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CO-EXPOSURE TO METHYLMERCURY AND INORGANIC ARSENIC IN BABY RICE CEREALS AND RICE-CONTAINING TEETHING BISCUITS

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Abstract

Background—Rice is an important dietary source for methylmercury (MeHg), a potent neurotoxin, and inorganic arsenic (As), a human carcinogen. Rice baby cereals are a dietary source of inorganic As; however, less is known concerning MeHg concentrations in rice baby cereals and rice teething biscuits.

Methods—MeHg concentrations were measured in 36 rice baby cereals, eight rice teething biscuits, and four baby cereals manufactured with oats/wheat (n=48 total). Arsenic (As) species, including inorganic As, were determined in rice baby cereals and rice teething biscuits (n=44/48), while total As was determined in all products (n=48).

Results—Rice baby cereals and rice teething biscuits were on average 61 and 92 times higher in MeHg, respectively, and 9.4 and 4.7 times higher in total As, respectively, compared to wheat/oat baby cereals. For a 15-g serving of rice baby cereal, average MeHg intake was 0.0092 μg day^{-1} (range: 0.0013–0.034 μg day^{-1}), while average inorganic As intake was 1.3 μg day^{-1} (range: 0.37–2.3 μg day^{-1}). Inorganic As concentrations in two brands of rice baby cereal (n=12/36 boxes of rice cereal) exceeded 100 ng/g, the proposed action level from the U.S. Food and Drug

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Administration. Log_{10} MeHg and inorganic As concentrations in rice baby cereals were strongly, positively correlated (Pearson's rho = 0.60, p<0.001, n=36).

Conclusions—Rice-containing baby cereals and teething biscuits were a dietary source of both MeHg and inorganic As. Studies concerning the cumulative impacts of MeHg and inorganic As on offspring development are warranted.

Keywords

neurodevelopment; carcinogen; baby rice; methylmercury; inorganic arsenic

INTRODUCTION[1]

Methylmercury (MeHg) is a potent neurotoxin; the fetal period is considered the most sensitive exposure window, while young children are a secondary population of concern [U.S. Environmental Protection Agency (U.S. EPA), 1997]. Fish ingestion is the primary dietary source of MeHg [National Research Council (NRC), 2000]. Fish tissue is also a rich source of beneficial nutrients, including omega-3 fatty acids, which benefit offspring neurodevelopment (Innis, 2007). Rice ingestion is an important exposure pathway for MeHg (Feng et al., 2008; Hong et al., 2016). Most rice is cultivated in flooded rice paddies, where anaerobic microbes convert less toxic inorganic mercury (Hg) to MeHg, which is bioaccumulated in rice grain (Windham-Myers et al., 2014). In a comprehensive review of 51 studies reporting rice Hg concentrations (Rothenberg et al., 2014), the highest quintile of rice MeHg (10.5–57.7 ng/g) was 5.2–29 times lower than the maximum acceptable MeHg level in fish (300 ng/g) (U.S. EPA, 2001a). However, rice does not contain the same beneficial nutrients as fish, and therefore MeHg's toxicity from rice may differ from fish (Rothenberg et al., 2011a, 2014).

Rice is also an important dietary source for inorganic arsenic (As) (Zhao et al., 2010), a non-threshold human carcinogen [International Agency for Research on Cancer (IARC), 2004]. In flooded rice paddies, inorganic As(V) is reduced to As(III), while As(V) is more concentrated near the roots due to oxygen leakage (Zhao et al., 2010). Both As(III) and As(V) are transported into rice plants by different pathways, and accumulated in rice grain (Zhao et al., 2010). Under submerged conditions, inorganic As is converted to dimethylarsinic acid (DMA) or monomethylarsonic acid (MMA) through microbial methylation (Zhao et al., 2010). DMA and MMA are also applied directly to agricultural fields as pesticides or herbicides (Zhao et al., 2010). Of the methylated As species, both MMA(III) and DMA(III) may be more cytotoxic and genotoxic than As(III) (Thomas et al., 2001); however, further studies are needed.

In the U.S., rice baby cereal is a common first food, which is introduced between four and six months (Karagas et al., 2016). Rice baby cereals and rice-containing infant snacks are

[1]Abbreviations: ANOVA (one-way analysis of variance); As (arsenic); AsO (arsenic oxide); AsT (total arsenic); CDC (Center for Disease Control and Prevention); CVAFS (cold vapor atomic fluorescence spectrometry); DDI-H_2O (double-distilled H_2O); FAO (Food and Agricultural Organization of the United Nations); Hg (mercury); DMA (dimethylarsinic acid); IARC (International Agency for Research on Cancer); MDL (method detection level); MeHg (methylmercury); MMA (monomethylarsonic acid); NRC (National Research Council); SD (standard deviation); SF-ICP-MS (sector field inductively coupled plasma-mass spectrometer); THg (total mercury); U.S. EPA (U.S. Environmental Protection Agency); U.S. FDA (U.S. Food and Drug Administration)

dietary sources of inorganic As [Carbonell-Barrachina et al., 2012; Jackson et al., 2012a; Karagas et al., 2016; Meharg et al., 2008; Signes-Paster et al., 2016; U.S. Food and Drug Administration (U.S. FDA), 2013]. In 2015, the European Commission stipulated that rice used for the production of food for infants and young children must have inorganic As concentrations below 100 ng/g (Commission Regulation (EU), 2015). In 2016, the U.S. FDA issued a proposed action level of 100 ng/g of inorganic As for rice products marketed to infants (U.S. FDA, 2016a).

Rice baby cereals are also likely a source of MeHg. To the best of our knowledge, just one study reported total Hg (THg) and MeHg concentrations in infant rice cereals (n=7, Brombach et al., 2017), while another study reported THg and total As (AsT) concentrations in rice baby cereals (n=91, Hernández-Martínez and Navarro-Blasco, 2013). There are no studies reporting both MeHg and inorganic As concentrations in rice baby cereals; however, adverse health impacts due to co-exposure may be synergistic (Cardenas et al., 2015). It is important to evaluate whether rice baby cereals and teething biscuits, which meet the FDA proposed action level (i.e., <100 ng/g inorganic As) (U.S. FDA, 2016a), are dietary sources of MeHg.

To address this knowledge gap, we quantified concentrations of THg, MeHg, AsT, inorganic As [=As(III)+As(V)], DMA and MMA, in rice baby cereals and rice teething biscuits purchased in the U.S. In addition, we also compared Hg and As concentrations between rice baby cereals, rice teething biscuits, and baby cereals manufactured with wheat or oats. Wheat/oat cereals served as a control; in previous studies, wheat/oat baby cereals had lower As concentrations compared to rice baby cereals (Carbonell-Barrachina et al., 2012; Hernández-Martínez and Navarro-Blasco, 2013), due to cultivation of wheat/oats in an upland environment.

METHODS

Market basket survey

Between September 2016 and June 2017, 48 boxes of baby foods were purchased, including 36 boxes of rice baby cereals, eight boxes of rice-containing teething biscuits marketed to infants, and four boxes of baby cereals manufactured with wheat or oats. Rice baby cereals represented five brands (n=3–12 boxes per brand), rice-containing teething biscuits represented two brands (n=1 or 7 per brand), and baby cereals containing wheat or oats represented two brands (n=2 per brand). Box labels indicated whether rice cereals were manufactured with brown rice, and whether rice grain was organic (Table 1). All products were purchased in the U.S., including South Carolina (n=28), California (n=9), Ohio (n=6), New York (n=3), and Florida (n=2). Both brands of teething biscuits were manufactured in China, while the sources of rice used for rice baby cereals and teething biscuits were uncertain. One brand of rice baby cereal (Brand 4) was discontinued in December 2016, while the other four brands of rice baby cereals were still available in June 2017.

Lab analyses

For THg, samples (~0.6 g) were weighed into 40 mL borosilicate glass vials with Teflon-lined lids. Samples were leached in 5 mL of freshly prepared 3:7 sulfuric acid: nitric acid (v/v) for four hours at room temperature. Vials were transferred to a 60–70°C water bath and gently heated for two more hours. After samples cooled, 0.35 mL of 0.2 N bromine monochloride was added, and the volume was raised to 35 mL using double-distilled H_2O (DDI-H_2O). Samples were held overnight. Just before analysis, hydroxylamine hydrochloride (0.050 mL) was added, and samples were further reduced with tin chloride, converting all Hg to elemental Hg. THg was analyzed following U.S. EPA Method 1631 (U.S. EPA, 2002), including quantification using cold vapor atomic fluorescence spectrometry (CVAFS) (Merx-T and Model III Detector, Brooks Rand Instruments, Seattle, WA).

Rice MeHg was analyzed using methods from Liang et al. (1996). Briefly, samples (~0.6 g) were weighed into a 50 mL polypropylene vial, and digested in 2 mL of 25% (w/v) potassium hydroxide-methanol in a 75°C oven for three hours. Then 6 mL of dichloromethane and 1.5 mL of hydrochloric acid were added, samples were shaken, centrifuged (4000 rpm = 3000 × *g*, 30 minutes), and phases were separated. Then 30 mL of DDI-H_2O was added, and vials were heated for 1.5 hours at 60–70°C to remove dichloromethane. MeHg extracts were analyzed following U.S. EPA Method 1630 (U.S. EPA, 2001b), including ethylation with sodium tetraethylborate, and quantification by gas chromatography-CVAFS (Model-III Detector, Brooks Rand Instruments, Seattle, WA).

AsT concentrations were analyzed following U.S. EPA 3050b (U.S. EPA, 1996). Briefly, ~1.0 g of sample was weighed into a 70 mL vial, 5 mL of nitric acid was added (Baker), and samples were gently refluxed in a 80°C water bath for 2 hours. Then 5 mL of hydrogen peroxide was added, and vials were heated for one more hour. After vials cooled, the volume was raised to 60 mL using DDI-H_2O. AsT concentrations were analyzed using a Finnigan ELEMENT XR double focusing magnetic sector field inductively coupled plasma-mass spectrometer (SF-ICP-MS) with internal standard Rh or Ir. For sample introduction, a Micromist U-series nebulizer (0.2 mL/min) (GE, Australia), quartz torch, and injector (Thermo Fisher Scientific, USA) were used.

As species, including inorganic As, DMA and MMA, were determined for rice baby cereals and teething biscuits (n=44/48). We did not speciate As in wheat/oat baby cereals (n=4) because the AsT concentrations were far below 100 ng/g (range: 15–24 ng/g) (Table 1). All wheat/oat cereals met the FDA proposed action level (i.e., <100 ng/g inorganic As) (U.S. FDA, 2016a) (Table 1). This differed from a majority (n=34/44 boxes) of rice-containing cereals and teething biscuits, which had AsT concentrations >100 ng/g. For rice-containing products, it was important to speciate As to determine whether samples exceeded the FDA proposed action level. A similar approach was used by Jackson et al. (2012b) in a study comparing products with and without organic brown rice syrup.

Methods for As speciation were previously described by Jackson (2015). Briefly, samples were weighed into 15 mL polypropylene vials, and three mL of 2% nitric acid was added. Vials were lightly capped and heated at 95°C for 45 minutes. After vials cooled, 0.5 mL of

30% hydrogen peroxide was added [to oxidize As(III) to As(V)], and samples were heated for another 45 minutes at 95°C. Samples were cooled, and an aliquot was analyzed. As speciation analysis was performed on an Agilent LC1260 liquid chromatograph coupled to a triple quadrupole ICP-MS (Agilent 8800), using an anion exchange column (Hamilton PRP-X100 10 mm 4.6 × 50 mm; Reno, NV) with a mobile phase of 40 mM ammonium carbonate at pH 9, a column temperature of 30°C and a flow rate of 1.5 mL min^{-1}. The ICP-MS was operated with the collision cell with oxygen as a reactive gas, and As was detected at m/z 91 as arsenic oxide (AsO).

Quality assurance/quality control data are summarized in Table 2. The limits of detection were 0.008 ng/g for THg, 0.002 ng/g for MeHg and 2 ng/g for AsT and As species. A majority of MMA concentrations (n=30/44, 68%) were below the detection level, and half the detection level (1 ng/g) was imputed. All other results exceeded the limits of detection.

THg and MeHg concentrations were analyzed at the University of South Carolina Mercury Lab, AsT concentrations were analyzed at the University of South Carolina Mass Spectrometry Lab, and As species were quantified at the Dartmouth College Core Facility for Trace Metals Analysis.

Statistics

Histograms were used to examine the distribution of each variable, and right-skewed variables were log_{10}-transformed. Bivariate associations were investigated using Pearson's correlation. Differences between groups were analyzed using Student's t-test (2-tailed), or oneway analysis of variance (ANOVA). For ANOVA, multiple comparisons were estimated using the Sidak test (with one categorical variable) or the Tukey-Kramer test (with two categorical variables) (Kirk, 1998), and p-values for pairwise comparisons were reported in the text. An alpha-level of 0.05 was chosen as a guide for significance. Data were analyzed using Stata (Version 9.2, StataCorp, College Station, Texas) and the R-platform (Version 3.2.1, Vienna, Austria).

RESULTS

Total mercury (THg) and methylmercury (MeHg)

In rice baby cereals, rice-containing teething biscuits, and wheat/oat baby cereals (n=48), concentrations of THg, MeHg, and %MeHg (of THg) ranged from 0.01–42 ng/g, 0.003–2.3 ng/g, and 1.9–107%, respectively (Table 1, Figure 1). Average THg concentrations in rice baby cereals and teething biscuits were 9.6 and 30 times higher, respectively, compared to wheat/oat baby cereals. Similarly, average MeHg concentrations in rice baby cereals and teething biscuits were 61 and 92 times higher, respectively, compared to wheat/oat baby cereals. Higher concentrations of THg and MeHg in rice baby cereals and teething biscuits, compared to wheat/oat cereals, were significant (when THg and MeHg were log_{10}-transformed) (ANOVA, $p<0.001$ for all pairwise comparisons, n=48). In addition, log_{10} MeHg concentrations were higher in rice teething biscuits compared to rice baby cereals, but not significantly (ANOVA, p=0.06, n=48). Log_{10} THg and log_{10} MeHg concentrations in all products (rice baby cereals, rice-containing teething biscuits, and wheat/oat cereals) were strongly, positively correlated (Pearson's rho=0.80, p<0.0001, n=48).

MeHg concentrations in rice baby cereal differed between brands (Figure 2a). Log_{10} MeHg was significantly higher in Brand 4 compared to Brands 1–3, and log_{10} MeHg was significantly higher in Brand 5 compared to Brand 3 (ANOVA, p<0.05, n=36). There is just one other study that reported MeHg concentrations in seven rice baby cereals (Brombach et al., 2017) (Table 3). Brand 4 MeHg concentrations (range: 1.0–2.3 ng/g) were within the range reported by Brombach (MeHg range: 0.94–3.3 ng/g, n=7, Brombach et al., 2017), while most MeHg concentrations for the other four brands were lower (range: 0.089–1.6 ng/g). There was no information available concerning brown versus white rice, and organic versus non-organic rice, in seven baby rice cereals from Brombach et al. (2017).

From Table 1, brown rice was the main ingredient for 19 (of 36) rice baby cereals, while 14 (of 36) rice baby cereals were labeled organic, including 10 (of 19) brown rice baby cereals. Brown rice cereals had significantly higher log_{10} THg and log_{10} MeHg concentrations compared to white rice cereals (2-tailed t-test, p<0.001 for both, n=36), while no significant differences were observed for log_{10} THg and log_{10} MeHg concentrations between organic and non-organic rice baby cereals (2-tailed t-test, p=0.60–0.83, n=36).

Total arsenic (AsT) and As species

AsT concentrations were measured in all products (n=48), which ranged from 14–860 ng/g (Table 1, Figure 3). Average AsT concentrations for rice baby cereals and teething biscuits were 9.4 and 4.7 times higher, respectively, compared to wheat/oat baby cereals. Higher AsT concentrations for rice baby cereals and teething biscuits compared to wheat/oat cereals were significant (when AsT was log_{10}-transformed) (ANOVA, p<0.001, n=48).

As species were determined in rice baby cereals and teething biscuits (n=44/48). We did not quantify As species for wheat/oat baby cereals because AsT concentrations were <100 ng/g (average: 21 ng/g, Table 1), which was noted in the methods. In rice baby cereals and teething biscuits (n=44), concentrations of inorganic As, DMA, and MMA ranged from 25–150 ng/g, 9.8–560 ng/g and <MDL–18 ng/g, respectively (Table 1). Inorganic As concentrations were significantly higher in rice baby cereals compared to teething biscuits (2-tailed t-test, p<0.01, n=44), which differed from MeHg. Log_{10} AsT was significantly, positively correlated with As species, including inorganic As, log_{10} DMA, and log_{10} MMA (Pearson's rho=0.63–0.86, p<0.0001, n=44).

From Table 1, inorganic As concentrations exceeded 100 ng/g for 12 of 36 rice baby cereals (33%), including all samples from Brand 4 (n=3/3) and Brand 5 (n=9/9). Brand 4 included two different lot numbers, while Brand 5 included five different lot numbers; therefore consistency within each brand was not due to analysis of rice cereal from the same lot. Inorganic As concentrations were compared between brands (Figure 2b); Brands 2, 4, and 5 had significantly higher inorganic As concentrations compared to one or more other brands (ANOVA, p<0.05 for all, n=36).

Average inorganic As concentrations in rice baby cereals for the present study (88 ng/g, n=36) were lower compared to U.S. infant rice cereals measured by the U.S. FDA (average: 117 ng/g, n=69) (U.S. FDA, 2013) (Table 3). Additionally, average inorganic As concentrations were similar or lower compared to rice baby cereals purchased in Spain, UK, USA, and China (average: 75–162 ng/g, from Carbonell-Barrachina et al., 2012; Meharg et al., 2008; Signes-Pastor et al., 2016) (Table 3).

Concentrations of inorganic As, $\log_{10}$ DMA, and $\log_{10}$ MMA in rice baby cereals were significantly higher in brown rice cereals compared to white rice cereals (2-tailed t-test, $p<0.0001$, $p<0.05$, $p<0.05$, respectively, n=36). Results were consistent with previous studies, comparing As species in brown and white rice (e.g., Sun et al., 2008). Log_{10} DMA and $\log_{10}$ MMA did not differ between and organic and non-organic cereals (2-tailed t-test, p=0.26, p=0.98, respectively, n=36), while inorganic As concentrations were significantly higher in non-organic rice baby cereals compared to organic rice baby cereals (2-tailed t-test, p=0.05, n=36). Meharg et al. (2008) also reported higher inorganic As concentrations for most non-organic rice baby cereals compared to organic rice baby cereals.

Correlation between MeHg and As species in rice baby cereals

Associations between MeHg and As species (inorganic As and DMA) in rice baby cereals were compared (n=36) (Figure 4). We did not include teething biscuits (n=8) because the trends for MeHg and As differed between rice baby cereals and teething biscuits, as noted above. We excluded wheat/oat cereals (n=4) because concentrations of As species (inorganic As and DMA) were not determined. In addition, 68% of MMA values were below the detection level (see methods); therefore concentrations of $\log_{10}$ MeHg were correlated with inorganic As and $\log_{10}$ DMA in rice baby cereals.

Log_{10} MeHg concentrations were positively correlated with inorganic As (Pearson's rho=0.60, $p<0.001$, n=36) and $\log_{10}$ DMA (Pearson's rho=0.52, $p<0.01$, n=36) (Figure 4). Brand 4 was discontinued in December 2016 (see Methods). When Brand 4 was removed (n=3) (i.e., the brand with the highest MeHg concentration), the correlation between $\log_{10}$ MeHg and inorganic As remained significant (Pearson's rho = 0.57, $p<0.001$, n=33). However, the association between $\log_{10}$ MeHg and $\log_{10}$ DMA was somewhat attenuated (Pearson's rho=0.33, p=0.06, n=33).

Dietary intake of MeHg and inorganic As (or AsT) for infants

To estimate dietary intake (μg day^{-1}), we assumed 15-g per serving of baby cereal or 7-g per serving of teething biscuits, based on the reference amounts used by U.S. FDA (U.S. FDA, 2016b). We also assumed one serving per day of one item. To calculate exposure (μg kg^{-1} day^{-1}), dietary intake was normalized by infant weight, using the Center for Disease Control and Prevention (CDC) Growth Charts (CDC, 2009). The median weights for boys and girls averaged 6.5 kg, 7.6 kg, 8.9 kg, and 10.0 kg for four, six, nine, and 12 month-old infants, respectively. Results for dietary intake and exposure are summarized in Table 4.

MeHg—In rice baby cereals, rice-containing teething biscuits, and wheat/oat cereals (n=48), average MeHg intake (μg day^{-1}) was 0.0092 μg day^{-1}, 0.0066 μg day^{-1}, and 0.00015 μg

day^{-1}, respectively. Average MeHg intake for rice baby cereals was 1.4 and 61 times higher, compared to teething biscuits and wheat/oat cereals, respectively.

For all ages (four, six, nine, and twelve months), average MeHg exposure (μg kg^{-1} day^{-1}) from rice baby cereals, rice-containing teething biscuits, and wheat/oat cereals was 0.0011 μg kg^{-1} day^{-1}, 0.00082 μg kg^{-1} day^{-1}, and 0.000019 μg kg^{-1} day^{-1}, respectively (n=48 × 4 =192). All values fell below the U.S. EPA reference dose (0.1 μg kg^{-1} day^{-1}) (U.S. EPA, 1997). The maximum MeHg exposure levels for rice baby cereals, teething biscuits, and wheat/oat cereals were 19, 71, and 2900 times lower than the EPA reference dose, respectively. Log_{10} MeHg exposure was higher in both rice baby cereals and teething biscuits, compared to wheat/oat cereals (ANOVA, $p<0.0001$, n=192), and was significantly higher for four month-old infants compared to 12 month-old infants (ANOVA, $p<0.01$, n=192). However, log_{10} MeHg exposure did not differ between rice baby cereals and teething biscuits (ANOVA, $p=0.60$, n=192).

As—Dietary inorganic As intake and exposure were estimated for rice baby cereals and teething biscuits, while AsT intake and exposure were determined for baby cereals manufactured with wheat/oats. In rice baby cereals and teething biscuits (n=44), average inorganic As intake was 1.3 μg day^{-1} and 0.35 μg day^{-1}, respectively, while average AsT intake for wheat/oat cereals was 0.31 μg day^{-1} (n=4). For all ages (four, six, nine, and twelve months), average inorganic As exposure through ingestion of rice baby cereals and teething biscuits was 0.16 μg kg^{-1} day^{-1} and 0.043 μg kg^{-1} day^{-1}, respectively (n=44 × 4 =176), while average AsT exposure through wheat/oat baby cereals was 0.038 μg kg^{-1} day^{-1} (n=4 × 4=16).

Average inorganic As intake (μg day^{-1}) in rice baby cereals was 3.8 times higher compared to rice-containing teething biscuits. Average inorganic As exposure (μg kg^{-1} day^{-1}) was also 3.8 times higher compared to rice-containing teething biscuits. Inorganic As intake (μg day^{-1}) and exposure (μg kg^{-1} day^{-1}) in rice baby cereals were 4.3 and 4.2 time higher, respectively, compared to AsT intake and exposure from wheat/oat baby cereals. If we assume AsT = inorganic As (for wheat/oat cereals) and combine results for rice baby cereals, teething biscuits, and wheat/oat baby cereals, log_{10} inorganic As exposure was significantly higher for rice cereals, compared to both teething biscuits and wheat/oat cereals (ANOVA, $p<0.0001$, n=192). In addition, log_{10} inorganic As exposure was significantly higher for four and six month-old infants compared to 12 month-old infants, and significantly higher for four month-old infants compared to nine month-old infants (ANOVA, $p<0.05$ for all, n=192).

DISCUSSION

Rice baby cereals and other infant foods containing rice are dietary sources of inorganic As (Carbonell-Barrachina et al., 2012; Jackson et al., 2012a; Karagas et al., 2016; Meharg et al., 2008; Signes-Paster et al., 2016; U.S. FDA, 2013), a non-threshold human carcinogen (IARC, 2004). To reduce infant exposure to inorganic As, in April 2016 the U.S. FDA proposed an action level for inorganic As concentrations in rice products marketed to infants (<100 ng/g) (U.S FDA, 2016a). Of five brands analyzed for this study, two brands exceeded the U.S. FDA proposed action level (Brands 4 and 5). Brand 4 was discontinued in December 2016, while Brand 5 was still available in stores in Columbia, South Carolina (in June 2017). Brand 5 is sold nationally; therefore U.S. infants ingesting rice baby cereal remain potentially at risk for elevated exposure to inorganic As.

Our results demonstrated that rice baby cereals and rice-containing teething biscuits were also dietary sources of MeHg for infants. MeHg concentrations in rice baby cereals and rice teething biscuits (this study: 0.89–2.3 ng/g, Table 1) were far below the U.S. EPA maximum safe level for fish tissue (300 ng/g) (U.S. EPA, 2001a), while MeHg exposure levels for rice baby cereals and rice teething biscuits (this study: 0.00013–0.0052 μg kg^{-1} day^{-1}, Table 4) were below the U.S. EPA reference dose for MeHg (0.1 μg kg^{-1} day^{-1}) (U.S. EPA, 1997). However, these guidelines were based on epidemiologic studies conducted among seafood consumers, not rice consumers (NRC, 2000; U.S. EPA, 1997). The toxicity of MeHg from rice may differ from fish because fish tissue is also rich source of beneficial nutrients that promote fetal brain development, unlike rice (Rothenberg et al., 2011a, 2014). There are few studies that have investigated children’s neurodevelopment among rice consumers, aside from our own studies. In rural Daxin, China, the median rice MeHg concentration was 2.3 ng/g (range: 0.32–15 ng/g, n=398), and a majority of MeHg intake among pregnant women was through rice ingestion (Hong et al., 2016). Within this cohort, significant adverse associations were observed between prenatal MeHg exposure (assessed using maternal hair THg) and infant cognition (assessed at 12 months) (n=270 mother/offspring pairs) (Rothenberg et al., 2016). Although most MeHg concentrations in rice baby cereals and teething biscuits were <2 ng/g (Table 1), the safe MeHg exposure level through rice ingestion, especially for infants, is uncertain. Therefore, more research on the potential health impacts via ingestion of rice and rice-based foods by infants is needed.

In the present study, both MeHg and AsT concentrations were significantly higher in rice baby cereals and rice-containing teething biscuits compared to wheat/oat cereals. Results for AsT were consistent with Carbonell-Barrachina et al. (2012), who reported lower As concentrations in non-rice infant cereals (including wheat/oat cereals) compared to infant rice cereals. Higher concentrations of both AsT and MeHg in rice baby cereals compared to wheat/oat cereals are a concern for children with celiac disease. The primary treatment is a gluten-free diet, including ingestion of rice [National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2016], which may lead to higher dietary intake of both MeHg and As. Results from this study suggest children with celiac disease should ingest oats instead of rice, provided oats are not contaminated with wheat during processing.

We also observed higher $\log_{10}$ MeHg concentrations (although non-significant) in teething biscuits compared to rice baby cereals, while the opposite trend was observed for inorganic As, i.e., significantly lower inorganic As concentrations in teething biscuits compared to rice baby cereals. As a result, the average MeHg intake for one 7-g serving of teething biscuits (~3 biscuits) was 0.0066 μg, compared to 0.0092 μg for one 15-g serving of rice baby cereal (Table 4). Based on these results, a baby ingesting just 4.2 biscuits (1.4 servings) would have approximately the same MeHg intake as one 15-g serving of rice baby cereal. On the other hand, a baby would need to ingest 11 biscuits (3.7 servings) to ingest the same amount of inorganic As in one 15-g serving of rice baby cereal. This is important because babies may ingest more rice snacks, including teething biscuits, compared to rice cereal. For example, in the New Hampshire Birth Cohort Study, 32.6% of 12 month-old infants ingested rice snacks within the previous two days, while ~7% ingested baby rice cereal (n=129) (Karagas et al., 2016). A stronger preference for rice snacks compared to rice baby cereal may therefore lead to higher MeHg exposure.

Log_{10} MeHg was more strongly correlated with inorganic As compared to DMA (Figure 4), which was unexpected. Inorganic As is more concentrated in the outer bran layer, which is removed during polishing, while DMA and MMA are accumulated in the rice endosperm, although MMA concentrations are lower (Carey et al., 2010, 2011; Lombi et al., 2009; Sun et al., 2008; Williams et al., 2005). From previous studies, MeHg was hypothesized to accumulate in the rice endosperm (i.e., white rice) (e.g., Meng et al., 2014; Rothenberg et al., 2011b), more similar to DMA. More studies are needed to verify the localization of MeHg in rice grain.

The combined health impacts due to co-exposure to MeHg and inorganic As are unknown. Individually, both elements are extremely toxic; MeHg is a neurotoxin (NRC, 2000), while inorganic As is a human carcinogen (IARC, 2004). Recent epidemiologic research suggests As exposure may also contribute to adverse neurodevelopmental impacts, similar to MeHg. In Bangladesh, As exposure was associated with decreased cognitive scores among 20– 40 month old infants, where lead levels were low (n=524) (Rodrigues et al., 2016). In Nepal, elevated As exposure among 12–16 year old children was associated with lower neurobehavioral test scores (n=522) (Vibol et al., 2015). In the U.S., low-level postnatal As exposure was associated with neurodevelopmental defects in seven-year old children (n=272) (Wasserman et al., 2014). Cardenas et al. (2015) investigated associations between cord blood As and Hg, and DNA methylation; the interaction between Hg and As was associated with epigenetic changes that may influence neurodevelopment. Therefore co-exposure to inorganic As and MeHg during infancy may adversely impact neurodevelopment, and these impacts may be synergistic.

CONCLUSIONS

U.S. infants are often weaned onto rice-containing cereals (Karagas et al., 2016). Our findings indicate that it is still possible to purchase rice baby cereals with elevated inorganic As concentrations (>100 ng/g) in the U.S. In addition, all rice baby cereals and teething biscuits contained MeHg, a potentially important dietary source of postnatal MeHg exposure. MeHg intake through rice ingestion may be more harmful than fish ingestion, and therefore, caution is advised. Results from this study suggest frequent ingestion of rice baby cereal and rice-containing teething biscuits will contribute to higher intake of both MeHg and inorganic As during the period when infant brains and bodies are rapidly developing; studies concerning their individual and combined impacts on children's health and development are warranted.

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Highlights

- Methylmercury (MeHg) and inorganic arsenic (As) were measured in rice baby foods
- MeHg was 61–92 times higher in rice-based baby foods compared to non-rice foods
- Total As was 4.7–9.4 times higher in rice-based foods compared to non-rice foods
- Inorganic As in 2 brands of rice cereals exceeded 100 ng/g, the proposed action level
- MeHg (log) and inorganic As in rice baby cereals were strongly, positively correlated

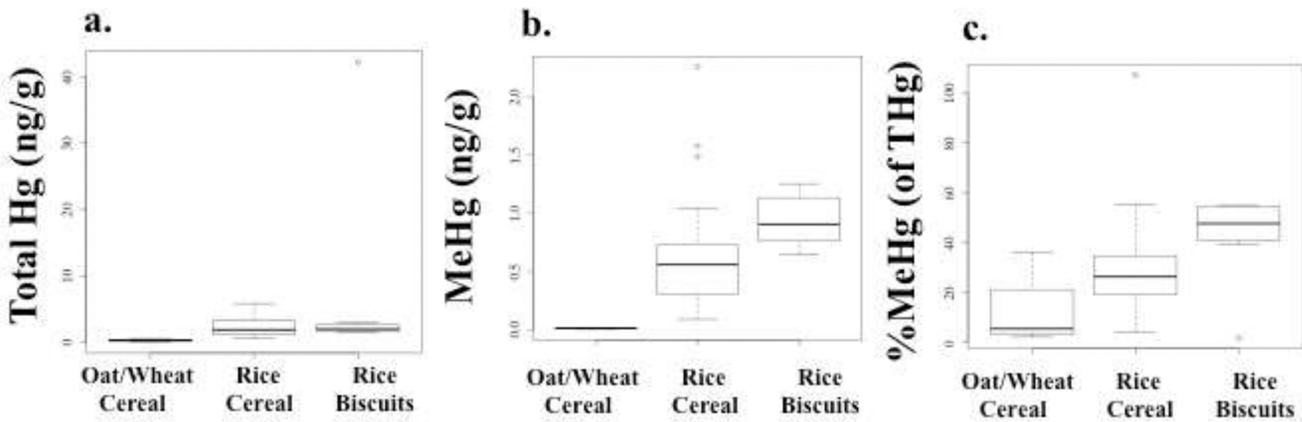

Figure 1.

Comparison between wheat/oat baby cereal (n=4), rice baby cereals (n=36) and rice baby teething biscuits (n=8) for a) total mercury (THg), b) methylmercury (MeHg), c) percent MeHg (of THg).

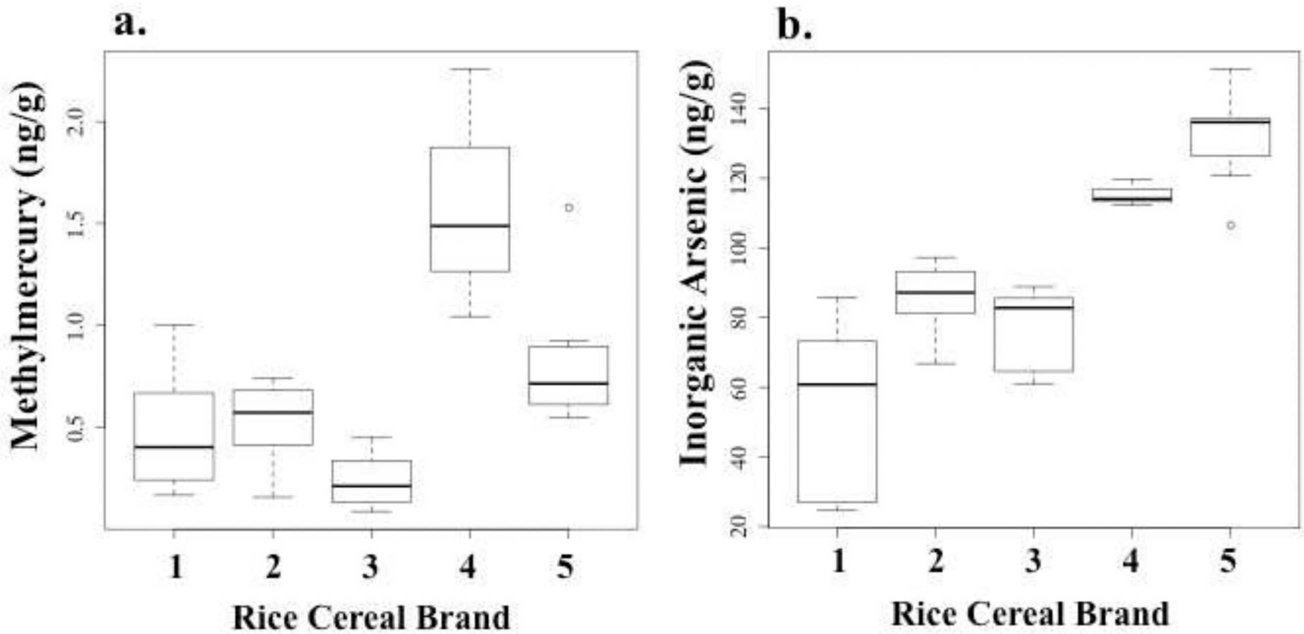

Figure 2.

Comparison between five brands of rice baby cereal for a) methylmercury (MeHg), and b) inorganic As. In Figure 2a, $\log_{10}$ MeHg was significantly higher: in Brand 4 compared to Brands 1–3, and in Brand 5 compared to Brand 3 (ANOVA, $p<0.05$, $n=36$). In Figure 2b, inorganic arsenic was significantly higher: in Brand 2 compared to Brand 1, in Brand 4 compared to Brands 1 and 3, and in Brand 5 compared to Brands 1–3 (ANOVA, $p<0.05$, $n=36$)

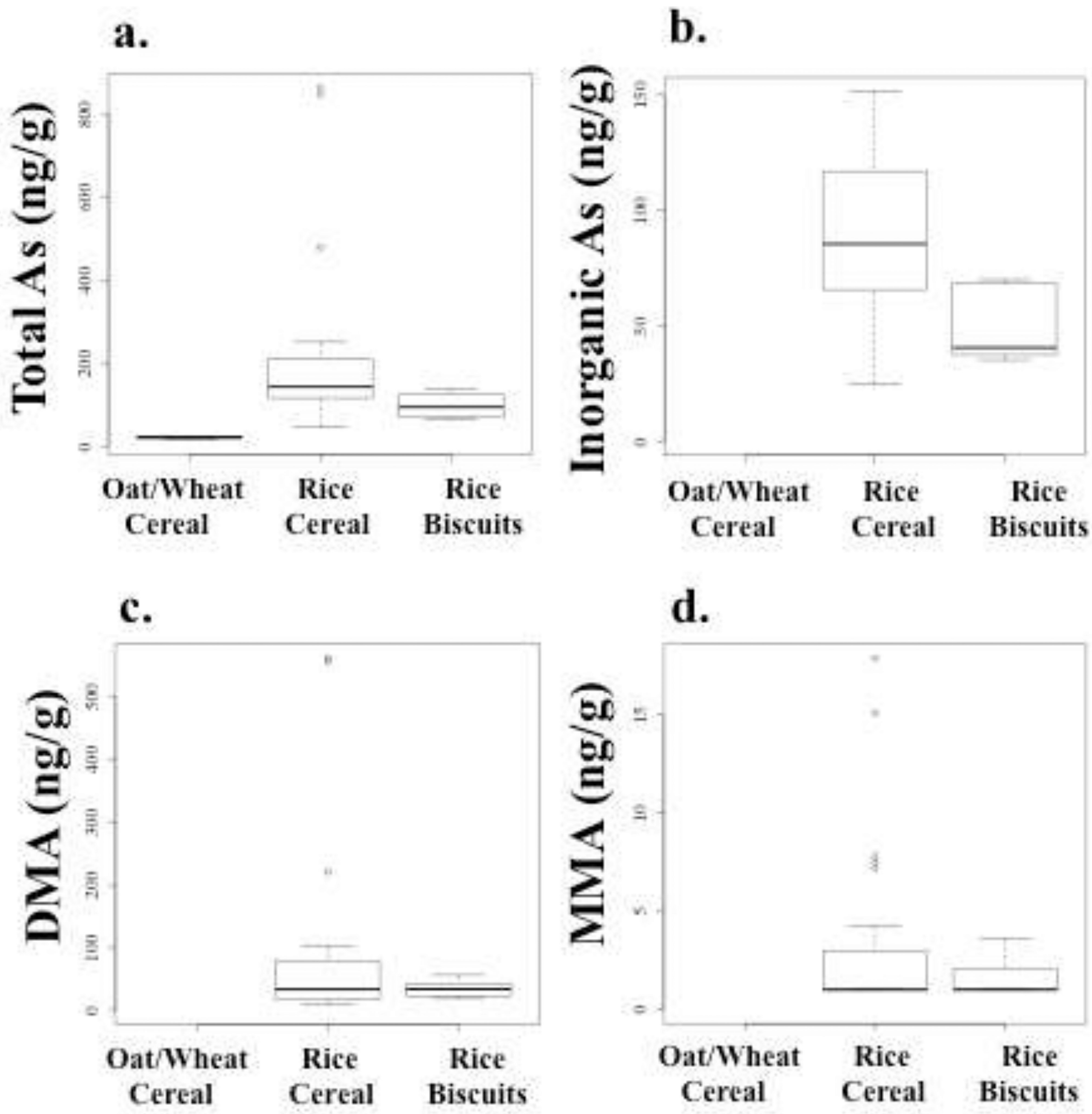

Figure 3.

Comparison between oat/wheat baby cereal (n=4), rice baby cereals (n=36) and rice baby teething biscuits (n=8) for a) total arsenic (AsT), b) inorganic arsenic (As), c) dimethylarsinic acid (DMA), and d) monomethylarsonic acid (MMA). Concentrations of As species (inorganic As, DMA, and MMA) were not determined in oat/wheat cereals.

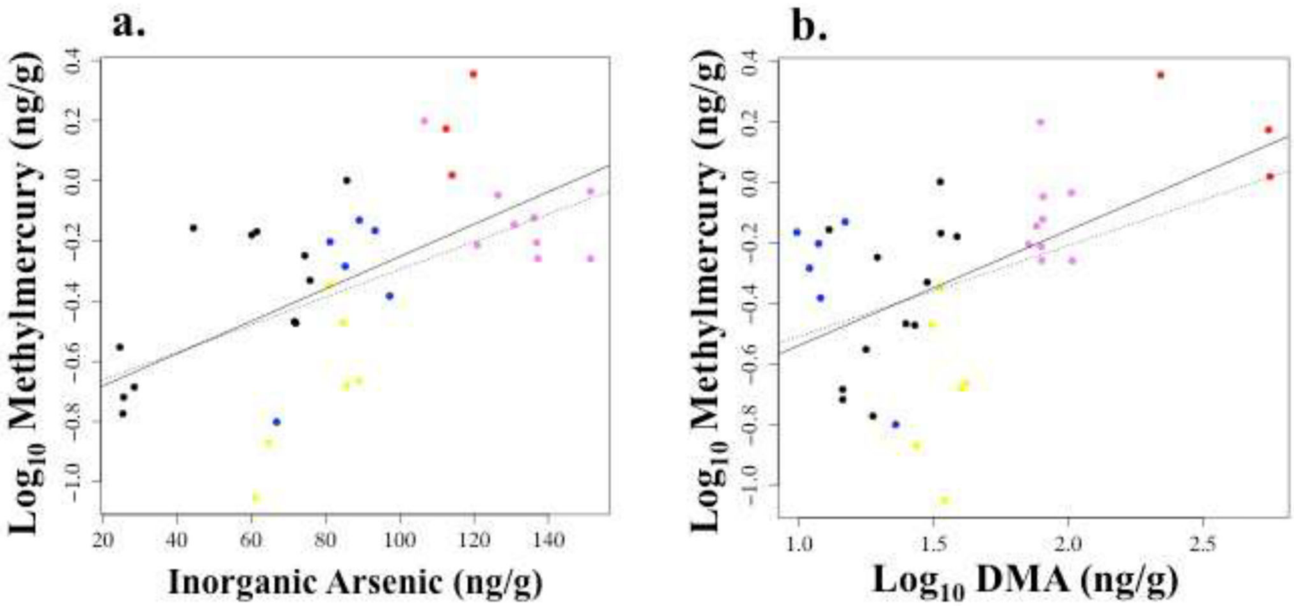

Figure 4.

Bivariate scatterplot for 36 rice baby cereals, including a) $\log_{10}$ methylmercury versus inorganic arsenic, and b) $\log_{10}$ methylmercury versus $\log_{10}$ dimethylarsinic acid (DMA). Legend: black = Brand 1, blue = Brand 2, yellow = Brand 3, red = Brand 4, and violet = Brand 5. Regression line (solid) for 36 rice baby cereals, and regression line (dotted) for 33 rice baby cereals (excluding Brand 4, red).

Table 1

Mercury and arsenic concentrations in rice baby cereals (n=36), rice teething biscuits (n=8) and wheat/oat baby cereals (n=4) (n=48 total).

a. Mercury

	Sample size (n)	THg (ng/g) Mean ± 1 SD (range)	MeHg (ng/g) Mean ± 1 SD (range)	%MeHg (of THg)	Organic rice n (%)	Brown rice n (%)
All rice baby cereals (5 brands)	36	2.2 ± 1.3 (0.53–5.8)	0.62 ± 0.45 (0.089–2.3)	29 ± 17 (4.5–107)	14 (48)	12 (41)
Rice baby teething biscuits	8	7.0 ± 14 (1.6–42)	0.94 ± 0.22 (0.65–1.3)	43 ± 18 (1.9–55)	NA	NA
Oat or wheat baby cereals	4	0.23 ± 0.18 (0.010–0.44)	0.01 ± 0.005 (0.003–0.015)	12 ± 16 (2.3–36)	NA	NA
Rice baby cereal Brand 1	12	1.7 ± 1.0 (0.53–4.6)	0.47 ± 0.26 (0.17–1.0)	35 ± 26 (4.5–107)	5 (42)	1 (8.3)
Rice baby cereal Brand 2	6	2.0 ± 0.38 (1.3–3.0)	0.52 ± 0.21 (0.15–0.74)	25 ± 7.7 (13–32)	6 (100)	6 (100)
Rice baby cereal Brand 3	6	0.98 ± 0.17 (9.7–1.3)	0.24 ± 0.13 (0.09–0.45)	24 ± 11 (9.7–44)	0 (0)	0 (0)
Rice baby cereal Brand 4	3	4.3 ± 1.3 (3.5–5.8)	1.6 ± 0.62 (1.0–2.3)	36 ± 5.8 (30–40)	3 (100)	3 (100)
Rice baby cereal Brand 5	9	3.4 ± 0.41 (2.7–4.2)	0.80 ± 0.32 (0.55–1.6)	24 ± 7.1 (16–38)	0 (0)	9 (100)

b. Arsenic

	Sample size (n)	AsT (ng/g) Mean ± 1 SD (range)	AsI (ng/g) Mean ± 1 SD (range)	DMA (ng/g) Mean ± 1 SD (range)	MMA (ng/g) Mean ± 1 SD (range)	Mean %AsI (of AsT)	Mean %DMA (of AsT)	Mean %MMA (of AsT)	Organic rice n (%)	Brown rice n (%)
All rice baby cereals (5 brands)	36	190 ± 180	88 ± 35	74 ± 130	2.8 ± 3.9	55	29	1.4	14 (48)	12 (41)

b. Arsenic

	Sample size (n)	AsT (ng/g) Mean ± 1 SD (range)	AsI (ng/g) Mean ± 1 SD (range)	DMA (ng/g) Mean ± 1 SD (range)	MMA (ng/g) Mean ± 1 SD (range)	Mean %AsI (of AsT)	Mean %DMA (of AsT)	Mean %MMA (of AsT)	Organic rice n (%)	Brown rice n (%)
		(46–860)	(25–150)	(9.8–560)	(<MDL–18)					
Rice baby teething biscuits	8	97 ± 30 (65–140)	50 ± 16 (35–70)	34 ± 13 (20–56)	1.6 ± 1.1 (<MDL–3.6)	52	35	2.0	NA	NA
Oat or wheat baby cereals	4	21 ± 4.2 (15–24)	NA	NA	NA	NA	NA	NA	NA	NA
Rice baby cereal Brand 1	12	100 ± 41 (46–150)	54 ± 23 (25–86)	24 ± 8.7 (13–39)	1.5 ± 1.9 (<MDL–7.5)	52	24	1.6	5 (42)	1 (8.3)
Rice baby cereal Brand 2	6	120 ± 10 (110–140)	86 ± 11 (67–97)	14 ± 4.8 (9.8–23)	1 ± 0 (<MDL)	69	11	<1	6 (100)	6 (100)
Rice baby cereal Brand 3	6	140 ± 32 (80–170)	78 ± 12 (61–89)	35 ± 5.4 (27–42)	2.1 ± 2.8 (<MDL–7.8)	57	25	1.6	0 (0)	0 (0)
Rice baby cereal Brand 4	3	730 ± 200 (480–860)	120 ± 3.8 (110–120)	446 ± 200 (220–560)	13 ± 5.5 (7.2–18)	17	59	1.8	3 (100)	3 (100)
Rice baby cereal Brand 5	9	220 ± 21 (190–250)	130 ± 14 (110–150)	84 ± 11 (71–100)	2.7 ± 1.1 (<MDL–4.3)	61	38	1.2	0 (0)	9 (100)

MeHg (methylmercury), SD (standard deviation); THg (total mercury)

AsI [inorganic arsenic, As(III) + As(V)], AsT (total arsenic), DMA (dimethylarsinic acid), MDL (method detection level), MMA (monomethylarsonic acid), SD (standard deviation)

Table 2

Quality assurance/quality control, including recovery of four standard reference materials (NIST 1568b, NIST 1515, ERM-580, and TORT2), and matrix spike recoveries.

	%Recovery						
	NIST 1568b (Rice) Mean ± 1 SD (n)	NIST 1515 (Apple leaves) Mean ± 1 SD (n)	ERM-580 (sediment) Mean ± 1 SD (n)	TORT2 (Lobster) Mean ± 1 SD (n)	Matrix spikes Mean ± 1 SD (n)	RSD Mean ± 1 SD (n)	MDL (ng/g)
Total Hg	96 ± 24[1] (6)	90 ± 8.1 (4)	108 ± 7.1 (2)	NA	99 ± 14 (8)	12 ± 14 (10)	0.008
MeHg	NA	NA	NA	107 ± 24 (4)	105 ± 31 (5)	15 ± 14 (7)	0.002
Total As	96 ± 6.4 (6)	NA	NA	NA	NA	5.9 ± 1.2 (6)	2.0
Inorganic As	107 ± 6.8 (5)	NA	NA	NA	92 ± 5 (2)	3.7 ± 3.2 (2)	2.0
DMA	100 ± 1.8 (5)	NA	NA	NA	108 ± 3 (2)	11 ± 1.7 (2)	2.0
MMA	94 ± 11 (5)	NA	NA	NA	94 ± 0 (2)	NA[2]	2.0

As (arsenic), DMA (dimethylarsinic acid), Hg (mercury), MDL (method detection level), MeHg (methylmercury), MMA (monomethylarsonic acid), RSD (relative standard deviation = 100 × standard deviation/mean)

[1] When one low value was removed, the mean ± 1 SD was 103 ± 20% (n=5).

[2] Samples randomly selected for replicate analyses had MMA concentrations below the detection level.

Table 3

Concentrations of methylmercury (MeHg) and inorganic arsenic (As) in rice baby cereals.

Reference	Sample size (n)	MeHg (ng/g) Mean ± 1 SD (range)	Inorganic As (ng/g) Mean ± 1 SD (range)	Country
This study	36	0.62 ± 0.45 (0.09–2.3)	88 ± 35 (25–150)	USA
Brombach et al., 2017	7	1.7 ± 0.81 (0.94–3.3)	NA	U. K.
U.S. FDA (2013)	69	NA	117 ± 42 (25–222)	USA
Signes-Pastor et al., 2016	53	NA	75 (8–323)	U. K.
Meharg et al., 2008	17	NA	120 ± 30 (60–160)	U. K.
Carbonell-Barrachina et al., 2012	14	NA	114 ± 15 (52–247)	China
Carbonell-Barrachina et al., 2012	5	NA	125 ± 14 (93–159)	USA
Carbonell-Barrachina et al., 2012	5	NA	162 ± 29 (107–267)	UK
Carbonell-Barrachina et al., 2012	7	NA	85 ± 10 (10–111)	Spain

Table 4

Methylmercury and inorganic arsenic intake (μg day^{-1}) and exposure (μg kg^{-1} day^{-1}). To obtain exposure, dietary intake was normalized by average infant weight at four, six, nine, and 12 months (CDC, 2009)

		Methylmercury intake (μg day^{-1})	Methylmercury exposure (μg kg^{-1} day^{-1})			
	Sample size (n)	**Average (range)**	**4 months Average (range)**	**6 months Average (range)**	**9 months Average (range)**	**12 months Average (range)**
Rice cereal	36	0.0092 (0.0013, 0.034)	0.0014 (0.00020, 0.0052)	0.0012 (0.00018, 0.0045)	0.0010 (0.00015, 0.0038)	0.00092 (0.00013, 0.0034)
Rice teething biscuits	8	0.0066 (0.0046, 0.0088)	0.0010 (0.00070, 0.0014)	0.00087 (0.00060, 0.0012)	0.00074 (0.00052, 0.00099)	0.00066 (0.00046, 0.00088)
Wheat/oat cereal	4	0.00015 (0.00005, 0.00023)	0.000023 (0.000008, 0.000035)	0.000020 (0.000007, 0.000030)	0.000017 (0.000006, 0.000026)	0.000015 (0.000005, 0.000023)
		Inorganic arsenic intake (μg day^{-1})	**Inorganic arsenic exposure (μg kg^{-1} day^{-1})**			
	Sample size (n)	**Average (range)**	**4 months Average (range)**	**6 months Average (range)**	**9 months Average (range)**	**12 months Average (range)**
Rice cereal	36	1.3 (0.37, 2.3)	0.20 (0.057, 0.35)	0.18 (0.049, 0.30)	0.15 (0.042, 0.26)	0.13 (0.037, 0.23)
Rice teething biscuits	8	0.35 (0.25, 0.49)	0.054 (0.038, 0.075)	0.046 (0.033, 0.065)	0.039 (0.028, 0.055)	0.035 (0.025, 0.049)
Wheat/oat cereal[1]	4	0.31 (0.22, 0.36)	0.048 (0.033, 0.055)	0.041 (0.029, 0.047)	0.036 (0.025, 0.042)	0.031 (0.022, 0.036)

[1]For wheat/oat cereals, total arsenic was used to estimate inorganic arsenic intake and exposure.