury.[15] Exposure of children to metals in toys and inexpensive jewelry via ingestion due to mouthing may significantly add to the present carcinogenic and non-carcinogenic risks from other sources.

Metals can be released from toy and jewelry matrices to gastric and intestinal fluids following ingestion. Significant amounts of metals may become bioavailable and harm various organs once having reached systemic circulation. Oral bioavailability is the fraction of a contaminant reaching the systemic circulation from the gastrointestinal tract after ingestion, and oral bioaccessibility is the fraction of the substance that becomes soluble in the gastrointestinal tract and is thus available for absorption.[16] Bioaccessibility can be used as an estimation of bioavailability, and when available, validated in vitro bioaccessibility tests might be preferred over in vivo bioavailability tests for their cost advantage and ethical considerations. A few studies have investigated the bioaccessibility of metals in toys and jewelry, concentrating mainly on Pb or Cd bioaccessibility in low-cost jewelry. Yost and Weidenhamer[17] used the U.S. Consumer Product Safety Commission (U.S.CPSC) test to determine accessible Pb in contaminated plastic jewelry (0.07 M HCl, no digestive enzymes). Total accessible Pb measured in nine items varied from 7.5 to 1290 μg per item. Weidenhamer et al.[18] investigated Cd bioaccessibility in contaminated jewelry using saline (representing saliva) and diluted HCl (ingestion) solutions. They found that Cd can leach to saline, and to a larger extent, to HCl solution. Brandon et al.[19] investigated

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Table 1. Concentrations of As, Cd, Cu, Ni, Pb, and Sb (Average [mg kg^{-1}] ± RSD [%]) in Low-Cost Jewelry and Toys

no.	item	description	As	Cd	Cu	Ni	Pb	Sb
1	MJ01	pewter ornament for scrapbooking	<4.51	***9.58*** ± *1*[a]	**2.68 × 10^{04}** ± *20*[b]	**2.50 × 10^{03}** ± *24*	***102*** ± *16*	139 ± *49*
2	MJ02	smiley face brads for scrapbooking	10.1 ± *3*	**180** ± *5*	142 ± *3*	***265*** ± *8*	**325** ± *9*	***211*** ± *10*
3	MJ03	pewter embellishments for scrapbooking	**431** ± *36*	**187** ± *4*	**1.25 × 10^{04}** ± *7*	**5.05 × 10^{03}** ± *6*	**4.36 × 10^{05}** ± *4*	**1.02 × 10^{03}** ± *58*
4	MJ05	pewter embellishments for scrapbooking	≤1.59[c]	***9.45*** ± *26*	**1.30 × 10^{04}** ± *2*	**2.28 × 10^{03}** ± *52*	***157*** ± *4*	25.0 ± *6*
5	MJ06	pewter embellishments for scrapbooking	1.57 ± *0*	***15.2*** ± *21*	**1.61 × 10^{04}** ± *12*	**3.23 × 10^{03}** ± *3*	***119*** ± *7*	17.5 ± *1*
6	MJ07	decorative metal beads for craft	3.56 ± *12*	1.40 ± *6*	**5.68 × 10^{05}** ± *2*	**9.20 × 10^{03}** ± *4*	**163** ± *10*	28.8 ± *5*
7	MJ08	bracelet with metal beads	***43.5*** ± *1*	**88.2** ± *0*	1.34 × 10^{03} ± *19*	**1.40 × 10^{04}** ± *1*	***86.1*** ± *46*	53.0 ± *0*
8	MJ09	decorative metal beads for craft	≤4.75	**263** ± *4*	**7.10 × 10^{05}** ± *21*	**1.10 × 10^{04}** ± *28*	**469** ± *4*	27.6 ± *7*
9	MJ10	bracelet with metal beads	<2.86[d]	***8.00*** ± *84*	**5.75 × 10^{05}** ± *0*	**8.24 × 10^{03}** ± *7*	***106*** ± *13*	23.2 ± *27*
10	MJ12	decorative pins for scrapbooking	***20.7*** ± *4*	**73.8** ± *5*	1.73 × 10^{03} ± *11*	**4.38 × 10^{03}** ± *3*	31.8 ± *38*	39.3 ± *16*
11	MJ13	decorative pins for scrapbooking	**56.8** ± *46*	**76.0** ± *1*	**3.16 × 10^{04}** ± *15*	**5.29 × 10^{03}** ± *36*	≤5.82	38.8 ± *33*
12	MJ14	jewelry piece - metal rose	**62.4** ± *0*	**203** ± *4*	***4.35 × 10^{03}*** ± *1*	5.94 ± *25*	**6.53 × 10^{05}** ± *11*	***272*** ± *33*
13	MJ15	jewelry piece - metal key	<4.76	**2.59 × 10^{05}** ± *14*	**1.36 × 10^{05}** ± *18*	**1.03 × 10^{03}** ± *69*	**1.08 × 10^{03}** ± *7*	60.7 ± *1*
14	MJ16	metal earring	<4.41	**1.66 × 10^{05}** ± *13*	**9.50 × 10^{04}** ± *8*	1.87 ± *23*	37.0 ± *16*	35.7 ± *16*
15	MJ17	jewelry metal pendant	<5.25	***12.7*** ± *70*	**1.58 × 10^{04}** ± *6*	≤1.74	***88.5*** ± *0*	38.6 ± *17*
16	MJ18	jewelry metal pendant	≤7.95	**3.67 × 10^{05}** ± *18*	**6.86 × 10^{04}** ± *85*	17.7 ± *62*	***100*** ± *1*	32.7 ± *43*
17	MJ19	bracelet beads	5.16 ± *2*	***8.62*** ± *41*	**1.53 × 10^{05}** ± *2*	24.1 ± *13*	10.7 ± *23*	***173*** ± *21*
18	MJ20	bracelet charm	≤5.36	**57.1** ± *74*	**9.79 × 10^{04}** ± *29*	≤1.42	<3.61	40.6 ± *21*
19	MJ24/2	bracelet - metal chain	**85.2** ± *5*	**82.5** ± *3*	**2.82 × 10^{04}** ± *3*	184 ± *3*	<3.33	48.2 ± *18*
20	MJ25	necklace - silver plastic	***15.7*** ± *15*	***17.5*** ± *3*	298 ± *39*	59.3 ± *47*	***85.2*** ± *4*	**631** ± *40*
21	PL02	eraser set shaped as food	***24.9*** ± *33*	0.23 ± *23*	10.8 ± *32*	1.37 ± *3*	***76.5*** ± *5*	***182*** ± *1*
22	PL05/1	jewelry design set - very small glass beads	**81.2** ± *22*	**771** ± *69*	19.2 ± *75*	2.99 ± *35*	≤8.03	18.1 ± *39*
23	PL05/2	jewelry design set - small glass beads	**207** ± *67*	**351** ± *19*	338 ± *7*	22.3 ± *57*	24.2 ± *92*	39.8 ± *69*
24	BP18	crayon set (tip and coating composite sample)	<1.46	**2.81** ± *10*	***301*** ± *15*	*25.1* ± *0*	<1.24	<1.17

[a]***Italic bold values*** indicate elevated total concentrations between 25% and 100% of the EU migration limit. [b]**Underlined bold values** indicate total concentration exceeding EU migration limit (see the text for limit values). [c]≤: Concentration analyzed in one or more of the replicates is below DL and the rest above DL. Average of measurements is given. [d]<: Concentrations analyzed in all replicates are below DL. Average of DL's is given.

bioaccessibility of different contaminants in consumer products by using a detailed physiologically based in vitro digestion model. They tested three toys (one finger paint and one chalk spiked with Pb, and one chalk contaminated by Pb) for Pb bioaccessibility (gastrointestinal bioaccessibility reported as 4.5−6.3% for finger paint, <1% for spiked chalk, 0.1−0.3% for contaminated chalk). Finally, Guney and Zagury[11] recently tested a limited number of samples (n = 4) and demonstrated that Pb and Cd in low-cost jewelry can become bioaccessible.

A systematic study investigating metal bioaccessibility in toys and low-cost jewelry in a large set of contaminated articles is missing in the literature. It is important to assess metal bioaccessibility in toys and low-cost jewelry and characterize risk for children when the following points are considered: children's significant exposure to metals from other sources, the extent of toy and jewelry contamination problem in North America, documented incidences and significant potential of exposure to contaminated items, and leaching potential of toxic elements from toys and low-cost jewelry in gastrointestinal tract. The objectives of this study are (1) to estimate gastrointestinal bioavailability of elements in selected contaminated items (n = 24) using three bioaccessibility protocols, (2) to evaluate and compare performances of protocols, and (3) to characterize the risks for children via oral exposure following ingestion.

EXPERIMENTAL SECTION

Sample Selection. Selected contaminated samples (n = 24) from a previously analyzed sample set[11] (n = 72) were tested to determine oral bioaccessibility. Samples belonged to the following categories: metallic toys and jewelry (MJ, n = 20), plastic toys (PL, n = 3), and brittle or pliable toys (BP, n = 1). MJ can have very high concentrations of metals. Low-cost jewelry can contain very high amounts of Pb or Cd,[11,17,18,20,21] and concentrations exceeding 80% (w/w) have been reported for many samples.[18−20] Pb, Sn, or Cu may come from leaded electronic waste which can be recycled for use in jewelry production.[22] Cd is used as a cheap substitute for banned Pb by manufacturers.[13] PL covers a wide variety of toys (including teethers and rattles) and may include metals used as stabilizers

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Table 2. Comparison of Three in Vitro Bioaccessibility Tests Used to Assess Gastrointestinal Bioavailability of As, Cd, Cu, Ni, Pb, and Sb

	IVG[a]	PBET[b]	EN 71-3[c]
test temperature	37 °C	37 °C	37 °C
presence of HCl	yes	yes	yes
presence of digestive salts and enzymes	yes	yes	no
mechanical agitation	yes (padded stirrer, at 100 rpm)	yes (padded stirrer, at 100 rpm)	no
volume of gastric solution	150 mL	100 mL	50 times (in mL) of sample's mass (in g)
gastric phase	yes	yes	yes
duration	1 h	1 h	2 h
pH of gastric phase	1.8	2.5	1.8
digestive compounds	HCl, NaCl, pepsin	HCl, pepsin, malate, citrate, lactic acid, acetic acid	HCl
intestinal phase	yes	yes	no
duration	1 h	4 h	
pH of intestinal phase	5.5	7.0	
digestive compounds	bile, pancreatin, Na_2CO_3	bile, pancreatin, Na_2CO_3	

[a]Rodriguez et al.[27] [b]Adapted from Ruby et al.[28] [c]British Standards[39]

during plastics production.[23] Finally, BP includes toys like play dough, carton puzzle, and chalk. One of the 24 items analyzed was selected from a list of previously screened toys for their metal content via XRF analysis (PL05), and five articles were similar to jewelry items previously recalled by Health Canada (samples MJ14-18).[24,25] All items were bought from the North American market: from dollar stores, toy shops, low-cost jewelry stores, retailer chains, and on the Internet.

Determination of Total Metal Content. For each sample, a part representative of a section of the item which may be subject to exposure was sampled and acid-digested. For the MJ category, the entire item was tested for MJ01, MJ02, MJ03, MJ05, MJ06, MJ12, and MJ13, whereas an intact part of an item (i.e., pendant from a jewelry) was used for the remaining articles (see Table 1 for detailed sample descriptions). Digestion was performed in duplicates via HNO_3 digestion on a hot plate, followed by optional additional digestion via $HClO_4$ or $HClO_4$/HF whenever necessary (Standard Method 3030).[26] Digestates and procedure blanks were centrifuged (5,000*g*), filtered (0.45 μm), diluted to 50 mL, and preserved at 4 °C until analysis. As, Cd, Cu, Ni, Pb, and Sb concentrations in the digestates were measured by ICP-OES with method detection limits (DLs) as (in $\mu g\ L^{-1}$); As, 19.5; Cd, 1.2; Cu, 2.4; Ni, 5.7; Pb, 16.6; Sb, 15.6. The concentrations of elements in toy/jewelry material (mg kg^{-1}) are presented in Table 1.

Determination of Oral Bioaccessibility. Samples were tested by using the in vitro gastrointestinal protocol (IVG, n = 24), the in vitro physiologically based extraction test (PBET, n = 12), and the protocol of European Standard on Safety of Toys for migration of elements (EN 71−3, n = 24; see Table 2 for test conditions and comparison). IVG[27] and PBET[28] are physiologically based in vitro bioaccessibility protocols mimicking the gastrointestinal conditions of infant physiology. These tests are conducted at 37 °C with the presence of digestive compounds, under controlled pH, and with mechanical agitation. The IVG protocol has been validated against in vivo studies to assess As, Cd, and Pb bioaccessibility for some soils, and is widely used in the assessment of metal bioaccessibility in soils.[27,29−34] Similarly, the PBET protocol has also been validated for various elements and is widely used to assess the bioaccessibility of metals in soils.[35−38] The EN 71−3 protocol[39] is a relatively more simple test (no in vivo/in vitro validation, only HCl is added, no mechanical agitation for testing glass/ceramic/metallic materials, no intestinal phase) used to determine the migration of As, Ba, Cd, Cr, Hg, Pb, Sb, and Se in different types of toy materials. It is a part of European Standard EN 71 which specifies safety requirements for toys. EN 71-3 is widely used for toy testing especially in Europe since this test is designed to verify compliance to migration limits stated in the European Toy Safety Legislation[40] (see Results and Discussion for values).

For all bioaccessibility tests, an entire item was tested for MJ01−06, MJ12, MJ13, and PL02 (varying mass). A 1 g sample was tested for PL05 and BP18, and an intact part of each item was tested for the remaining samples (i.e., pendant from jewelry, varying mass). The tests were performed in triplicates (except in duplicates for the samples MJ12−18) and six procedure blanks for each test were processed. Ten mL of sample was taken from each replicate and from the procedure blank both at the end of gastric phase (for gastric (G) bioaccessibility) and intestinal phase (for gastrointestinal (GI) bioaccessibility). After centrifugation (5000 × g) and filtration (0.45 μm), 1 mL of HNO_3 was added to the samples and they were preserved at 4 °C until analysis. The concentrations of As, Cd, Cu, Ni, Pb, and Sb were measured via ICP-OES. Then, migrated amounts (in μg) of elements (= elemental concentration × volume of gastric or intestinal liquid), as well as their migratable concentrations (in $mg.kg^{-1}$) of metals in toy/jewelry material (= migrated amount ÷ sample mass) were calculated (Tables 3 and 4).

Risk Characterization. Chemical daily intake (CDI, μg kg $bodyweight^{-1}\ d^{-1}$) was calculated assuming one time exposure to jewelry or toy sample (via the ingestion of an entire item, an intact part from entire item, or a mass of 1 g; depending on the sample) for the elements having significant bioaccessibility values (Cd, Cu, Ni, and Pb) according to the following formula:

$$\mathrm{CDI} = \frac{\mathrm{BAcc} \times \mathrm{EF}}{\mathrm{BW}} \quad (1)$$

where BAcc (μg) is the GI bioaccessible quantity of an element via one time exposure determined via the IVG or PBET protocols (Table 3), EF is exposure frequency (1 d^{-1},

Table 3. Gastric/Gastrointestinal Bioaccessible Quantities (in μg, mean (n = 3)) of Cd, Cu, Ni, and Pb in Selected Samples Measured via IVG, PBET, and EN 71-3 Protocols

	EN 71-3 (gastric)				IVG (gastrointestinal)				PBET (gastrointestinal)			
	Cd	Cu	Ni	Pb	Cd	Cu	Ni	Pb	Cd	Cu	Ni	Pb
MJ01	<0.11[a]	17.7	112	<0.87	<0.31	81.7	384	<2.50	<0.21	15.5	747	≤1.75
MJ02	1.13	<0.18	2.48	<0.85	5.53	1.41	15.2	<2.50	14.5	1.49	78.2	<1.67
MJ03	<0.33	≤0.84[b]	95.0	1.63×10^{03}	<0.31	21.3	535	1.43×10^{03}	≤0.22	29.4	533	1.26×10^{03}
MJ05	0.80	≤0.40	54.0	<1.05	<0.31	≤0.66	124	<2.49	≤0.26	2.52	231	<1.67
MJ06	<0.13	0.85	15.7	<1.04	<0.31	<0.51	83.3	<2.49	0.42	1.64	227	≤2.56
MJ07	<0.07	88.7	39.7	<0.57	<0.31	451	243	<2.50	<0.21	99.1	1.47×10^{03}	<1.67
MJ08	0.27	201	73.2	<0.83	<0.31	≤1.58	8.88	<2.49				
MJ09	1.66	774	10.5	<0.83	≤0.37	338	9.71	<2.50	≤0.49	624	18.0	<1.67
MJ10	0.44	298	97.6	<0.82	0.65	645	46.2	<2.50	0.44	731	73.1	<1.67
MJ12	0.80	0.67	19.8	<0.90	≤0.33	2.86	21.1	<2.50				
MJ13	≤0.12	18.5	17.9	<0.95	<0.31	41.6	55.9	<2.50				
MJ14	1.60	≤1.49	<0.50	112	<0.19	1.42	<0.37	705	0.45	11.7	<0.52	756
MJ15	96.5	2.54	2.53	<1.33	128	1.75	4.92	<2.50	139	9.89	13.0	<1.67
MJ16	13.0	29.2	0.49	<0.39	12.1	1.49	<0.78	<2.50	21.6	3.14	<0.52	<1.66
MJ17	<0.12	0.36	<0.32	<1.01	<0.31	5.08	≤1.56	≤2.83				
MJ18	172	5.31	1.21	<1.71	347	9.69	≤1.58	<2.49	286	34.0	1.43	<1.66
MJ19	<0.12	478	<0.29	<0.93	<0.31	217	≤1.72	<2.50				
MJ20	<0.07	1.91	<0.18	<0.58	<0.31	6.23	≤2.12	<2.50				
MJ24-2	<0.28	2.96	20.3	<2.24	<0.31	12.2	50.0	<2.49				
BP18	0.23	0.67	0.94	≤1.09	0.34	1.25	1.58	≤2.65				
SRM54d	21.8	12.9	<0.26	392	28.9	19.1	≤1.09	329	12.9	31.6	≤0.60	353

[a]<: Concentrations analyzed in all replicates are below DL. Average of DLs is given. [b]≤: Concentration analyzed in one or more of the replicates is below DL and the rest above DL. Average of measurements is given.

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Table 4. Gastric/Gastrointestinal Bioaccessible Concentrations (in mg kg^{-1}, mean (n = 3)) of Cd, Cu, Ni, and Pb in Selected Samples Measured via IVG, PBET, and EN 71-3 Protocols

	EN 71-3 (Gastric)				IVG (gastrointestinal)				PBET (gastrointestinal)			
	Cd	Cu	Ni	Pb	Cd	Cu	Ni	Pb	Cd	Cu	Ni	Pb
MJ01	<0.10[a]	16.0	106	<0.82	<0.32	83.0	***396***	<2.56	<0.21	15.7	***757***	≤1.77[b]
MJ02	1.09	<0.17	2.39	<0.82	5.35	1.34	14.6	<2.40	***13.7***[c]	1.40	73.8	<1.59
MJ03	<0.10	≤0.26	29.9	**502**[d]	<0.10	6.88	172	**423**	≤0.07	9.31	171	**366**
MJ05	0.63	≤0.32	42.5	<0.82	<0.24	≤0.51	97.1	<1.96	≤0.20	1.97	182	<1.31
MJ06	<0.10	0.67	12.4	<0.82	<0.24	<0.40	65.5	<1.96	0.33	1.28	178	≤2.00
MJ07	<0.10	128	57.6	<0.82	<0.45	652	***353***	<3.62	<0.30	143	**2.12 × 10[03]**	<2.40
MJ08	0.26	195	70.2	<0.82	<0.30	≤1.55	8.88	<2.47	-[e]			
MJ09	1.55	733	10.3	<0.82	≤0.38	351	9.71	<2.67	≤0.46	567	17.4	<1.78
MJ10	0.44	301	97.7	<0.82	0.65	645	45.9	<2.52	0.44	734	73.7	<1.67
MJ12	0.73	0.61	18.4	<0.82	≤0.34	2.89	21.8	<2.60				
MJ13	≤0.10	15.9	15.3	<0.82	<0.27	35.7	48.3	<2.15				
MJ14	0.83	≤0.82	<0.26	***57.9***	<0.18	1.34	<0.34	**647**	0.23	5.93	<0.27	**389**
MJ15	**60.2**	1.55	1.56	<0.82	**80.0**	1.07	3.05	<1.54	**85.5**	5.99	7.96	<1.03
MJ16	**26.7**	63.3	1.01	<0.82	**24.8**	3.10	<1.64	<5.25	**44.0**	6.64	<1.09	<3.49
MJ17	<0.10	0.29	<0.26	<0.82	<0.25	4.12	≤2.12	≤2.27				
MJ18	**81.5**	2.50	0.58	<0.82	**165**	4.60	≤0.77	<1.19	**136**	16.2	0.68	<0.79
MJ19	<0.10	420	<0.26	<0.82	<0.27	191	≤1.54	<2.19				
MJ20	<0.10	2.70	<0.26	<0.82	<0.43	8.30	≤2.81	<3.49				
MJ24-2	<0.10	1.06	7.56	<0.82	<0.11	4.39	18.2	<0.90				
BP18	0.22	0.66	0.92	≤1.07	0.34	1.23	1.56	≤2.62				
SRM54d	21.7	12.9	<0.26	390	28.9	19.0	≤1.09	328	12.9	31.6	≤0.60	353

[a] <: Concentrations analyzed in all replicates are below DL. Average of DL's is given. [b] ≤: Concentration analyzed in one or more of the replicates is below DL and the rest above DL. Average of measurements is given. [c] ***Italic bold values*** indicate bioaccessible concentration between 25% and 100% of the EU migration limit. [d] **Underlined bold values** indicate bioaccessible concentration exceeding EU migration limit (see the text for limit values). [e] (-): Sample not tested.

representing one time exposure), and BW is the mean body weight (9.2 kg for 6−12 mo-old infants, 11.4 kg for 1−2 yr-old toddlers, 13.8 kg for 2−3 yr-old toddlers, and 18.6 kg for 3−6 yr-old young children[5]).

A hazard index (HI, no unit) for oral exposure to elements via ingestion was calculated according to the following formula:

$$HI = CDI/RfD \quad (2)$$

where RfD is the reference dose (RfD for Cd:[41] 0.5 $\mu g.kg^{-1}\ d^{-1}$, suggested limit value for Pb exposure from toys:[42] 3.6 $\mu g\ kg^{-1}\ d^{-1}$, minimal risk level for Cu:[43] 10 $\mu g\ kg^{-1}\ d^{-1}$, RfD for Ni:[44] 20 $\mu g\ kg^{-1}\ d^{-1}$).

Quality Assurance/Quality Control. In order to assess the accuracy of the digestion method, one standard reference material (SRM54d, tin-base bearing metal) was analyzed in duplicate (reference values (%w/w): 7.04 for Sb, 3.62 for Cu, 0.62 for Pb, and 0.002 for Ni). The obtained results were consistent with the certified values (%w/w; 8.98 for Sb, 3.50 for Cu, 0.65 for Pb, and 0.004 for Ni; within 20% of the certified values for Sb, Cu, and Pb). In order to assess the reproducibility of the bioaccessibility protocols, the bioaccessibilities of selected elements (As and Cu for the IVG protocol, As and Pb for PBET protocol) in one standard reference material (SRM2710, Montana highly elevated trace element concentration soil) was determined in triplicate by using the IVG and PBET protocols. GI bioaccessibility of As and Cu according to the IVG protocol were 29.2% and 57.6%, respectively (relative standard deviation [RSD], ± 4.9% and ±7.1%, respectively). These values are comparable to the values reported by Pouschat and Zagury (As, 25.2%; Cu, 46.5%; standard deviations [SD], ± 0.3% and ±2.8%, respectively).[45,46] The GI bioaccessibility of As and Pb according to PBET were 23.0% and 22.1%, respectively (RSD, ± 7.4% and ±0.9%, respectively). These values are at the lower end of the As and Pb bioaccessibilities measured using PBET by five different laboratories as reported by Koch et al.[47] According to this study, the interlaboratory variability of As and Pb bioaccessibility for SRM 2710 was high, accompanied by high reproducibility RSDs (22−44% for As, 45−83% for Pb). SRM54d was also tested via the IVG, PBET, and EN 71-3 protocols to provide a basis of comparison for future studies. This reference material is mentioned in Health Canada's protocol C-08 (determination of migratable lead in consumer products) to be used as control sample[48] and therefore was considered suitable in this study to be analyzed via bioaccessibility protocols (results given in Tables 3 and 4).

Total metal concentrations in blanks from the digestion and bioaccessibility experiments were always below or very close to the method DLs. The RSDs of duplicates for each analyzed sample were calculated (see Table 1 for digestions, the RSD values for the bioaccessibility protocols were calculated but are not reported). The RSD values were less than 25% for the majority of the analyses. However, for some samples, results from duplicates showed larger differences. This was attributed to sample heterogeneity during sampling (samples had to be prepared from different sections of the same toy, or similar sections of two or more identical jewelry items were used) and/or to the variability of the chemical composition of different items of the same type. It has been already shown that individual samples of the same type of jewelry can vary greatly in terms of metals concentrations (i.e., individual samples tested for the same type of bracelet by different laboratories showed analyses of 99.1%, 67.0%, and 0.07% Pb [w/w]), indicating opportunistic use of source materials for jewelry[20]

and resulting in varying concentrations for different production batches.

RESULTS AND DISCUSSION

Metal Contamination in Toys and Jewelry. Total (Table 1) and bioaccessible concentrations of elements (Table 4) in 20 MJ, 3 PL, and 1 BP samples were compared to migration limits stated in the European Union (EU) Toy Safety Directive[40] as well as to the recently introduced total Cd limit (100 mg kg^{-1}) in jewelry.[49] These limits were used since the EU Toy Safety Directive provides a more comprehensive approach to the chemical safety of toys than North American legislations due to its scientific basis, the large number of selected contaminants, and separate limits defined for different categories.[15] Migratable concentration limits defined in this directive are (in mg kg^{-1}); As:47, Cd:23, Cu:7,700, Ni:930, Pb:160, Sb:560, (in scraped-off toy material, applicable to the categories MJ and PL in this study); and, As:3.8, Cd:1.9, Cu:622.5, Ni:75, Pb:13.5, Sb:45 (lower limits defined for dry, brittle, powder-like or pliable toy material; applicable to the category BP). When the total concentration of an element in a toy exceeds the EU migration limit, it can be said that further migration analysis is necessary to determine whether exposure to this toy is safe or not. Also, in the following discussion, the total concentration of an element was stated as elevated if it was between 25 and 100% of the limit value.

The samples analyzed in this study were mainly contaminated by highly toxic Cd (number of samples with elevated concentrations, 22; number of samples exceeding the EU limit, 15) and Pb (elevated, 15 samples; exceeding, 6 samples). As, Cu, Ni, and Sb contamination was also present in some samples (elevated, 10, 17, 13, and 6 samples, respectively; exceeding, 6, 15, 11, and 2 samples, respectively). In some items, the total Pb and Cd concentrations exceeded the EU limits up to several thousand times (Pb concentrations up to 65% (w/w) and Cd as high as 37% (w/w) in jewelry). In addition to Pb and Cd, some MJ items also had very high concentrations of Cu and Ni. All samples except PL02 (eraser shaped as food) had at least one elemental concentration among six exceeding the EU limit. The sample PL02 could also be categorized in the BP category. If done so, the contamination in this item exceeds the lower EU limits specially defined for the BP category. Finally, the EU limit for total Cd (100 mg kg^{-1} in jewelry)[49] was exceeded in seven MJ.

When the U.S. and the Canadian limits are considered (which regulate only total Pb and Cd concentrations in toys and/or jewelry), it was found that 11 MJ samples exceeded the U.S. and the Canadian Pb limit (100 and 90 mg kg^{-1}, respectively).[50,51] The U.S. limit for total Cd (300 mg kg^{-1} in children's jewelry, when exceeded further migration analysis is necessary to ensure extracted Cd quantity via EN 71-3 is less than 200 μg)[52] was exceeded in three articles (jewelry items MJ15, MJ16, and MJ18; 200 μg limit exceeded only in MJ18 (see Table 3 for results)). The Canadian Cd limit (130 mg.kg^{-1} in children's jewelry)[53] was exceeded in seven items.

Bioaccessibility of As, Cd, Cu, Ni, Pb, and Sb. According to the results for the oral bioaccessibility of six elements (Tables 3 and 4), Cd, Cu, Ni, and Pb were present above DLs in gastric and intestinal fluids from 20 of 24 samples. Arsenic was below DL in all gastric and intestinal extracts, and Sb was present in low concentrations in two samples (MJ02 and MJ05, maximum bioaccessible concentration: 15.7 mg kg^{-1} according to IVG, a value well below the EU limit). Therefore, the results for these elements were not presented. Also, results for MJ25 (plastic jewelry), PL02 (eraser set), PL05/1, and PL05/2 (glass beads from a children's jewelry design set) were not included in Tables 3 and 4 since the concentrations of all six elements in gastric and intestinal fluids were below DLs.

The results from the IVG protocol showed that the bioaccessible concentrations of Cd exceeded the EU limit of 23 mg kg^{-1} in MJ15, MJ16, and MJ18 (jewelry items, having the highest total Cd concentrations among all samples). Pb bioaccessible concentrations were above the EU limit of 160 mg kg^{-1} in MJ03 and MJ14 (one metallic embellishment and one jewelry, having the highest Pb total concentrations among all samples). Ni bioaccessible concentrations were elevated (25−100% of the EU limit of 930 mg.kg^{-1}) in MJ01 and MJ07 (two metallic toys).The values for bioaccessible Cu were well below the EU limit. In summary, five items were found to exceed the EU standard limit values for Cd or Pb.

Twelve items were tested using the PBET protocol, and they gave similar results to the ones obtained via the IVG protocol. GI bioaccessibility values exceeded the EU limits in the same five articles for Cd (MJ15, MJ16, and MJ18) and Pb (MJ03 and MJ14). Similarly for Ni, bioaccessible concentration was elevated for MJ01. Furthermore, it exceeded the EU limit for MJ07. Bioaccessible Cu in all samples was well below the EU limit. Overall, six items had bioaccessible concentrations exceeding the EU limits for Cd, Ni, or Pb.

The more simple gastric-only EN 71-3 protocol generally yielded bioaccessible metal concentrations lower than IVG and PBET protocols. However, for Cd, the same articles (MJ15, MJ16, and MJ18) had bioaccessible concentrations exceeding the EU limit, with values being generally lower than the ones provided by the other two protocols. For Pb, bioaccessible concentration in MJ03 exceeded the limit, but not in MJ14 (elevated concentration). Bioaccessible Ni and Cu in all samples were well below the EU limits. In summary, four samples exceeded the EU standard limits for Cd or Pb, when the EN 71−3 protocol was used. Lower results in terms of bioaccessible concentrations could be attributed to the absence of mechanical agitation, intestinal phase, and digestive enzymes in this protocol.

For the IVG and PBET protocols, the G and GI bioaccessibilities of four metals were compared via paired-sample *t*-test using the results for samples having bioaccessibility values above DL. For the IVG protocol, the difference between G and GI bioaccessibilities was significant for Ni (average, in mg kg^{-1}, 96.5 for GI vs 79.2 for G; $n = 13$; $p < 0.05$) and for Cu (average, in mg.kg^{-1}, 134 vs 89.4; $n = 15$; $p < 0.1$). For the PBET protocol, GI bioaccessibility exceeded G for all four metals, but the difference was significant only for Cu (average, in mg kg^{-1}, 168.8 vs 40.6, $n = 9$; $p < 0.1$). Although the differences were not statistically significant for all samples, GI bioaccessibility was higher than G in many samples for IVG and especially for PBET. Therefore, it can be said that conducting a two-phase (gastric and intestinal) bioaccessibility test could be safer than using only the gastric phase of that test while assessing oral metal bioaccessibility from jewelry and toys.

Comparison of Tests. A regression analysis was performed to compare the EN 71-3, IVG, and PBET protocols by using the overall bioaccessibility data for sample pairs with values above DL. Also, two-tailed paired-sample *t*-test was used to check the null hypothesis that the mean of data set pairs from different protocols are statistically similar. These analyses were done for the results of Cd, Cu, Ni, and Pb between IVG−EN

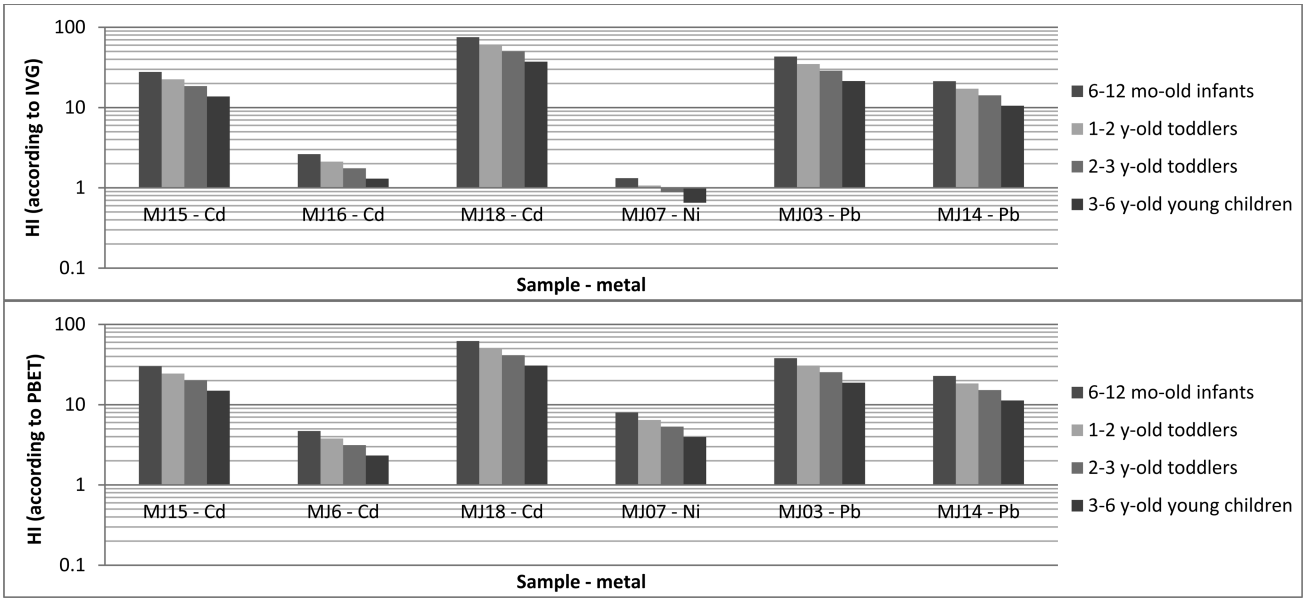

Figure 1. Hazard index (HI) values for selected samples and metals (n = 6, according to IVG and PBET protocols) from oral exposure to contaminated metallic toys and jewelry for 6−12 mo-old infants, 1−2 yr-old and 2−3 yr-old toddlers, and 3−6 yr-old young children.

71-3, PBET−EN 71-3, and PBET−IVG pairs (a total of 12 analyses for four metals and three test pairs). Overall, the tests were compared below only considering the results for Cd, Cu and Ni since the degrees of freedom for Pb was low (n = 2).

The regression analysis yielded fits between test pairs with moderate to very high R^2 values and low y-intercepts with the only exception of PBET−EN 71-3 pair for Ni (Cd, R^2 between 0.923 and 0.954, n between 6 and 7, $p < 0.005$; Cu, R^2 between 0.313 and 0.665, n between 9 and 14, $p < 0.05$; Ni, $R^2 = 0.344$ for IVG−EN 71-3 pair [n = 13, $p < 0.05$], and $R^2 = 0.634$ for PBET−IVG pair [n = 9, $p = 0.01$]). This indicated a good fit and related results between test pairs. Also, overall, none of the t values between test pairs were large enough to show a significant difference, meaning that tests did not differ from each other when predicting bioavailabilities (with the only exception of PBET−EN 71-3 pair for Ni, $p < 0.1$). This has been found notable given the fact that these tests have different final pH values (5.5 for IVG, 7.0 for PBET, and 1.8 for EN 71-3). Lower metal solubility for the IVG and PBET protocols could be expected at the end of intestinal phase due to higher end pH, in comparison to the metal concentrations at the end of the gastric-only EN 71-3 protocol. The presence of organic molecules in gastrointestinal fluids in IVG and PBET may be responsible for sustained metals solubilization during the intestinal phase via organic ligands formation.

The individual results for selected samples and metals were also compared by using student's t-test and considering the values from replicate analyses (for Cd, MJ15, MJ16, MJ18; Cu, MJ07, MJ09, MJ10; Ni, MJ01, MJ03, MJ07; Pb, MJ03, MJ14; samples with high metal bioaccessibility leading to HI > 1 as discussed in the next section). The analyses were performed between IVG−EN 71-3, PBET−EN 71-3, and PBET−IVG pairs (results for eleven samples used, three test pairs, a total of 33 analyses done). The results indicated significant differences ($p < 0.05$) between the measured bioaccessibilities of Cu (MJ07 for EN 71-3−IVG and IVG−PBET pairs, MJ10 for EN71-3−PBET pair), Ni (MJ01 and MJ07, all three pairs), and Pb (MJ14, all three pairs). In total, 12 of 33 tests indicated a significant difference between measured concentrations via different bioaccessibility tests in the same sample for the same metal. In other words, different bioaccessibility tests predicted different bioavailability for some of the selected metallic toys and low-cost jewelry. Since no study has been conducted on the use and validation of in vitro bioaccessibility tests regarding toy and inexpensive jewelry testing, it is not possible to conclude on the accuracy of the measured values or to recommend one test among the others. This being said, EN 71-3 is not physiologically based and has not been subjected to in vivo−in vitro validation studies. Moreover, since EN 71-3 has the potential to underestimate bioaccessibility as discussed above, it could be safer to use a two-phase bioaccessibility test like IVG or PBET for the assessment of bioaccessibility of potentially toxic elements in jewelry and toys. However, more information is needed about the impacts of multiple factors impacting mobilization of metals in body fluids (i.e., item-to-item variation in electroplating, effect of item damage [due to biting behavior of children or damage from normal use]) before specific tests can be recommended with higher confidence.

Comparison of Total and Bioaccessible Concentrations of Metals. A regression analysis was performed by using the total metal and the bioaccessibility data from the IVG protocol for samples with values above DL. For Cd ($R^2 = 0.833$, $C_{bioaccessible} = 0.00036 \times C_{total} + 2.97$, n = 6, $p = 0.011$) and Cu ($R^2 = 0.804$, $C_{bioaccessible} = 0.00086 \times C_{total} + 10.7$, n = 17, $p < 0.001$), total and bioaccessible metal concentrations were correlated. However, it should be noted that total metal concentration data distribution is definitely far from normal distribution, and has values with unproportionately higher weight in regression analysis which can affect the quality of the regression and the subsequent comparison (Table 1). For example, for Cu, when the highest three total metal concentration and its corresponding bioaccessibility values were removed from the regression, R^2 decreased to 0.230.

For Ni, total and bioaccessible metal concentrations had no apparent relationship ($R^2 = 0.0001$, $C_{bioaccessible} = 0.00036 \times C_{total} + 94.6$, $p = 0.970$, n = 13). Especially for Ni, and also for Cd and Cu in some samples, total concentrations failed to accurately predict bioaccessible concentrations. Finally for Pb, it

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was not appropriate to draw conclusions due to low number of data points ($n = 3$). Since total and bioaccessible concentrations are different and do not always well correlate, total concentration may not be a good indicator of metal bioavailability for toys and low-cost jewelry. Therefore, bioaccessibility testing is recommended to estimate bioavailability when assessing risk from exposure to toys and inexpensive jewelry rather than evaluating the risk based on total concentrations.

Risk Characterization. The results of the risk characterization (Figure 1) performed for six samples with total metal concentrations exceeding the EU migration limits for Cd, Ni, and Pb showed that one time exposure to these items may lead to HI values exceeding 1. For items contaminated by Cd (jewelry articles MJ15, MJ16, and MJ18) and Pb (metallic toy MJ03 and jewelry piece MJ14), HI values calculated using the bioaccessible quantities measured via the IVG and PBET protocols were both similar and very high. For Ni-contaminated MJ07 (craft beads), HI values were higher than 1 according to the results of both tests for 6−12 mo old infants and 1−2 y old toddlers. For 2−3 y old toddlers and 3−6 y old young children, HI values were above 1 according to the results from PBET but not from IVG. Due to their lower mean body weight, 6−12 mo old infants had the highest HI values among the four age groups.

Back calculations using the formula 1, accounting for the mean body weight of 6−12 mo old infants, and taking HI = 1 yielded limit bioaccessible quantities of 4.6 μg for Cd, 92 μg for Cu, 184 μg for Ni, and 33.1 μg for Pb. In other words, exceeding these bioaccessible quantities will yield HI values >1 for 6−12 mo old infants in case of oral exposure via ingestion. When compared to the bioaccessible quantities measured via the IVG and PBET bioaccessibility protocols (Table 3), these values (for both tests) were exceeded in four items for Cd (for MJ02, in addition to previously discussed MJ15, MJ16, and MJ18 which were identified as hazardous according to the EU limit), three items for Cu (for MJ07, MJ09, and MJ10), three items for Ni (for MJ01 and MJ03, in addition to previously identified MJ07), and two items for Pb (for previously identified MJ03 and MJ14). In summary, 10 of 20 articles in MJ category had HI > 1 and thus could be hazardous to 6−12 mo old infants in the case of oral exposure following ingestion.

It should be finally noted that HI values presented here are appropriate when based on the assumption that exposure duration to ingested items is around typical average digestion time for food for children, resulting in an orocoecal (from ingestion to the large intestine) transit time close to 5 h.[28] This exposure time is roughly represented by one bioaccessibility test. In other words, following ingestion, a small contaminated item rests in the gastrointestinal tract for a certain limited time and then is eliminated from the body. However, in some cases, contaminated jewelry can stay in the gastrointestinal tract for longer times following ingestion.[9,10] In this case of prolonged exposure, the risk will be higher. Research on prolonged exposure to contaminated metallic toys and jewelry is therefore recommended. Furthermore, a more detailed risk assessment for exposure to contaminated toys and jewelry considering additional pathways (i.e., the mobilization of metals in saliva) as well as variability and uncertainty of different exposure parameters (i.e., mouthing time, body weight, etc.) is also recommended.

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Notes

The authors declare no competing financial interest.

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