# Effects of Inorganic Arsenic in Infant Rice Cereal on Children's Neurodevelopment

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*Prepared for:*
**Healthy Babies Bright Futures**

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# Contents

# Acronyms and Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| $As^{III}$ | Arsenite |
| $As^{V}$ | Arsenate |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| $BMDL_{10}$ | Benchmark dose lower confidence limit |
| CalEPA | California Environmental Protection Agency |
| CONTAM | Contaminants in the Food Chain |
| DHHS | U.S. Department of Health and Human Services |
| DMA | Dimethylarsinic acid |
| EFSA | European Food Safety Authority |
| EPA | U.S. Environmental Protection Agency |
| FCID | Food Consumption Intake Database |
| FDA | Food and Drug Administration |
| FITS | Feeding Infants and Toddlers Study |
| HBBF | Healthy Babies Bright Futures |
| IARC | International Agency for Research on Cancer |
| IRIS | Integrated Risk Information System |
| kg bw | Kilograms of body weight |
| LOAEL | Lowest observed adverse effect level |
| LOD | Limit of detection |
| MassDEP | Massachusetts Department of Environmental Protection |
| MENTOR-3P | Modeling Environment for Total Risk with Physiologically Based Pharmacokinetic Modeling for Populations |
| MMA | Monomethylarsonic acid |
| MRL | Minimal Risk Level |
| NHANES | National Health and Nutrition Evaluation Survey |
| NHEXAS | National Human Exposure Assessment Survey |
| NOAEL | No observed adverse effect level |
| PBPK | Physiologically based pharmacokinetic |
| POD | Point of departure |
| ppb | Parts per billion |
| REL | Reference Exposure Level |
| RfD | Reference dose |
| SHEDS | Stochastic Human Exposure and Dose Simulation |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| TDS | Total Diet Study |
| TEL | Threshold Effects Exposure Limit |
| TMAO | Trimethylarsine oxide |
| USDA | U.S. Department of Agriculture |
| WPPSI | Wechsler Preschool and Primary Scale of Intelligence |
| WWEIA | What We Eat in America |

# Executive Summary

Healthy Babies Bright Futures (HBBF) asked Abt Associates to examine inorganic arsenic exposures associated with consumption of infant rice cereal, rice, and other rice products, and to evaluate the feasibility of quantitatively estimating IQ loss as a result of arsenic exposure from these rice products. This report summarizes the results of those efforts.

Arsenic is a known toxicant that is commonly found in foods containing rice, such as infant rice cereal. Exposures to arsenic are associated with numerous adverse health effects, including cancer, cardiovascular disease, and adverse neurodevelopmental effects (Agency for Toxic Substances and Disease Registry [ATSDR], 2007). The Food and Drug Administration (FDA) recently proposed a standard of 100 ppb for arsenic in infant rice cereal based on a risk analysis and feasibility considerations. In support of this proposed standard, FDA conducted a risk assessment based on cancer endpoints, along with an exposure assessment. Additionally, FDA conducted a systematic literature review on inorganic arsenic exposures during pregnancy and through early childhood, and concluded that these exposures "may increase the risk of adverse health effects, including impaired development during pregnancy and childhood and neurodevelopmental toxicity in infants and young children, and that these adverse effects may persist later in life" (FDA, 2016a, p. 4).

As described in the FDA risk assessment, one in every six children in the world has a developmental disability, and in most cases these disabilities affect the nervous system (Grandjean and Landrigan, 2006). An expert committee of the National Research Council concluded that 25% of these disorders arise from interactions between environmental factors and individual susceptibility (Grandjean and Landrigan, 2006). Given this, and FDA's findings of neurotoxic risk in infants and young children, we developed estimates of IQ loss due to consumption of rice and rice products in infancy and early childhood in order to demonstrate the benefits of reducing arsenic exposure. We drew upon information from the peer-reviewed literature on arsenic exposure estimates for a variety of infant rice cereal, rice, and rice product consumption and concentration scenarios, as well as the information contained in the FDA reports. Likewise, we drew upon dose-response and dose conversion information also published in the peer-reviewed literature. We first conducted a review of the literature on the association between arsenic and neurodevelopmental effects. We then followed established methods used in benefit–cost analyses in support of regulatory standards for developing IQ loss estimates and valuing these losses for a variety of arsenic exposure scenarios. We concluded that, while there are uncertainties, it is feasible to draw upon the relationships from the peer-reviewed literature to quantify and monetize IQ loss associated with exposures to arsenic from infant rice cereal, rice, and other rice products.

Our findings indicate that:

- In the U.S. population of children aged 0-6, replacing all rice and rice products with alternate foods containing no arsenic would result in additional annual earnings of approximately $12 to $18 billion by avoiding losses of more than 9 million IQ points per year.
- Across the U.S. population, replacing infant rice cereal containing arsenic with an alternate infant food not containing arsenic would result in additional annual earnings of approximately $1.2 to $1.8 billion by avoiding losses of almost 1 million IQ points per year.

Our estimates of IQ loss resulting from exposures to arsenic in infant rice cereal vary widely, and are associated with a number of uncertainties that are detailed in our report. The current literature does not identify the most sensitive window of exposure associated with neurodevelopment, nor how best to model the association between low-dose arsenic exposures and IQ loss. Nonetheless, our results suggest that the IQ losses associated with consumption of arsenic in infant rice cereal are not negligible, and a large portion of the U.S. population is impacted. Our results also show that even relatively small IQ losses per child have significant economic impacts when considered on a national scale.

Additionally, our exposure analysis includes a number of important findings:

- Our analysis shows that exposures to arsenic from infant rice cereal approach or exceed existing health-based limits for arsenic levels (based on health effects other than IQ loss), leaving little room for additional exposures from other dietary sources, such as snacks, apple juice, and drinking water.
- Although there are limited data on consumption of infant rice cereals in specific populations that may have high rice consumption rates (e.g., certain ethnic groups or those with celiac disease), preliminary evidence suggests that some infants may face significantly higher levels of exposure to arsenic than both FDA's exposure estimates and the high exposure scenarios considered in our analysis. For example, Munera-Picazo et al. (2014a) found that children under 5 years old with celiac disease had an inorganic arsenic intake that was ten times higher than the mean daily inorganic arsenic intake from FDA's risk assessment report.
- The serving size assumptions used in FDA's exposure assessment for infant rice cereal may underestimate exposures to – and therefore health risks from – arsenic. Using alternate exposure assumptions based on a study by Shibata et al. (2016) results in arsenic exposure estimates that are approximately twice as large as those generated using exposure assumptions from FDA (2016c).
- Implementation of FDA's proposed new standard of 100 ppb would result in only a minimal decrease in arsenic exposures to infants from current exposure levels. This is based on recently collected arsenic levels in rice cereal, which demonstrate that most cereal arsenic levels are less than 100 ppb. Further reducing the proposed new standard for arsenic in infant rice cereal, reducing infant rice cereal consumption, or switching to an alternative infant food would be more effective ways of reducing arsenic exposures.

We did not perform an analysis to suggest a specific regulatory level for arsenic in rice cereal. However, our analysis demonstrates that it is feasible to quantitatively consider neurological effects in setting such a level. Additionally, if such a level is set, we recommend not only considering full-scale IQ loss, as we did in our benefits calculations, but quantitatively evaluating additional endpoints that may be more sensitive. We also recommend that FDA consider the alternative serving size estimates from Shibata et al. (2016), which will result in more health-protective exposure assumptions.

# Report Outline

Abt Associates prepared this report for Healthy Babies Bright Futures to evaluate inorganic arsenic exposures to U.S. children from consumption of infant rice cereal, and to quantify the benefits of avoided neurotoxicity resulting from reducing these exposures. In Section 1, we present basic background on sources of arsenic and its health effects. Section 2 describes existing and proposed regulations for inorganic arsenic concentrations in infant rice cereals. To assess exposures to infant rice cereal, we performed literature searches to identify sources of data on infant rice cereal consumption, inorganic arsenic concentrations in infant rice cereals, and existing estimates of arsenic exposures in U.S. children, as presented in Section 3. In Section 4, we present arsenic exposure estimates for various scenarios of infant rice cereal consumption. Additionally, we describe health-based limits for arsenic (Section 4.2) and compare our exposure estimates to these values (Section 4.3). Section 5 presents our review of the literature on the association between arsenic exposures and adverse effects on neurodevelopment, with a specific focus on quantifying IQ loss in infants and children due to arsenic exposure. In Section 6, we draw upon this literature to estimate IQ losses in children based on consumption of infant rice cereal and other rice products, and the economic benefits of decreasing this risk. Our conclusions on the risk posed by inorganic arsenic in infant rice cereal are presented in Section 7. Appendix A contains a discussion of the potential adverse health effects of a common form of organic arsenic in rice, DMA, which is believed to be less toxic than inorganic arsenic. Appendix B presents summaries of studies on the association between arsenic exposures and IQ loss that were not used in our analyses.

# 1. Background on Arsenic Sources and Health Effects

Arsenic is a naturally occurring element that is ubiquitous in the environment (ATSDR, 2007). It occurs naturally in soil, minerals, and metal ores and can be released to air and water through natural processes (e.g., gusts of wind, leaching) or human activities such as mining, smelting, and burning of fossil fuels (ATSDR, 2007; International Agency for Research on Cancer [IARC], 2012). Arsenic concentrations in soil and water vary widely across the United States, due to variations in geological deposits as well as in the historical usage of pesticides containing arsenic (ATSDR, 2007). Arsenic is typically found in the environment in combination with other elements, forming both inorganic and organic compounds (IARC, 2012).

Humans are commonly exposed to arsenic via ingestion of contaminated food and water (IARC, 2012). Inhalation exposures are not a primary route of exposure in the general population (IARC, 2012). Foods that are high in arsenic include rice, rice-based products, fruit, fruit juices, vegetables, and fish (Xue et al., 2010; Williams et al., 2005). Ingestion of rice is of particular concern because rice plants have greater ability to uptake arsenic than other crops and are grown in flooded conditions, which increase the potential for uptake (FDA, 2016a). Consumer Reports analyzed different types of infant rice cereals and found concentrations of inorganic arsenic around five times higher than those in alternatives such as oatmeal (Consumer Reports, 2012). Infant rice cereal is one of the most common types of food ingested by infants under 1 year old and thus may represent a significant source of exposure. In addition, children and infants are at greater risk for adverse health effects from dietary exposures to arsenic than adults because they consume greater amounts of food relative to their body weight and are more susceptible to the effects of toxicants (FDA, 2016c).

Arsenic in rice is primarily found in the inorganic forms of arsenite ($As^{III}$) and arsenate ($As^{V}$), and the organic forms of monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The forms of arsenic present in any given rice or rice product depend on the specific variety of rice used, as well as the location where the rice is grown (Williams et al., 2005). Inorganic arsenic in rice grown in the United States has been found to comprise an average of 42% of total arsenic present in rice (Williams et al., 2005). In an analysis of arsenic in rice available in the U.S. market, FDA found wide variation in inorganic arsenic concentrations, ranging from 23 to 249 parts per billion (ppb) (FDA, 2016a). High concentrations of DMA in foods containing rice have also been measured: the mean DMA concentration ranged from 32 to 131 ppb in rice grain and from 7 to 123 ppb in rice products, while infant rice cereal was found to contain an average of 52 ppb of DMA (FDA, 2016c). In contrast, rice appears to contain very low concentrations of MMA. In FDA's analysis of rice sold in the U.S., the highest observed concentration of MMA was 12 ppb (FDA, 2016c).

Exposures to arsenic have been linked to a variety of cancers and noncancer health effects, including cardiovascular disease and adverse neurodevelopmental effects (ATSDR, 2007). IARC concluded there is sufficient evidence that arsenic and inorganic arsenic compounds cause lung, skin, and bladder cancer in humans, and limited evidence for kidney, liver, and prostate cancers (Straif et al., 2009). Inorganic arsenic compounds are considered to be more hazardous to human health than organic forms of arsenic (FDA, 2016c). Once ingested, inorganic arsenic is partially metabolized to MMA, and then to DMA, before excretion in the urine (ATSDR, 2007). This is believed to be a detoxification process (i.e., a mechanism to reduce the adverse effects of exposures), because DMA is more readily excreted than inorganic arsenic (Cohen et al., 2006). Exposure to DMA in animals has

resulted in renal, urinary, and developmental effects (ATSDR, 2007; EFSA, 2009); however, these effects have occurred at exposure levels that are higher than those expected from dietary exposures in humans. In this report, we focus on inorganic arsenic only, but we caution that further research is needed on the effects of DMA in humans. Appendix A provides a more detailed discussion of these potential effects.

Based on a systematic review of the literature on inorganic arsenic exposures in pregnancy, infancy and early childhood, FDA concluded that "exposure to inorganic arsenic during these life stages may increase the risk of adverse health effects, including impaired development during pregnancy and childhood and neurodevelopmental toxicity in infants and young children, and that these adverse effects may persist later in life" (FDA, 2016a, p. 4). Additionally, the National Academy of Sciences (NAS) concluded that evidence from animal studies provides support for an association between arsenic exposures and neurological deficits (NAS, 2013). Laboratory studies have identified possible mechanisms of action for these effects: arsenic has been shown to increase neurotoxic oxidative stress, change concentrations of neurotransmitters, and impair development of fetal brain neurons (NAS, 2013). The neurodevelopmental effects of arsenic are discussed further in Section 5.

# 2. Standards for Inorganic Arsenic in Infant Rice Cereal

Since inorganic arsenic is known to adversely impact human health and is present in a variety of foods, standards have been enacted to limit exposures to arsenic from dietary sources, including infant rice cereal. In 2015, the European Commission introduced a maximum allowable limit of 100 ppb for inorganic arsenic in rice destined for infant food products, which applies to products sold throughout the European Union. There is currently no similar standard for rice in infant foods sold in United States; however, in April 2016, the FDA proposed setting a limit of 100 ppb for inorganic arsenic in infant rice cereal. Although both limits are 100 ppb, the European Commission standard applies to all infant foods containing rice (e.g., infant rice snacks in addition to infant rice cereal) and is thus more health-protective. In Sections 2.1 and 2.2, we describe how the European Commission standard and the proposed FDA standard were derived, respectively.

## 2.1 European Commission Standard

The European Commission standard of 100 ppb for inorganic arsenic in rice intended for use in infant foods is derived from a risk assessment of the cancer effects of inorganic arsenic that was conducted by the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM) (European Commission, 2015). The CONTAM panel modeled the dose-response data from key epidemiological studies on the association between arsenic exposures and cancers of the lung, skin, and bladder, as well as skin lesions (EFSA, 2009). This standard does not consider a quantitative risk of neurological effects. Based on a benchmark response of 1% extra cancer risk, the CONTAM panel identified a range of benchmark dose lower confidence limit[1] ($BMDL_{10}$) values between 0.3 and 8 µg/kg bw/day (EFSA, 2009). To put these levels into context, exposure to three average-sized servings of infant rice cereal at the current mean arsenic concentration in the U.S. market is expected to result in arsenic exposures between 0.3 and 0.5 µg/kg bw/day in infants (FDA, 2016c), not considering arsenic from other sources. An analysis of inorganic arsenic concentration and food consumption data across Europe indicated that the estimated dietary exposures in both average and high consumers of arsenic-containing foods were within the range of $BMDL_{10}$ values identified, possibly placing individuals at risk for adverse health effects (EFSA, 2009). Moreover, dietary exposures in children were estimated to be two to three times higher than in adults (EFSA, 2009). A more recent analysis of arsenic exposure and rice consumption data in Europe concluded that three daily portions of rice-based infant food would constitute a significant source of inorganic arsenic exposures in infants (EFSA, 2014). Thus, the European Commission decided to reduce the allowable standard for inorganic arsenic in infant rice cereal and selected a maximum allowable limit of 100 ppb (European Commission, 2015). However, the regulation does not clearly state whether this value is based on feasibility considerations, health protectiveness, or a combination of both factors.

[1] The benchmark dose lower confidence limit is the lower 95% confidence interval for the estimated dose associated with the benchmark response level. In this case, it refers to the arsenic dose associated with a 1% increase in risk of the adverse health endpoints of cancer and skin lesions.

## 2.2 Proposed FDA Standard

FDA is proposing a new limit or "action level" of 100 ppb for inorganic arsenic in rice cereal. FDA states that the proposed limit is based on a number of considerations including "extensive testing of rice and non-rice products, a 2016 risk assessment that analyzed scientific studies showing an association between adverse pregnancy outcomes and neurological effects in early life with inorganic arsenic exposure, and an evaluation of the feasibility of reducing inorganic arsenic in infant rice cereal" (FDA, 2016b). In addition to evaluating the literature on adverse pregnancy outcomes and neurological effects, FDA "developed a mathematical model for lung and bladder cancer outcomes associated with consumption of inorganic arsenic in rice and rice products" (FDA, 2016b). The proposed limit, however, is not based on a quantitative risk assessment of noncancer health effects; FDA states only that the new proposed limit is expected to lead to an unquantifiable reduction in these risks. In addition, the proposed FDA regulation does not directly address additional species of arsenic (i.e., organic forms) that may be present in rice.

The proposed FDA standard of 100 ppb as a limit for inorganic arsenic in infant rice cereal is based on: (1) an analysis of inorganic arsenic concentrations in infant rice cereals on the market; (2) evaluation of the feasibility of reducing these concentrations; (3) a quantitative risk assessment for arsenic and cancer endpoints; and (4) a qualitative assessment of the adverse neurodevelopmental effects of inorganic arsenic exposure in infants. According to a 2014 evaluation of arsenic in infant rice cereals, nearly half of the products currently on the market would already be able to achieve the proposed standard (FDA, 2016a). FDA concluded that the proposed standard is achievable with the use of current good manufacturing practices, including selecting rice sources with lower levels of arsenic contamination (FDA, 2016a). Implementing the proposed standard is expected by FDA to reduce the mean concentration of inorganic arsenic in brown infant rice cereals from 119.0 to 79.0 ppb, and in white infant rice cereals from 103.9 to 83.5 ppb (FDA, 2016a). FDA states that a corresponding reduction in neurodevelopmental effects is expected to occur, although it cannot be quantified. In terms of lifetime cancer risk, the proposed standard is expected to result in a 37% and 18.8% decrease in risk attributable to brown and white rice, respectively (FDA, 2016a). An additional justification for the proposed standard is that it corresponds to the level recently implemented by the European Commission for rice in processed food intended for infants and young children (FDA, 2016a).

# 3. Infant Rice Cereal Consumption, Arsenic Concentration, and Exposure Data

We performed a search for data on arsenic concentrations in food products marketed toward infants and toddlers, in order to begin to investigate risk from infant rice cereals and identify possible alternatives. We also identified national-level data sources (e.g., the National Health and Nutrition Examination Survey [NHANES]) and conducted a literature search to locate additional sources of data published since 2000 on infant rice cereal consumption and arsenic exposure estimates in infants aged less than 1 year old. Sections 3.1 and 3.2 describe sources of data on arsenic concentrations in infant foods and on infant rice cereal consumption, respectively. Section 3.3 presents published estimates of daily arsenic exposures in infants, which draw upon the data sources in Sections 3.1 and 3.2. In Section 3.4, we compare the consumption and exposure data from these sources. Data gaps and limitations are discussed in Section 3.5.

## 3.1 Sources of Data on Arsenic Concentrations in Infant Food

We performed a search to identify data on arsenic concentrations in infant rice cereal and in similar alternative infant foods (e.g., infant oat cereal) available on the U.S. market. We searched EBSCOhost and Google Scholar for terms including "arsenic," "inorganic arsenic," "infant rice cereal," "cereal grains," "gluten free," and "oatmeal." Although not specifically marketed towards infants, grains such as oats, barley, and quinoa can also be incorporated into an infant's diet as an alternative to infant rice cereal; we also present estimates of arsenic concentrations in these alternative grains.

Table 1 displays the mean arsenic concentrations found in samples of infant rice cereal, infant non-rice cereals, and alternative grains. With the exception of those from FDA's Total Diet Study (TDS), all results in Table 1 are inorganic arsenic concentrations. The FDA TDS results represent total arsenic concentrations. In future testing, FDA has indicated that results will be speciated in order to provide results specific to the inorganic form of arsenic.

**Table 1. Mean Arsenic Concentrations in Infant Rice Cereals, Infant Non-Rice Cereals, and Alternative Grains Sold in the United States**

| Type of Food Product Analyzed | Number of Samples | Mean Arsenic Concentration (ppb) | Source of Data |
|---|---|---|---|
| **Infant Rice Cereals** | | | |
| Infant Brown Rice Cereal | 59 | 119.9 | FDA testing conducted in 2013 and 2014 (FDA, 2016c) |
| | 65 | 119.0 | Combined Consumer Reports (2012) data and FDA data from 2013 and 2014 (FDA, 2016c) |
| | 3 | 133.3 | Brockman and Brown (2012) analysis |
| Infant Rice Cereal (All Types) | 76 | 103.0 | FDA (2014) analysis |
| | 12 | 97.0 | Consumer Reports (2012) analysis |

| Type of Food Product Analyzed | Number of Samples | Mean Arsenic Concentration (ppb) | Source of Data |
|---|---|---|---|
| | 24 | 42.0* | Total Diet Study: Market Baskets 2006 through 2011 (FDA, 2016d) |
| | 31 | 91.3 | Juskelis et al. (2013) analysis |
| | 9 | 121.5 | Brockman and Brown (2012) analysis |
| | 5 | 125.0 | Carbonell-Barrachina et al. (2012) analysis |
| Infant Rice with Apples Cereal | 24 | 34.0* | Total Diet Study: Market Baskets 2006 through 2011 (FDA, 2016d) |
| Infant White Rice Cereal | 92 | 103.9 | FDA testing conducted in 2013 and 2014 (FDA, 2016c) |
| | 86 | 105.3 | Combined Consumer Reports (2012) data and FDA data from 2013 and 2014 (FDA, 2016c) |
| Mixed Grain Cereal | 8 | 62.8 | Juskelis et al. (2013) analysis |
| Organic Brown Rice Cereal | 7 | 93.3 | Juskelis et al. (2013) analysis |
| | 3 | 134 | Brockman and Brown (2012) analysis |
| Organic Rice Cereal | 2 | 97.9 | Juskelis et al. (2013) analysis |
| Organic Whole Grain Rice | 1 | 158.0 | Juskelis et al. (2013) analysis |
| Organic Whole Grain Rice Cereal | 2 | 104.5 | Juskelis et al. (2013) analysis |
| Organic Whole Grain Rice Cereal with Apples | 1 | 105.0 | Juskelis et al. (2013) analysis |
| Rice Single Grain Cereal | 10 | 100.6 | Juskelis et al. (2013) analysis |
| **Infant Non-Rice or Mixed Grain Cereals** | | | |
| Infant Multigrain Cereal** | 6 | 30.0 | FDA (2014) analysis |
| Infant Non-Rice Cereal*** | 30 | 13.9 | FDA (2014) analysis |
| Infant Oatmeal Cereal | 23 | LOD* | Total Diet Study: Market Baskets 2006 through 2011 (FDA, 2016d) |
| Oat Ring Cereal | 30 | 17.2 | FDA (2014) analysis |
| **Alternative Grains** | | | |
| Barley | ND | 10.4 | Consumer Reports (2014) analysis |
| Buckwheat | ND | 5.6 | Consumer Reports (2014) analysis |
| Bulgur | ND | 8.4 | Consumer Reports (2014) analysis |
| Cream of Wheat | 24 | LOD* | Total Diet Study: Market Baskets 2006 through 2011 (FDA, 2016d) |
| Farro | ND | 7.3 | Consumer Reports (2014) analysis |

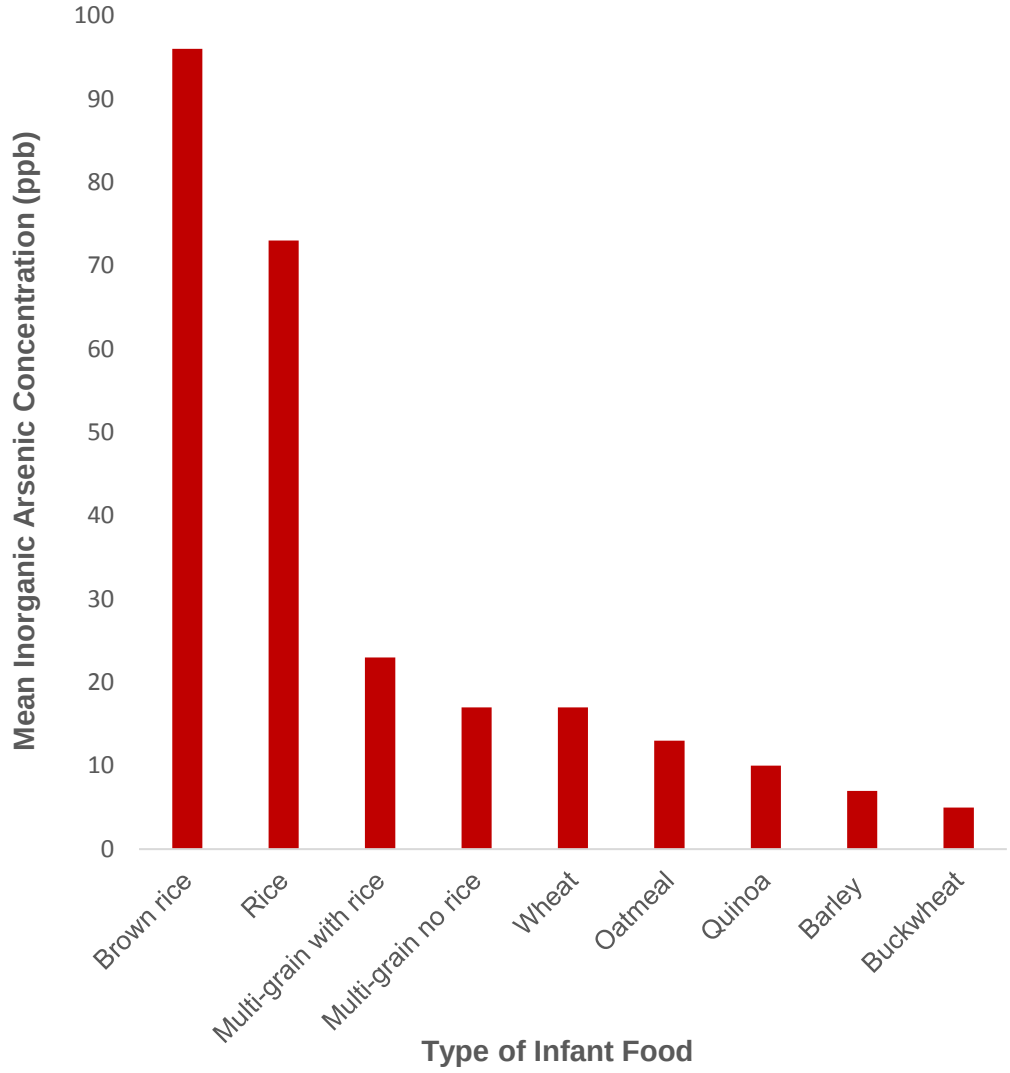
| Type of Food Product Analyzed | Number of Samples | Mean Arsenic Concentration (ppb) | Source of Data |
|---|---|---|---|
| Millet | ND | 12.1 | Consumer Reports (2014) analysis |
| Oatmeal | 24 | LOD* | Total Diet Study: Market Baskets 2006 through 2011 (FDA, 2016d) |
| Quinoa | ND | 12.5 | Consumer Reports (2014) analysis |
| | 30 | 7.9 | FDA (2014) analysis |

Note: ND indicates no data. LOD indicates limit of detection.
*This value represents total arsenic concentration (i.e., not specific to inorganic arsenic). FDA's Total Diet Study had an LOD of 10 ppb.
** Samples contain rice and other grains.
*** Includes cereals with oats, corn, wheat, and multigrains. No samples contain rice.

As shown in Table 1, products that do not contain rice have significantly lower concentrations of inorganic arsenic than infant rice cereals and other products containing rice. The mean arsenic concentrations in infant rice cereals ranged from 34 to 133 ppb, whereas the highest mean arsenic concentration observed in infant cereals not containing rice was 17 ppb. Concentrations of arsenic in alternative grains ranged from approximately 6 to 13 ppb. However, data on alternative grains marketed specifically towards infants were limited. We were also unable to locate published data on infant food products specifically labeled as gluten-free.

To help fill this data gap, HBBF conducted independent testing on infant foods comprised of alternative grains, as well as infant rice cereals. We were provided with the pre-publication testing results shown in Figure 1, which confirm that infant non-rice cereals contain lower concentrations of arsenic than infant rice cereals. Details on the sampling methods, laboratory analyses, and testing results can be found in the report "Arsenic in Infant Rice Cereal: A national survey of arsenic contamination in 105 cereals from leading brands" (HBBF, 2017).

**Figure 1. Concentrations of Inorganic Arsenic in Infant Foods Tested by Healthy Babies Bright Futures**




It is important to note that the data presented in this section are restricted to foods similar to infant rice cereal that are intended to be primary sources of nutrition in infants. High concentrations of arsenic have also been found in fruit juices and infant snacks containing rice (FDA, 2016c). Additionally, some children may be exposed to arsenic through well water or other sources. In a recent analysis of infant rice snacks, Karagas et al. (2016) observed mean inorganic arsenic concentrations up to 201 ppb. The data presented on inorganic arsenic concentrations, which suggest that infant rice cereals may be a significant source of arsenic in infants, should be considered in light of these additional dietary sources of arsenic.

## 3.2 Sources of Data on Infant Rice Cereal Consumption

To identify sources of data on infant rice cereal consumption, we searched EBSCOhost and Google Scholar for terms including “infant rice cereal,” “consumption,” “infant,” and “diet.” We identified

two national-level sources of data – What We Eat in America (WWEIA), which is part of NHANES, and the Nestlé Feeding Infants and Toddlers Study (FITS) – and a recent study of children in New Hampshire by Karagas et al. (2016). The consumption data we identified provide information on the mean amount of infant rice cereal ingested per day and per eating occasion, and the prevalence of consumption of infant rice cereal during the first year of life.

### 3.2.1 What We Eat In America, NHANES

NHANES contains a dietary intake interview section entitled "What We Eat in America" (U.S. Department of Agriculture [USDA], 2014). Typically released every 2 years, WWEIA is created and administered as a partnership between USDA and the U.S. Department of Health and Human Services (DHHS) (USDA, 2014). WWEIA consists of two interviews (in person and by phone), in which participants are asked to recall complete information on dietary intake during the previous 24-hour period. For each reported food, participants are asked to describe the amount consumed and the source (USDA, 2014). To help standardize the process, dietary recalls are collected using a computerized system, and participants are provided with booklets and three-dimensional models to assist in estimating food portions. Daily total intakes of various foods and nutrients are calculated using food and portion size data (USDA, 2014).

Per the results of WWEIA surveys conducted in 2003-2010, the mean amount of uncooked rice per capita (i.e., across the total population, including consumers and non-consumers) ingested by infants (less than 1 year old) from infant rice cereal per day is 0.664 g/kg bw (FDA, 2016c). When considering only infants who consume infant rice cereal, the mean amount of uncooked rice ingested per eating occasion of infant rice cereal is 1.125 g/kg bw (FDA, 2016c).

### 3.2.2 Nestlé Feeding Infants and Toddlers Study

The Nestlé FITS is designed to assess nutrition in U.S. children from birth through the first few years of life. Conducted in 2002 and 2008, each cycle of FITS consists of a random sample of approximately 3,000 children (Fox et al., 2004; Briefel et al., 2010). Children are recruited using the New Parent Database, which consists of prenatal and postnatal records for children born throughout the United States (Briefel et al., 2010). Parents or caregivers of participating children complete a single 24-hour dietary recall and are asked general questions on diet, such as the timing of introduction of certain foods. Information on an additional 24-hour period is collected in a subset of participants (Briefel et al., 2010).

Results of FITS indicate that consumption of infant rice cereal is common during the first year of life: in the 2008 cycle, the percentage of infants aged 4-5 months, 6-8 months, and 9-11 months old who had eaten infant rice cereal in the past 24 hours was 50%, 79%, and 51%, respectively (Siega-Riz et al., 2010). These numbers represent a decrease in consumption from the 2002 FITS, in which the percentages of children in these age groups consuming infant rice cereal were 65%, 82%, and 64%, respectively (Siega-Riz et al., 2010). In an analysis of the 2002 FITS data, Briefel et al. (2004) found that almost 30% of infants were given foods before the age of 4 months, even though it is recommended that infants consume only breast milk or formula during this period (Briefel et al., 2004). The FITS data also indicate a high prevalence of consumption of other potential dietary sources of arsenic, such as apple juice and non-infant cereals (24% and 43% in infants aged 9-11.9 months, respectively) (Siega-Riz et al., 2010). Using 2002 FITS data, Mennella et al. (2006)

compared the diet of Hispanic and non-Hispanic infants and found that Hispanic infants were significantly more likely to eat rice between the ages of 6 and 11 months.

Using data from FITS 2002, Fox et al. (2006) estimated average portion sizes per eating occasion by calculating averages per child from the total daily amount consumed and number of eating occasions, then summing individual estimates and dividing by the total number of consumers. The average portion size per eating occasion of dry infant rice cereal in 4-5 month olds, 6-8 month olds, and 9-11 month olds was 3.1, 4.5, and 5.2 tablespoons, respectively (Fox et al., 2006). For jarred infant rice cereal, the average amount per eating occasion in 6-8 month olds and 9-11 month olds was 5.6 and 7.4 tablespoons, respectively (Fox et al., 2006).

### 3.2.3 Karagas et al. (2016)

In their 2016 paper "Association of Rice and Rice-Product Consumption with Arsenic Exposure Early in Life," Karagas et al. aimed to examine dietary sources of arsenic exposure in U.S. infants aged less than 1 year old. The researchers recruited 954 infants delivered to mothers in New Hampshire participating in a birth cohort study. Children participating in the study were of high socioeconomic status (as indicated by high levels of maternal education) and almost exclusively white. Information on general dietary patterns of infants (e.g., age of introduction to solid foods, source of home water supply) was collected via structured interview at age 4, 8, and 12 months. During the final interview, detailed information on weekly consumption of rice products (including rice-based snacks and products containing brown rice syrup) was obtained.

Karagas et al. (2016) found that consumption of rice cereal in infants was widespread: the majority of infants (64%) were introduced to infant rice cereal between the ages of 4 and 6 months, with 80% of participants reporting consumption by the age of 12 months. During the dietary interview at 12 months of age, 43% of infants were found to have consumed products containing rice in the past week and 25% of infants had eaten rice during the week. Consumption of other products containing rice or rice syrup was also reported in around a quarter of the infants, at an average of five to six servings per week. Karagas et al. (2016) concluded that most children studied were exposed to rice and rice products during their first year of life.

## 3.3 Estimates of Daily Arsenic Exposures from Infant Rice Cereal

To identify estimates of daily arsenic exposures from infant rice cereal, we searched EBSCOhost and Google Scholar for terms including "infant rice cereal," "arsenic," "inorganic arsenic," and "daily exposure." In addition to the FDA risk assessment, the following section describes four studies we located from the primary literature.

### 3.3.1 FDA Risk Assessment

In its 2016 publication "Arsenic in Rice and Rice Products Risk Assessment Report", FDA used consumption data from the most recent available cycle of WWEIA (2009-2010), as well as from all available years (2003-2010), to generate arsenic exposure estimates (FDA, 2016c). WWEIA data were used to calculate per capita and per eating occasion intake estimates for infant rice cereal in infants less than 1 year old. Given the lack of longitudinal data on infant rice cereal consumption rates, FDA assumed that lifetime average consumption rates could be approximated by the per capita daily intakes, which estimate intakes for the entire population and thus include consumers and non-consumers of rice and rice products. To calculate intake estimates per eating occasion, FDA defined

an eating occasion as "a single instance of consumption of rice as a single food (not as an ingredient in NHANES/WWEIA codes for food mixtures), regardless of whether the rice was consumed as a meal or as a snack" (FDA, 2016c, p. 53). The mean number of rice-eating occasions per day was also calculated using the WWEIA data.

Results of the FDA risk assessment indicated that the mean per capita daily intakes of infant rice cereal and of all rice products for infants less than 1 year old were 0.664 g/kg bw and 0.925 g/kg bw, or approximately 2 and 3 tablespoons of dry infant rice cereal, respectively. Consumption of rice in the first year of life peaked between 5 and 9 months old, with around 60% of infants consuming infant rice cereal during this period. Because the most recent WWEIA cycle showed decreased rice consumption in infants, data from 2003-2010 were used to generate conservative estimates.[2] The mean intake of rice from dry infant cereal per eating occasion was estimated to be 1.125 g/kg bw.

Given mean inorganic arsenic concentrations of 119.0 ppb in brown infant rice cereal and 103.9 ppb in white infant rice cereal, this translates to estimates of the mean inorganic arsenic exposures from rice cereal per eating occasion of 0.134 µg/kg bw and 0.117 µg/kg bw for white and brown rice, respectively. In infants less than 1 year old, the mean per capita daily intakes (calculated by averaging the daily intakes of all individuals in the sample) of inorganic arsenic from infant rice cereal and from rice plus rice products were 0.069 µg/kg bw/day and 0.0941 µg/kg bw/day, respectively.

In addition to the per capita and per eating occasion estimates for infants less than 1 year old, FDA also analyzed exposures using "what if" scenarios to evaluate the effects of reducing inorganic arsenic exposures in this population. In the "what if" scenario to investigate the impact of changing frequency of infant rice cereal consumption, FDA calculated that consumption of three average-sized servings (approximately 3.5 tablespoons each) of infant rice cereal per day at an inorganic arsenic concentration of 103.9 ppb would result in a daily arsenic exposure of 0.3 to 0.5 µg/kg bw/day, depending on the month of age. Reducing consumption to one serving per day would reduce inorganic arsenic exposures to an estimated 0.1 to 0.15 µg/kg bw/day.

### 3.3.2 Xue et al. (2010)

In their 2010 paper "Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 2003-2004 NHANES Data," Xue et al. aimed to improve upon existing estimates of dietary arsenic exposures in the general U.S. population by: (1) using the peer-reviewed U.S. EPA Stochastic Human Exposure and Dose Simulation (SHEDS) model to estimate total and inorganic arsenic exposure; (2) obtaining food and water arsenic concentration and consumption data from larger, more recent (and thus more representative) databases; and (3) validating the model using duplicate diet and biomarker data.

Xue et al. (2010) obtained food and water consumption data from the 2003-2004 NHANES WWEIA, and additionally used information from the U.S. EPA's Food Consumption Intake Database (FCID) to break down reported foods into raw ingredients. Concentrations of arsenic in food and water were estimated using FDA's TDS and a Natural Resources Defense Council database, respectively. Once the dietary exposures were modeled using SHEDS, the resulting urinary arsenic concentrations were

[2] Conservative estimates are those that lead to higher assessments of risk; they are intended to represent maximum likely exposures, rather than mean exposures.

estimated using the Modeling Environment for Total Risk with Physiologically Based Pharmacokinetic Modeling for Populations (MENTOR-3P) system. To evaluate the modeling approach used, Xue et al. (2010) compared their estimates to dietary and biomarker data from the National Human Exposure Assessment Survey (NHEXAS) and NHANES, respectively.

Results of the modeling indicated that dietary arsenic exposures are greatest for children under the age of 5. Exposures to total arsenic from food sources were approximately 14 times greater than those from drinking water. Table 2 displays modeled estimates of the distribution of inorganic arsenic and total arsenic exposures from food sources in infants less than 1 year old.

**Table 2. Estimates of Arsenic Exposure from Dietary Sources in Infants Using the SHEDS Model and 2003-2004 NHANES Data (µg/kg bw/day)**

| Arsenic Species | Mean ± SD | Percentile | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5th | 25th | 50th | 75th | 95th | 99th |
| Inorganic | 0.23 ± 0.19 | 0.01 | 0.09 | 0.21 | 0.31 | 0.53 | 0.80 |
| Total | 0.62 ± 0.53 | 0.05 | 0.27 | 0.56 | 0.84 | 1.45 | 2.08 |

Source: Table 1 from Xue et al. (2010)

Comparing results to the duplicate diet and biomarker data showed that the modeled estimates closely predicted both urinary arsenic concentrations and arsenic intake from food (e.g., mean duplicate and modeled intakes of 0.185 µg/kg bw/day and 0.192 µg/kg bw/day). The researchers concluded that food sources are more significant contributors to arsenic exposures than drinking water in the U.S. In addition, they concluded that their modeling approach is an effective method for estimating arsenic exposures in the U.S. population.

### 3.3.3 Karagas et al. (2016)

In the Karagas et al. (2016) study on consumption of infant rice cereal described previously in Section 3.2.3, the researchers also obtained biomarker samples to estimate arsenic exposures. Urine samples were collected at age 12 months, along with records of all products consumed during the 2 days prior to urine sample collection. Urine was analyzed for total and speciated arsenic (e.g., MMA, DMA) concentrations. Karagas et al. (2016) compared urinary arsenic concentrations in consumers and non-consumers of six types of rice-containing food products: rice, infant rice cereal, non-infant rice cereal, adult food with rice, baby food with rice, and snacks made with rice. In the two days prior to urine collection, 55% of infants consumed a product containing rice. Overall, the median urinary concentrations of total arsenic, inorganic arsenic, and DMA were 4.11 µg/L, 0.24 µg/L, and 3.00 µg/L, respectively. Infants who consumed rice, rice snacks, or rice cereal had significantly higher mean concentrations of total urinary arsenic (5.83 µg/L, 4.97 µg/L, and 9.53 µg/L, respectively) than those who did not consume rice (2.85 µg/L).

Since the Karagas et al. (2016) paper does not include daily rice intake estimates, we estimated the average daily inorganic arsenic intake based on the reported urinary arsenic concentration. In order to do so, we first estimated the urinary arsenic concentration attributable to infant rice cereal exposures by subtracting the concentration found in infants who reported no rice intake (2.85 µg/L) from the concentration in infants who consume infant rice cereal (9.53 µg/L). Using an equation from a study by Tsuji et al. (2015) (described in Section 4.2.2) to convert total urinary arsenic concentrations to daily inorganic arsenic intakes and assuming an average infant body weight of 9.2 kg from EPA's *Exposure Factors Handbook* (U.S. EPA, 2011a), the total urinary arsenic concentration from infant

rice cereal exposures (6.68 µg/L) in infants 12 months of age is associated with an estimated daily inorganic arsenic intake of approximately 0.3 µg/kg bw/day. Karagas et al. (2016) concluded that infant rice cereal, as well as other foods such as infant rice snacks, contributes to arsenic exposures during the first year of life.

### 3.3.4 Carignan et al. (2016)

Carignan et al.'s (2016) paper, "Potential Exposure to Arsenic from Infant Rice Cereal," draws upon data from several sources to estimate arsenic exposures to 6- to 12-month-olds in the United States from infant rice cereal. Average and high arsenic exposure scenarios were assessed using central tendency and upper bound estimates, respectively. For the average exposure scenario, the median inorganic and organic arsenic concentrations (0.20 µg/g and 0.12 µg/g, respectively) from FDA's 2013 analysis of infant rice cereal were used (FDA, 2013), along with EPA's mean recommended body weight values (7.2 kg for 3- to 6-month-olds, and 9.2 kg for 6- to 12-month-olds) from the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2008). The high arsenic exposure scenarios were calculated using the maximum concentrations of arsenic (0.37 µg/g for total and 0.25 µg/g for inorganic) from the FDA analysis (FDA, 2013) and the 5$^{th}$ percentile body weights (5.7 kg for 3- to 6-month-olds, and 7.1 kg for 6- to 12-month-olds) recommended by EPA (U.S. EPA, 2008). Estimates of the mean amount of infant rice cereal per eating occasion in 3- to <6-month-olds and 6- to <12-month-olds were obtained from Fox et al.'s (2006) analysis of the 2002 FITS and used for both scenarios, as no data on upper bound portion sizes could be located. The authors multiplied the mean serving size of infant rice cereal by the concentration of total and inorganic arsenic in these products, and then divided by body weight. Carignan et al. (2016) assessed mean daily arsenic exposures for the average and high scenarios assuming one to four portions of infant rice cereal per day. Table 3 shows arsenic exposure estimates based on total arsenic concentrations. The authors did not present the estimates generated using inorganic arsenic concentrations.

**Table 3. Average and High Estimates of Total Arsenic Exposures to Infants from Carignan et al. (2016)**

| Servings of Infant Rice Cereal per Day | 3 to <6 Months | | 6 to <12 Months | |
|---|---|---|---|---|
| | Average Exposure (µg/kg bw/d) | High Exposure (µg/kg bw/d) | Average Exposure (µg/kg bw/d) | High Exposure (µg/kg bw/d) |
| 1 | 0.32 | 0.76 | 0.37 | 0.89 |
| 2 | 0.63 | 1.52 | 0.74 | 1.77 |
| 3 | 0.95 | 2.28 | 1.11 | 2.66 |
| 4 | 1.27 | 3.04 | 1.48 | 3.55 |

Source: Table 1 from Carignan et al. (2016)

### 3.3.5 Shibata et al. (2016)

In their 2016 paper, "Risk Assessment of Arsenic in Rice Cereal and Other Dietary Sources for Infants and Toddlers in the United States," Shibata et al. aimed to determine whether arsenic contamination at the levels observed in infant rice cereal sold in the United States poses a risk to infants and toddlers, when considering the endpoint of lifetime cancer risk. The authors defined limits

for safe doses of arsenic using ATSDR's Minimal Risk Levels (MRLs) for acute and chronic oral consumption of arsenic of 5.0 µg/kg/day and 0.5 µg/kg/day, respectively. Average daily doses of inorganic arsenic from specific dietary sources (water, infant formula, rice cereal, and other infant foods) were calculated for infants from age 4 to 24 months, using assumptions for inorganic arsenic concentration, serving size, and body weight. Inorganic arsenic concentration data were obtained from FDA (2013) and Signes-Pastor et al.'s (2016) analysis of infant rice cereals in the European Union. Inorganic arsenic in infant rice cereal was assumed to have a triangular distribution with a minimum value of 23 ppb, most likely value of 91 ppb, and maximum value of 283 ppb. Amounts of infant rice cereal consumed from ages 4 to 24 months were obtained from Fox et al.'s (2006) analysis of FITS data, while body weight assumptions were derived from the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2008); both variables were assumed to be normally distributed. Shibata et al. (2016) performed Monte Carlo simulations (n = 1,000,000) to estimate ranges of possible inorganic arsenic exposures. Table 4 shows the 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles of arsenic exposure in 4-11 month olds.

**Table 4. Average Daily Doses of Inorganic Arsenic from Infant Rice Cereal (µg/kg/day)**

| Age (Months) | Percentile of Exposure (µg/kg/day) | | |
|---|---|---|---|
| | 25$^{th}$ | 50$^{th}$ | 75$^{th}$ |
| 4-5 | 0.051 | 0.23 | 0.46 |
| 6-8 | 0.12 | 0.29 | 0.53 |
| 9-11 | 0.11 | 0.30 | 0.53 |

Source: Table 3 from Shibata et al. (2016)

Infant rice cereal was found to be the largest contributor to overall arsenic exposure, accounting for 55% of the total average dose in 4-24 month olds from drinking water and dietary sources. Shibata et al. (2016) calculated hazard quotients[3] for acute (≤14 days) and chronic (≥1 year) exposures to arsenic from dietary sources. The authors found that, while acute exposures did not pose a health risk, arsenic in infant rice cereal at the 50$^{th}$ and 75$^{th}$ percentiles of chronic exposures presented cancer risks to infants and toddlers.

## 3.4 Comparison of Consumption and Exposure Estimate Data

The prevalence of consumption of infant rice cereal in the United States appears to be high; each of the consumption sources identified report that the majority of infants consume infant rice cereal during the first year of life. Karagas et al. (2016) found that 64% of infants ate infant rice cereal between the ages of 4 and 6 months old. Data from the 2008 FITS indicate that the percentage of infants consuming infant rice cereal at the age of 4-5 months, 6-8 months, and 9-11 months was 50%, 79%, and 51%, respectively (Siega-Riz et al., 2010). While the analysis of WWEIA data presented in the FDA risk assessment does not provide the exact proportion of children consuming infant rice cereal during specific age ranges in the first year of life, it notes that consumption peaked at age 5 months (FDA, 2016c), which is slightly earlier than observed in the FITS study. The Karagas et al. (2016) paper reports that 80% of infants had consumed infant rice cereal by the age of 12 months.

[3] Hazard quotients are calculated by dividing the observed exposure level by a reference dose; values above 1 indicate that there is potential for adverse health effects.

Estimates of the mean amount of infant rice cereal (i.e., number of tablespoons) consumed per eating occasion were similar in the national-level sources identified. The mean daily per capita and per eating occasion amounts from the FDA risk assessment, which are based on WWEIA data, are 0.664 and 1.125 g/kg bw for infants less than 1 year old, translating to approximately 2 and 3.5 tablespoons of infant rice cereal, respectively (FDA, 2016c). Per the 2002 FITS data, the mean amounts of infant rice cereal consumed per eating occasion in 4-5 month olds, 6-8 month olds, and 9-11 month olds are 3.1, 4.5, and 5.2 tablespoons, respectively (Fox et al., 2006). Averaged across the first year of life, these estimates are approximately equivalent. Despite this, estimates of arsenic exposures from infant rice cereal vary widely, as shown in Table 5.

**Table 5. Estimates of Arsenic Exposure from Infant Rice Cereal**

| Source | Age Studied | Consumption Scenario | Estimate of Daily Inorganic Arsenic Exposure from Infant Rice Cereal (µg/kg bw/day) |
|---|---|---|---|
| FDA (2016c) | Infants less than 1 year old | Average exposure<br>1 serving per day | 0.10-0.15 |
| | | High exposure<br>3 servings per day | 0.30-0.50 |
| Xue et al. (2010)* | Infants less than 1 year old | Average exposure<br>50th percentile of exposure | 0.12 |
| | | High exposure<br>95th percentile of exposure | 0.30 |
| Carignan et al. (2016)** | 3 to <6 months | Average exposure assumptions and 1 serving per day | 0.19 |
| | | High exposure assumptions and 1 serving per day | 0.51 |
| | | Average exposure assumptions and 3 servings per day | 0.56 |
| | | High exposure assumptions and 3 servings per day | 1.53 |
| | 6 to <12 months | Average exposure assumptions and 1 serving per day | 0.15 |
| | | High exposure assumptions and 1 serving per day | 0.41 |
| | | Average exposure assumptions and 3 servings per day | 0.45 |
| | | High exposure assumptions and 3 servings per day | 1.23 |
| Shibata et al. (2016) | 4-5 month olds | Average exposure<br>50th percentile | 0.23 |
| | | High exposure<br>75th percentile | 0.46 |
| | 6-8 month olds | Average exposure<br>50th percentile | 0.29 |

| Source | Age Studied | Consumption Scenario | Estimate of Daily Inorganic Arsenic Exposure from Infant Rice Cereal (µg/kg bw/day) |
|---|---|---|---|
| | | High exposure 75th percentile | 0.53 |
| | 9-11 month olds | Average exposure 50th percentile | 0.30 |
| | | High exposure 75th percentile | 0.55 |
| Karagas et al. (2016) | 12 month olds | Average consumption in infants sampled; estimated from biomarker data | 0.30 |

*Xue et al. (2010) exposure estimates are based on total inorganic arsenic exposures; exposures from infant rice cereal were estimated using the assumption from Shibata et al. (2016) that infant rice cereal constitutes 55% of total dietary exposures. However, since Shibata et al. (2016) include drinking water as part of diet, whereas Xue et al. (2010) do not, this assumption likely results in an underestimate of the true values.

**Carignan et al. (2016) present data only for total arsenic; inorganic arsenic exposure estimates were calculated using the concentration data presented in the paper. For the average exposure assumptions, the authors used median arsenic concentrations and mean body weight assumptions. High exposure assumptions used the maximum arsenic concentrations and 5th percentile body weight.

The variation in Table 5 is due to differences in ages of infants examined, as well as to differing exposure assumptions. The arsenic exposure estimates for an average infant consuming one serving of infant rice cereal per day range from 0.10 to 0.30 µg/kg/day. In general, these estimates of average exposures to infant rice cereal tend to assume one serving per day. However, assumptions for the number of grams of infant rice cereal per tablespoon differ. For example, FDA assumes that there are 2.5 grams of infant rice cereal per tablespoon, based on USDA recommendations (FDA, 2016c). However, Shibata et al. (2016) weighed a tablespoon of a popular infant rice cereal product sold in the U.S. and found that one tablespoon was equivalent to 4.6 grams of rice cereal. Due largely to this assumption, the estimates from Shibata et al. (2016) are higher than those from the FDA analysis.

As can be seen in Table 5, estimates of high exposures to infant rice cereal vary even more widely, from a low of 0.30 µg/kg/day to a high of 1.53 µg/kg/day. This can be explained by differences in defining high exposures (e.g., 95th percentile of exposure, or three servings of rice cereal per day) as well as differences in methodology. The lowest estimates came from the Xue et al. (2010) study, which used FDA's TDS data as the basis for inorganic arsenic concentrations. The TDS data found the lowest arsenic concentrations in rice cereal compared to all other sources, as shown in Table 1. On the other hand, the highest estimates (from Carignan et al. (2016)) were generated by assuming that a child at the 5th percentile of body weight ate three full infant rice cereal servings per day. In Section 4, we draw upon the assumptions and methods described here to investigate the potential impacts of reducing infant rice cereal consumption or concentration.

## 3.5 Data Gaps and Limitations

Overall, there are sufficient data on concentrations of arsenic in infant rice cereal. However, detailed data on consumption of infant rice cereal during the first year of life are more limited, which makes it difficult to generate accurate estimates of arsenic exposures from infant rice cereal during the first

year of life. The sources of data on consumption of infant rice cereal that we identified – WWEIA, FITS, and Karagas et al. (2016) – only provide a snapshot of consumption during 1-3 days in the first year of life. In addition, the three-day food diaries in Karagas et al. (2016) were completed at 12 months of age, not earlier in infancy when the frequency of rice cereal consumption may peak. It is not known how much dietary intake varies for individual infants, and thus these snapshots may not be representative of overall dietary intake. In future work, it may be possible to further analyze sources such as the WWEIA data using statistical methods to estimate usual intakes, which estimate the probability of regular consumption based on the two-day diaries. However, variation in foods eaten by infants is likely smaller than in older children and adults (Fox et al., 2006). An additional limitation of the paper by Karagas et al. (2016) is that the authors did not study a representative sample of U.S. infants.

There are also limitations in the dietary recall methods used to estimate consumption of infant rice cereal. While WWEIA and FITS provide tools and information to assist with portion size estimates, inaccuracies in the amounts of infant rice cereal reported likely remain. In addition to the difficulties in estimating portion sizes, misreporting may occur due to incomplete recall or intentional modification of responses (e.g., from parents wanting to report socially desirable responses). As Briefel et al. (2004) noted, "energy intakes from FITS 2002 suggested that there may have been some degree of over-reporting of amounts of foods and beverages by some respondents" (p. S18). The primary limitation of the consumption data sources identified is that they do not provide information on percentiles of arsenic consumption in infants; since the distribution is unknown, it is difficult to determine arsenic exposures in the highest consumers and thus characterize the greatest risks to infants. The percentiles of arsenic exposure estimates from Xue et al. (2010) and Shibata et al. (2016) were generated using modeling procedures, rather than actual consumption data.

Data gaps also remain in populations of infants, such as those in certain ethnic groups or those with celiac disease, who may eat more rice than the general population. In these populations, data from studies of older children and adults suggest that consumption of infant rice cereal or other rice products is likely higher than for infants in general; however, data are lacking on the consumption amounts during the first year of life. In an analysis of WWEIA data for individuals aged 2 or older, rice consumption on a daily basis was low (3.4%) in the general population, but high (32.6%) in individuals of Asian or multiracial ethnicity (FDA, 2016c). Additionally, Hispanic infants are significantly more likely than non-Hispanic infants to consume rice during their first year of life (Mennella et al., 2006). In its risk assessment of rice and rice products, FDA acknowledged that its approach of using per capita estimates (as described above in Section 3.3.1) is likely not appropriate for estimating arsenic exposure in these high consumer populations.

For individuals with celiac disease, consuming a gluten-free diet is an accepted treatment for managing the disease. Individuals with celiac disease often substitute products with gluten (e.g., wheat, barley, rye) with rice and rice products, which are gluten-free (Gilbert-Diamond et al., 2011). However, information on rice consumption in individuals with celiac disease is currently not included in FDA's risk assessment report (FDA, 2016c) or draft guidance for industry (FDA, 2016a). Given data on this population of rice consumers, there is reason to suspect a higher than average risk of inorganic arsenic exposures from rice and rice products. A recent dietary recall study of persons with celiac disease (n=984) estimates that these individuals consume up to 10 servings of rice products per week or 1.75 g/kg bw/day (Thompson & Jackson, n.d.). This is approximately five times higher than the estimated daily intake of rice and rice products in individuals aged 0-50 years old from the FDA

risk assessment, which was 0.332 g/kg bw (FDA, 2016c). Additionally, a recent study found that, during the first 5 years of life, children with celiac disease had an inorganic arsenic intake of 0.61-0.78 µg/kg bw/day (Munera-Picazo et al., 2014a). By comparison, in FDA's risk assessment report, the mean daily inorganic arsenic intake from all rice in children aged 0-6 years old was 54.4 ng/kg bw (0.0544 µg/kg bw/day), which is an order of magnitude smaller (FDA, 2016c). Similarly, Munera-Picazo et al. (2014b) found a daily intake of inorganic arsenic of 0.45 µg/kg bw in adults with celiac disease. In contrast, the mean daily inorganic arsenic intake from all rice consumption in adults is 31.9 ng/kg bw (0.0319 µg/kg bw) in FDA's risk assessment report (FDA, 2016c). As the authors concluded, "these values indicate that a health risk to these consumers cannot be excluded" (Munera-Picazo et al., 2014b, p. 1358). In addition to those following a medically-prescribed gluten free diet, limiting gluten has become a more popular diet choice in the U.S., which may lead to an increased consumption of rice products.

In summary, key data gaps remain in infant consumption data: information on the distribution of infant cereal consumed during the first year of life, as well as studies on consumption in populations such as infants of different ethnicities and those following a gluten-free diet. The available studies indicate that exposure to arsenic in these populations may be underestimated. Data on arsenic concentration in infant rice cereal are comprehensive and come from a variety of sources; however, data on arsenic concentrations in alternative grains are lacking, and are supplemented by the HBBF analysis. Improving infant consumption data sources would lead to more accurate estimates of dietary arsenic exposures during the first year of life and help to characterize health risks to infants.

# 4. Comparison of Exposures from Infant Rice Cereal to Health-Based Limits for Arsenic

In Section 4.1, we draw upon the sources outlined in Section 3 to estimate the arsenic exposures associated with various scenarios of infant rice cereal consumption and concentrations. Section 4.2 describes existing health-based limits for oral exposures to arsenic. We compare our exposure estimates to these health-based limits in Section 4.3.

## 4.1 Estimates of Arsenic Dose Associated with Various Scenarios of Infant Rice Cereal Consumption

We estimated the changes in arsenic exposures associated with six hypothetical exposure scenarios of reduced infant rice cereal consumption or reduced arsenic concentration in infant rice cereal. In each exposure scenario, we assumed that infants consume a total of three servings of food, whether infant rice cereal or an alternate such as oatmeal, per day. Alternate infant foods were assumed to have an average inorganic arsenic concentration of 15 ppb.[4]

We first estimated the avoided arsenic exposures associated with the expected reduction of arsenic in infant rice cereal resulting from FDA's proposed new standard of 100 ppb. To do so, we assumed an initial inorganic arsenic concentration in infant rice cereal of 103.9 ppb, the current mean concentration in product available in today's market, and a decrease to 83.5 ppb, the expected mean under the proposed standard (FDA, 2016c). These concentrations refer to infant white rice cereal, not infant brown rice cereal, as the former is far more commonly consumed by U.S. infants (FDA, 2016c). We estimated the resulting impacts on exposures to arsenic for both high and low consumers of infant rice cereal. Our high consumer exposure assumptions are based on the "what if" scenario from the 2016 FDA risk assessment of consumption of three average-sized servings of infant rice cereal per day (FDA, 2016c). For the scenario involving average consumption of infant rice cereal, we assumed consumption of only one average-sized serving of infant rice cereal per day, per the FDA risk assessment (FDA, 2016c), and of two servings of an alternate infant food. Using these same assumptions for high and low consumers, we also investigated the effect of a potential lower standard of 50 ppb for inorganic arsenic in infant rice cereal by assuming an initial inorganic arsenic concentration of 103.9 ppb and final concentration of 20.8 ppb, the expected mean associated with this alternative lower limit (FDA, 2016c).

In our next two scenarios, we assumed that the proposed FDA standard will be implemented. We investigated the changes in arsenic exposures given reduced consumption of infant rice cereal at a mean inorganic arsenic concentration of 83.5 ppb, as expected under the proposed 100 ppb standard (FDA, 2016c). We did so for high consumers (i.e., initial consumption of 3 servings of infant rice cereal per day) and either a partial (decrease to 1 serving per day) or complete reduction (0 servings per day) of infant rice cereal consumption. We assumed that replacement of infant rice cereal in the

[4] This concentration approximates recent testing of multigrain and non-rice cereals, including testing by FDA (2014) and HBBF (2017).

partial and complete reduction scenarios was with an alternate grain that contained 15 ppb of arsenic. Table 6 presents a summary of our six exposure scenarios.

**Table 6. Scenarios and Assumptions Used to Estimate Changes in Arsenic Exposures**

| Exposure Scenario | Type of Consumer | Concentration of Inorganic Arsenic in Infant Rice Cereal (ppb) | | Consumption of Infant Rice Cereal (Servings per Day) | | Assumptions |
|---|---|---|---|---|---|---|
| | | Initial | Final | Initial | Final | |
| Implement FDA's proposed new standard of 100 ppb arsenic in infant rice cereal | High | 103.9 | 83.5 | 3 | 3 | • 103.9 ppb is the mean arsenic concentration in infant rice cereal in today's market<br>• 83.5 ppb is the expected mean arsenic concentration in infant rice cereal under proposed new FDA standard<br>• 20.8 ppb is the expected mean arsenic concentration in infant rice cereal under alternate standard of 50 ppb<br>• All infants consume 3 servings of food (infant rice cereal or non-rice cereal) per day. For example, in initial scenarios with 1 serving of infant rice cereal per day, assume 2 servings of non-rice cereal at an arsenic concentration of 15 ppb |
| | Average | 103.9 | 83.5 | 1 | 1 | |
| Implement alternate new standard of 50 ppb arsenic in infant rice cereal | High | 103.9 | 20.8 | 3 | 3 | |
| | Average | 103.9 | 20.8 | 1 | 1 | |
| Reduce infant rice cereal consumption | High | 83.5 | 83.5 | 3 | 1 | |
| Replace infant rice cereal with alternate food | High | 83.5 | 83.5 | 3 | 0 | |

As noted in Section 3.4, assumptions for infant rice cereal weight (i.e., the number of grams per tablespoon) vary between sources and have a significant impact on the daily arsenic exposure estimates. We examined the nutrition facts of popular brands of infant rice cereal in the U.S. and found that the assumption from Shibata et al. (2016) of 4.6 grams per tablespoon was closer to the estimates on packaging than the FDA assumption of 2.5 grams per tablespoon. In order to examine the effects of this assumption on arsenic dose estimates, we calculated doses for all the aforementioned scenarios using the set of assumptions in both of these sources. In FDA (2016c), the amount of infant rice cereal consumed per serving during the first year of life was 1.125 g/kg bw. To enable a direct comparison, we used the infant rice cereal consumption data presented in Shibata et al. (2016), as well as body weight data from the *Exposure Factors Handbook* (U.S. EPA, 2011), to estimate average consumption of infant rice cereal during the first year of life only (i.e., not from ages 4-24 months, as presented in the paper). Using the Shibata et al. (2016) assumptions, we estimate consumption of infant rice cereal per serving of 2.148 g/kg bw during the first year of life. Using their respective assumptions for grams per tablespoon, the amounts used for FDA and Shibata et al. (2016) translate to approximately 3.5 and 3.7 tablespoons per eating occasion, respectively.

Table 7 and Table 8 present estimates of daily arsenic doses (in µg/kg bw/day) associated with our infant rice cereal exposure scenarios, based on the FDA (2016c) and Shibata et al. (2016) assumptions, respectively.

**Table 7. Estimates of Changes in Arsenic Exposure Associated with Changes in Infant Rice Cereal Consumption or Concentration in 0 to <1 Year Olds, Using FDA's (2016c) Serving Size Assumptions**

| Scenario | | Mean Arsenic Intake per Day (µg/kg bw/day) | | |
|---|---|---|---|---|
| | | Initial | Final | Change |
| Implement FDA's proposed new standard of 100 ppb arsenic in infant rice cereal | High consumer (3 servings per day) | 0.35 | 0.28 | 0.07 |
| | Average consumer (1 serving per day) | 0.15 | 0.13 | 0.02 |
| Implement alternate new standard of 50 ppb arsenic in infant rice cereal | High consumer (3 servings per day) | 0.35 | 0.07 | 0.28 |
| | Average consumer (1 serving per day) | 0.15 | 0.06 | 0.09 |
| Reduce infant rice cereal consumption (3 servings per day to 1 serving per day) | | 0.28 | 0.13 | 0.15 |
| Replace infant rice cereal with alternate food (3 servings per day to 0 servings per day) | | 0.28 | 0.05 | 0.23 |

**Table 8. Estimates of Changes in Arsenic Exposure Associated with Changes in Infant Rice Cereal Consumption or Concentration in 0 to <1 Year Olds, Using Shibata et al.'s (2015) Serving Size Assumptions**

| Scenario | | Mean Arsenic Intake per Day (µg/kg bw/day) | | |
|---|---|---|---|---|
| | | Initial | Final | Change |
| Implement FDA's proposed new standard of 100 ppb arsenic in infant rice cereal | High consumer (3 servings per day) | 0.67 | 0.54 | 0.13 |
| | Average consumer (1 serving per day) | 0.29 | 0.24 | 0.04 |
| Implement alternate new standard of 50 ppb arsenic in infant rice cereal | High consumer (3 servings per day) | 0.67 | 0.13 | 0.54 |
| | Average consumer (1 serving per day) | 0.29 | 0.11 | 0.18 |
| Reduce infant rice cereal consumption (3 servings per day to 1 serving per day) | | 0.54 | 0.24 | 0.29 |
| Replace infant rice cereal with alternate food (3 servings per day to 0 servings per day) | | 0.54 | 0.10 | 0.44 |

As shown in Table 7 and Table 8, using assumptions from Shibata et al. (2016) results in arsenic dose estimates that are almost twice as high as those derived using assumptions from FDA (2016c). These tables additionally show that, regardless of assumptions used, the changes in arsenic exposures resulting from FDA's proposed new standard of 100 ppb are minimal. Implementing an alternate limit of 50 ppb would decrease arsenic exposures by approximately four times as much as the proposed new standard. Assuming the 100 ppb standard is enacted, reducing infant rice cereal consumption or replacing infant rice cereal with an alternate grain would be effective methods for reducing arsenic exposures.

## 4.2 Health-Based Limits for Arsenic Exposures

In this section, we discuss health-based limits for arsenic that are relevant to assessing exposures from infant rice cereal. In Section 4.2.1, we describe the purpose of the reference dose (RfD) and the existing RfD for arsenic in the United States, which is based on the endpoint of skin changes and possible vascular complications. Section 4.2.2 describes the approach used by Tsuji et al. (2015) to calculate an RfD for arsenic based on the endpoint of adverse neurodevelopmental effects, which, to the best of our knowledge, is the only published estimate of its kind. Section 4.2.3 discusses minimal risk levels (MRLs) for oral exposures to arsenic. Lastly, Section 4.2.4 presents Shibata et al.'s (2016) estimates for maximum contaminant levels (MCLs) for arsenic in infant rice cereals, which are based on the MRLs.

### 4.2.1 U.S. EPA's IRIS (1991) Reference Dose for Chronic Oral Exposures

The Integrated Risk Information System (IRIS) reports an RfD or a reference concentration for chemicals that may pose a health threat to humans for noncancer health effects such as neurotoxicity. IRIS defines the RfD as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (U.S. EPA, 1993). In other words, the RfD is a threshold value that is assumed to be protective of the entire population; exposures below this value are not expected to lead to adverse health effects.

The RfD is derived by first taking either the highest dose that is without an adverse effect (the NOAEL), the lowest dose at which an adverse effect is observed (the LOAEL), or a dose at a specific response level modeled from a toxicological or epidemiological study. This dose (termed the point of departure, POD) is then divided by a series of uncertainty factors, which are typically given a value of 3 or 10, to obtain the RfD. Uncertainty factors may be applied to account for animal-to-human extrapolation, human inter-individual variability, use of a LOAEL instead of a NOAEL, and database insufficiency, as well as additional extrapolations. The total number of uncertainty factors used and the value of each depends on the available data. For example, an uncertainty factor for animal-to-human extrapolation is not applied if the POD has been derived from a study in humans.

The existing RfD[5] in IRIS of 0.3 µg/kg bw/day for chronic oral exposures to arsenic is based on endpoints of skin changes (specifically, hyperpigmentation and keratosis [formation of dark and scaly

[5] IRIS is updating the arsenic assessment, but the new RfD estimates are not final.

patches on the skin, respectively]) and possible vascular complications. Studies by Tseng (1977) and Tseng et al. (1968) on the skin effects of arsenic exposures in drinking water were used to derive the RfD. The mean concentration of arsenic in the well water of the reference group in the study, 9 µg/L, was used as a NOAEL. This NOAEL was converted to a daily intake of arsenic of 0.8 µg/kg/day by adding estimates of arsenic exposures from food based on Abernathy et al. (1989). EPA chose to apply an uncertainty factor of 3 to account for "both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals" (U.S. EPA, 1991). However, EPA also noted a lack of consensus among staff regarding choice of the RfD, with suggested values ranging between 0.1 and 0.8 µg/kg bw/day.

### 4.2.2 Tsuji et al.'s (2015) Reference Dose for the Neurodevelopmental Effects of Arsenic

In their 2015 paper "Low-Level Arsenic Exposure and Developmental Neurotoxicity in Children: A Systematic Review and Risk Assessment," Tsuji et al. present methods for developing an alternative RfD for arsenic based on the endpoint of adverse neurodevelopmental effects. After reviewing and evaluating the available literature on this endpoint, Tsuji et al. (2015) selected a study by Hamadani et al. (2011) as the basis of the RfD. Specifically, the authors derived the RfD using the low-dose linear relationship observed in Hamadani et al. (2011) of 2.6 verbal IQ points lost per 100 µg/L increase in speciated urinary arsenic levels in 5-year-old girls. It is important to note that this linear relationship is reported as a subanalysis in Hamadani et al. (2011); the study focuses on results generated from the log-linear regression models and does not report details on the derivation of the linear function.[6] Tsuji et al. (2015) selected a loss of 1 IQ point as the basis for the POD (i.e., the authors estimated the dose that would be expected to lead to a 1-point decrease in IQ). Given the aforementioned relationship of -2.6 verbal IQ points lost per 100 µg/L of urinary arsenic, the urinary arsenic concentration associated with a 1-point IQ loss was 38.5 µg/L. This concentration was then converted to a daily arsenic dose (i.e., the POD) using Equation 1, which is explained in Table 9.

$$Arsenic\ dose\ (\mu g/kg\ bw/day) = \frac{UAs \times UER}{FUE \times BM} \qquad \text{(Equation 1)}$$

**Table 9. Parameters and Input Values Used to Estimate Dietary Arsenic Dose from Urinary Arsenic Concentrations in Tsuji et al. (2015)**

| Parameter | | Value | Derivation |
|---|---|---|---|
| UAs | Urinary arsenic concentration (µg/L) | 38.5 | 1-point loss in IQ based on linear relationship between IQ loss and urinary arsenic concentration in 5-year-old girls from Hamadani et al. (2011) |
| UER | Urinary excretion rate (L/day) | 0.4 | Average rate of urinary excretion in 5-year-olds in the U.S. from study by Walker and Griffin (1998) |
| FUE | Fraction of oral dose excreted in urine | 0.7-0.9 | Estimated from study of recovery of arsenic in urine and feces after intravenous dosing |

[6] An email to the study authors asking for more information on the linear analysis was not returned.

| | | | |
|---|---|---|---|
| | | | and oral dosing in water (Freeman et al., 1995; Roberts et al., 2002, 2007) |
| BM | Body mass (kg) | 14.9 | Average body mass reported in Hamadani et al. (2011) |

Source: Table 5 from Tsuji et al. (2015)

The assumptions used by Tsuji et al. (2015) resulted in an estimate for the POD of 1.10-1.47 µg/kg bw/day, depending on the value used for the fraction of total dose excreted in the urine (as shown in Table 9). Tsuji et al. (2015) note that the urinary excretion rate used is based on U.S. children and may be an overestimate of the true value for children in Bangladesh, who have smaller body sizes. As a sensitivity analysis for their assumption of 0.4 L/day, the researchers also calculated the RfD using a smaller value of 0.355 L/day, which decreased the estimated dose by a factor of 1.13 (and thus would have resulted in a lower, more protective RfD).

Tsuji et al. (2015) applied uncertainty factors of 1 or 3 to the POD of 1.10-1.47 µg/kg bw/day to derive the final RfD. Since the researchers considered the POD to be a minimal LOAEL, an uncertainty factor for LOAEL-to-NOAEL conversion was used. An uncertainty factor between 1 and 3 was selected, based on what was used in prior standards for arsenic, as well as characterization by the authors that the amount of variation in IQ explained by arsenic is very small. The authors opted not to apply an uncertainty factor for individual sensitivity or variability, since the Hamadani et al. (2011) study was conducted using a sensitive population. The final arsenic RfD for the endpoint of neurodevelopmental effects from Tsuji et al. (2015), as rounded by the authors, was 0.4-1.0 µg/kg bw/day.

### 4.2.3 Agency for Toxic Substances and Disease Registry (2007) Minimal Risk Level

The CDC's ATSDR sets minimal risk levels (MRLs) for exposures to chemicals, which are defined as "an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure" (U.S. EPA, 2002, p. 2-9). Thus, the MRL for oral exposures to arsenic represents the daily dose (from dietary and drinking water sources) below which no adverse effects would be expected. MRLs are derived using the same process as the RfD, by applying uncertainty factors to a POD (see Section 4.2.1 for details). Unlike RfDs, the MRLs are associated with a specific duration of exposure, either acute (defined as ≤14 days), intermediate (15-364 days), or chronic (≥1 year) (U.S. EPA, 2002).

The MRL for acute-duration oral exposures to inorganic arsenic is 0.005 mg/kg bw/day (50 µg/kg bw/day), based on a study of accidental arsenic contamination of soy sauce by Mizuta et al. (1956). Mizuta et al. (1956) estimated that individuals were exposed to 0.05 mg/kg/day of arsenic over the course of several weeks, which resulted in gastrointestinal symptoms (nausea, vomiting, and diarrhea) as well as facial swelling. An uncertainty factor of 10 was applied to the value of 0.05 mg/kg/day to account for extrapolation from the LOAEL to the NOAEL, resulting in an MRL of 0.005 mg/kg bw/day. ATSDR determined that there was insufficient information to set an MRL for exposures to arsenic of intermediate duration. For chronic oral exposures, the MRL for inorganic arsenic is the same as the IRIS RfD – 0.0003 mg/kg bw/day – and was also derived based on studies of skin lesions by Tseng and colleagues. Since we expect that infants are exposed to rice cereal more frequently than 14 days, we consider only the chronic MRL for comparison to arsenic doses from infant rice cereal.

### 4.2.4 Shibata et al.'s (2016) Maximum Contaminant Level for Arsenic in Infant Rice Cereal

Using ATSDR's MRLs and estimates of daily exposures to arsenic in dietary sources other than infant rice cereal, Shibata et al. (2016) derived maximum contaminant levels (MCLs) for inorganic arsenic in infant rice cereal. The MCLs represent the "maximum allowable levels of chemicals considering public health and acceptable risk" (Shibata et al., 2016, p. 5). The authors calculated MCLs by considering average exposure levels in infants across each month of life, from 4 to 24 months old. The equations used to estimate MCLs for acute and chronic exposures to infant rice cereal ($MCL_{rc,acute}$ and $MCL_{rc,chronic}$, respectively) are displayed below.

$$MCL_{rc,acute} = \left(\sum_{4}^{24}\left((MRL_{acute} \times BW_t - \left(MCL_w \times V_{w,t} + C_{if} \times V_{if,t} + C_0 \times (V_{fr,t} + V_{v,t} + V_{m,t})\right)\right) \times V_{rc,t}^{-1}\right) \times 21^{-1}$$

$$MCL_{rc,chronic} = \left(\sum_{4}^{24}\left((MRL_{chronic} \times BW_t - \left(MCL_w \times V_{w,t} + C_{if} \times V_{if,t} + C_0 \times (V_{fr,t} + V_{v,t} + V_{m,t})\right)\right) \times V_{rc,t}^{-1}\right) \times 21^{-1}$$

Where

| | | |
|---|---|---|
| $BW_t$ | = | Body weight (kg) at month *t* |
| $MCL_w$ | = | Maximum Contaminant Level for arsenic in water, 0.010 mg/L |
| $V_{w,t}$ | = | Volume of water consumed per day (L/day) during month *t* |
| $C_{if}$ | = | Concentration of inorganic arsenic in infant formula |
| $V_{x,t}$ | = | Volume of specified type of infant food *x* consumed per day (g/day) during month *t* (*fr* = fruits, *v* = vegetables, *m* = meat, *rc* = rice cereal) |
| $C_0$ | = | Concentration of inorganic arsenic in infant foods containing fruit, meat, or vegetables |

To create a distribution of arsenic exposure estimates during infancy, Shibata et al. (2016) performed Monte Carlo simulations. The most health-protective value for $MCL_{rc,acute}$ – 0.4 µg/g (or 400 ppb) – was calculated when considering children at the 25$^{th}$ percentile of exposure. Since non-infant rice cereal exposures at the 50$^{th}$ percentile were above the chronic MRL, the $MCL_{rc,chronic}$ was set at 0.0 µg/g (or 0 ppb). That is, arsenic exposures from other dietary sources (including drinking water) during this period of life already expose children to levels of arsenic above the MRL, leaving no room for exposure to arsenic from infant rice cereals.

## 4.3 Comparison of Health-Based Limits to Infant Rice Cereal Exposure Scenarios

Our exposure estimates suggest that a child eating three servings per day of infant rice cereal with inorganic arsenic concentrations of 103.9 ppb (i.e., the average in today's market) would have a daily arsenic intake of either 0.35 or 0.67 µg/kg bw/day, depending on the assumptions used. Both estimates are above the IRIS RfD and ATSDR chronic MRL of 0.3 µg/kg bw/day, and thus suggest that these infants are at risk for adverse health effects from these exposures. Assuming the proposed

new standard of 100 ppb is implemented, our results suggest that high consumers of infant rice cereal may still be at risk, with arsenic dose estimates of 0.28-0.54 µg/kg bw/day.

Based on Tsuji et al.'s (2015) estimate of an RfD for adverse neurodevelopmental effects (0.4 to 1.0 µg/kg bw/day), high consumers of infant rice cereal may also be at risk for this endpoint. Moreover, it should be noted that the Tsuji et al. (2015) RfD may be considered an upper bound estimate for these effects. This is because the Tsuji et al. (2015) study does not follow the process that EPA uses in estimating RfDs for similar effects. For example, in Tsuji et al. (2015), the authors chose to apply an uncertainty factor of either 1 or 3 for LOAEL-to-NOAEL extrapolation, but did not apply an uncertainty factor for individual differences because their POD was based on a study in children, who constitute a sensitive population. We would have applied an uncertainty factor of 10 for individual differences, based on the IRIS assessment of methylmercury. The IRIS methylmercury assessment is analogous to the arsenic analysis in two ways: (1) it was based on neurological effects in a non-U.S. cohort, and (2) the doses of methylmercury needed to be estimated from biomarker data (U.S. EPA, 2001). It is unclear how the biological response in the Bangladeshi population compares to that in the U.S. population, which is genetically more diverse. In addition, we would have applied a factor of either 3 or 10 for LOAEL-to-NOAEL extrapolation. The POD in Tsuji et al. (2015) is based on the loss of 1 IQ point in Bangladeshi children; since this is not a trivial effect, the full factor of 10 could be applied for this extrapolation. Thus, we would have applied uncertainty factors of either 3 or 10 for LOAEL-to-NOAEL extrapolation and 10 for individual differences, resulting in an overall uncertainty factor of 30 or 100.[7] This would have resulted in an RfD for neurodevelopmental effects ranging from 0.01 µg/kg bw/day to 0.05 µg/kg bw/day. It is also possible that additional studies could be modeled, resulting in a different POD than that used by Tsuji et al. (2015).

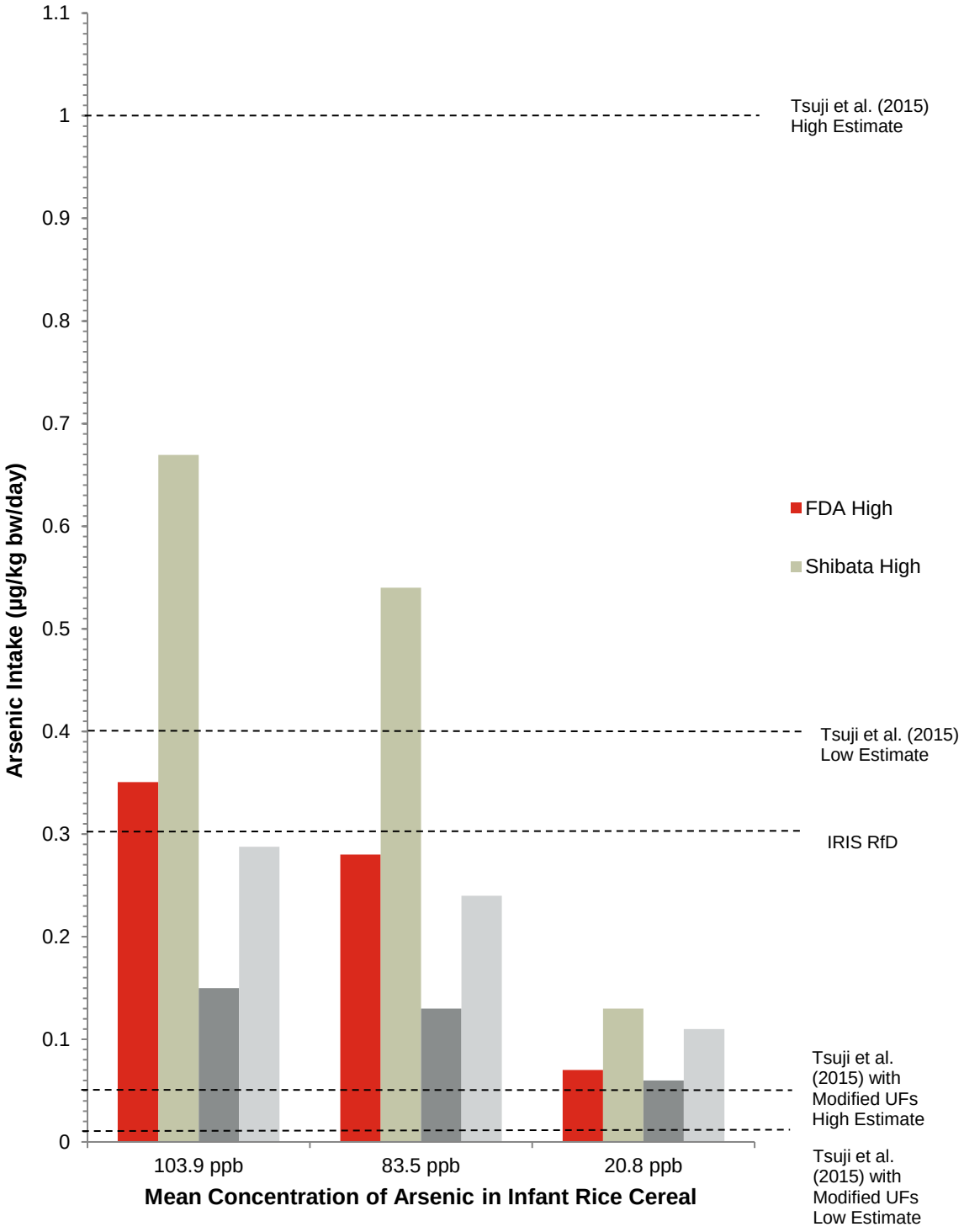
Figure 2 compares our arsenic intake estimates to the health-based limits described in Sections 4.2.1 to 4.2.3, as well as our RfD estimates derived by modifying the UF assumptions in Tsuji et al. (2015). It is important to note that infant rice cereal only constitutes a fraction of total arsenic exposures in infants; in most of our scenarios, arsenic exposures from infant rice cereal consumption leave little or no margin for arsenic exposures from alternate sources. Our arsenic dose estimates include only arsenic from infant rice cereal and do not include other sources such as rice snacks, apple juice, or drinking water. It is possible that adding in additional sources of arsenic would raise the majority of infants over the current IRIS RfD and ATSDR chronic MRL. Indeed, when Shibata et al. (2016) considered chronic exposures to inorganic arsenic from dietary exposures other than infant rice cereal, the authors found that these exposures, on average, were greater than the MRL for arsenic. Additionally, neither our high infant rice cereal exposure estimates, nor those used by FDA, represent potentially susceptible groups such as those on a medically prescribed gluten-free diet. It is anticipated that these groups may consume doses of arsenic from infant rice cereal and other rice products at concentrations above even the least protective existing RfD estimates.

Table 7 and Table 8 show that the expected decreases in arsenic exposures given implementation of the proposed standard, for both average and high consumers of infant rice cereal, are minimal. If the

[7] When they derived their REL (see Section 6.1.3), CalEPA chose to apply an uncertainty factor of 10 for inter-individual variation because the Wasserman et al. (2004) study was limited to a specific population and an uncertainty factor of 3 for use of a LOAEL. Alternatively, a confidence interval bound of the POD could be modeled (e.g., upper and lower bounds on the loss of 1 IQ point).

FDA enacts a new standard at the proposed level, we recommend reducing infant rice cereal consumption or replacing it with alternate grains such as oatmeal or quinoa in order to reduce exposures to arsenic.

**Figure 2. Mean Daily Arsenic Intake Estimates from Infant Rice Cereal Compared to Reference Doses for Arsenic**



# 5. Review of the Literature on Arsenic Exposures and Decreased Intelligence

As previously stated, FDA recently reviewed the literature and concluded that there is an association between arsenic exposures and adverse neurodevelopmental effects (FDA, 2016c). In addition, NAS (2013) concluded that there was an association between low-level exposures to arsenic and neurological deficits, based on evidence from epidemiological and laboratory studies. We conducted a review of the literature for epidemiological studies on the association between arsenic and neurodevelopment, as a first step towards quantifying IQ loss associated with exposures to arsenic. In Section 5.15.2, we describe our methods for identifying studies and provide an overview of studies on the association, which are discussed further in Section 5.2.

## 5.1 Identification of Studies

We first conducted a search for literature reviews or meta-analyses. Our search identified 3 relevant reviews: Bellinger (2013), Rodríguez-Barranco et al. (2013), and Tsuji et al. (2015). Bellinger (2013) found cause for concern regarding the neurodevelopmental effects of arsenic, but concluded that there are too many uncertainties (e.g., in timing of exposure and in the form of the dose-response relationship) to be able to conduct a risk assessment on this endpoint. However, Rodríguez-Barranco et al. (2013) and Tsuji et al. (2015) drew upon the body of literature identified to perform further quantitative analyses. Rodríguez-Barranco et al. (2013) performed meta-analyses of the association between IQ and arsenic exposures, as measured by both water arsenic concentrations and urinary arsenic concentrations. The authors found that a 50% increase in urinary arsenic levels was associated with a decrease in full-scale IQ of -0.39 points in children aged 5-15. For water arsenic concentrations, a 50% increase was associated with a -0.56 point decrease in full-scale IQ. Tsuji et al. (2015) developed a reference dose, as previously described in Section 4.2.2.

We examined the studies identified in each of the three aforementioned reviews. We excluded studies that examined neurodevelopmental effects other than decrements in cognitive function, such as impaired attention and behavioral problems. While these are important to understanding the weight of evidence between arsenic and neurological effects in general, and for determining a potential regulatory level in risk assessment, a goal of our work was to quantify IQ loss specifically. The endpoint of IQ loss has an existing method available for monetization in the economic literature, which can be used to quantify the benefits of reductions in exposure. We additionally excluded studies that were rated as low quality in Rodríguez-Barranco et al. (2013) or Tsuji et al. (2015); both reviews used standardized, established methodologies for rating the quality of epidemiological studies. We additionally searched the primary literature for studies published since the most recent literature review, Tsuji et al. (2015). Our search identified two studies: Wasserman et al. (2016) and Rodrigues et al. (2016). Table 10 summarizes the 13 primary research studies on the association between arsenic and decreased intelligence that met our criteria.

**Table 10. Studies on the Association between Arsenic and Decreased Intelligence**

| Study | Study Type | Location | Sample Size | Age at Intelligence Testing | Measure of Intelligence | Water Arsenic Data (µg/L) | Arsenic Biomarker Data (Urine in µg/L Unless Otherwise Specified) | Key Findings on the Relationship between Arsenic and Intelligence | Control for Confounders |
|---|---|---|---|---|---|---|---|---|---|
| Hamadani et al. 2010 | Prospective cohort | Bangladesh | 2112 | 18 months | BSID (MDI and PDI), MacArthur's Communicative Development Inventory (Comprehension and Expression) | Median (10th %, 90th%) during pregnancy = 66 (1, 410) | Median (10th %, 90th%):<br>Maternal during pregnancy = 96.3 (46, 219)<br>Child at 18 months = 34.6 (18, 80.2) | No significant associations found between any measure of intelligence and any arsenic exposure measure | Varying confounders including age, gestational age, HOME, height-for-weight z-score, assets, and Bayley testers or interviewers |
| Hamadani et al. 2011 | Prospective cohort | Bangladesh | 1700 | 5 years | WPPSI, adapted for use in Bangladeshi children | NA | Median:<br>Early gestation = 81 (24, 380)<br>Late gestation = 84 (26, 415)<br>Child at 1.5 years = 34 (12, 155)<br>Child at 5 years = 51 (20, 238) | Verbal and full scale IQ were significantly associated with urinary arsenic concentrations in girls<br>Associations were slightly stronger for concurrent arsenic exposure (β = -1.4, 95% CI: -2.7, -0.1) than at 1.5 years (β = -0.74, 95% CI: -1.9, 0.4), late gestation (β= -1.35, 95% CI: -2.4, -0.3), or early gestation (β = -0.92, 95% CI: -2.0, -0.2) | Sex, age, father's education, mother's BMI, mother's IQ, assets, housing, number of children in the household, gestational age, birth length, concurrent height-for-age score, and testers |
| Rocha-Amador et al. 2007 | Cross-sectional | Mexico<br>3 rural areas: Moctezuma, Salitral, and 5 de Febrero | 132 | 6-10 years | WISC-Revised, Mexican version | Mean (SD):<br>Moctezuma = 5.8 (1.3)<br>Salitral = 169 (0.9)<br>5 de Febrero = 194 (1.3) | Mean (SD):<br>Moctezuma = 12.6 (2.0)<br>Salitral = 116 (2.2)<br>5 de Febrero = 52.5 (2.2) | Significant associations found between IQ and water arsenic (β = -6.15, $p < 0.01$) and urinary arsenic (β = -5.72, $p < 0.05$) | Blood lead, mother's education, socioeconomic status, height-for-age-z-score, transferrin saturation |
| Rosado et al. 2007 | Cross-sectional | Mexico | 602 | 6-8 years | WISC-Revised, Mexican version; Visual-Spatial Abilities with Figure Design; Peabody Picture Vocabulary test | NA | Mean (SD) = 58.1 (33.2) | Significant associations found between urinary arsenic and decreased performance on neurodevelopmental tests | Age, sex, mother's school education, mercury concentration, blood lead |

| Study | Study Type | Location | Sample Size | Age at Intelligence Testing | Measure of Intelligence | Water Arsenic Data (µg/L) | Arsenic Biomarker Data (Urine in µg/L Unless Otherwise Specified) | Key Findings on the Relationship between Arsenic and Intelligence | Control for Confounders |
|---|---|---|---|---|---|---|---|---|---|
| Tofail et al. 2009 | Prospective cohort | Bangladesh | 1799 | 7 months | BSID<br>2 problem solving tests | NA | Median (IQR):<br>GW 8 = 81 (37-207)<br>GW 30 = 84 (42-230) | No significant associations found between any measure of intelligence and any arsenic exposure measure | Age, sex, mother's and father's education, housing, assets, income, mother's BMI and parity, and child's birth length and head circumference, gestational age, length in z-scores |
| von Ehrenstein et al. 2007 | Cross-sectional | India | 351 | 5-15 years | WISC (only subsets deemed culturally appropriate) | Mean (SD):<br>Lifetime average = 59 (133)<br>Lifetime peak = 147 (322)<br>Prenatal = 110 (243) | Mean (SD) = 78 (61) | Urinary arsenic concentrations were more strongly associated with decreased IQ<br>For urinary exposures, IQ change per 100 µg/L (95% CI) = -0.07 (-0.2 to 0.09) | Age, sex, maternal and paternal education, father's occupation, number of rooms in house, type of house building material, BMI, and mother's age |
| Wang et al. 2007 | Cross-sectional | China | 720 | 8-12 years | Combined Raven's Test - the Rural in China (similar to Wechsler Intelligence Scale) | Mean (SD):<br>Low = 2 (3)<br>Medium = 142 (106)<br>High = 190 (183) | NA | Mean IQ in the control group significantly higher than in the medium arsenic group (105 vs. 101, $p < 0.05$) and the high arsenic group (105 vs. 95, $p < 0.01$) | Did not adjust for confounders since no statistical differences in age, income or parental education between groups |
| Wasserman et al. 2004 | Cross-sectional | Bangladesh | 201 | 10 years | WISC | Mean (SD) = 118 (145) | Mean (SD) = 116.6 (148.8) | High water arsenic levels (> 50) significantly associated with decreased IQ compared to low levels (< 5.5)<br>Water arsenic concentrations of 10 and 50 µg/L were associated with decreases in IQ of 3.8 and 6.4 points, respectively<br>Associations between urinary arsenic and IQ were smaller and not statistically significant | Maternal education, maternal intelligence, house type, TV access, height, head circumference |

| Study | Study Type | Location | Sample Size | Age at Intelligence Testing | Measure of Intelligence | Water Arsenic Data (µg/L) | Arsenic Biomarker Data (Urine in µg/L Unless Otherwise Specified) | Key Findings on the Relationship between Arsenic and Intelligence | Control for Confounders |
|---|---|---|---|---|---|---|---|---|---|
| Wasserman et al. 2007 | Cross-sectional | Bangladesh | 301 | 6 years | WPPSI, adapted for use in Bangladeshi children | Mean (SD) = 120.1 (134.4) | Mean (SD) = 110.7 (132.8) | Water arsenic associated with IQ, β (SE) = -1.06 (0.57), p = 0.07 | Maternal education, maternal intelligence, home stimulation, school attendance, height, head circumference, and water manganese |
| Wasserman et al. 2011 | Cross-sectional | Bangladesh | 299 | 8-11 years | WISC | Mean (SD) = 43.3 (73.7) | Urine:<br>Mean (SD) = 78.1 (72.2)<br>Mean (SD), adjusted for creatinine = 246.5 (183.9) mg/g creatinine<br>Blood:<br>Mean (SD) = 4.8 (3.2) µg/L | Blood arsenic was associated with decreased IQ, β(SE) = -3.80 (2.20)<br>No association of IQ with water or urinary arsenic<br>Urinary arsenic adjusted for creatinine showed negative association with IQ (data not shown) | Maternal age, IQ, school attendance, home environment, SES, child head circumference, plasma ferritin |
| Wasserman et al. 2014 | Cross-sectional | U.S. | 272 | 8-10 years | WISC | Mean = 9.9 | Toenail = 4.7 (4.60) ppm | Compared to those with water arsenic levels < 5 µg/L, children with ≥ 5 µg/L had significant decreases in IQ of 5-6 points, but no consistent dose-response relationship between water arsenic and IQ<br>No association observed between IQ and toenail arsenic | Maternal IQ, maternal education, HOME score, number of siblings, and school district |

| Study | Study Type | Location | Sample Size | Age at Intelligence Testing | Measure of Intelligence | Water Arsenic Data (µg/L) | Arsenic Biomarker Data (Urine in µg/L Unless Otherwise Specified) | Key Findings on the Relationship between Arsenic and Intelligence | Control for Confounders |
|---|---|---|---|---|---|---|---|---|---|
| Wasserman et al. 2016 | Prospective cohort | Bangladesh | 299 | Baseline: 8-11 years<br><br>Follow up: 11-14 years | WISC | Baseline: Same as Wasserman et al. (2011)<br><br>Follow-up: NA | Baseline: Same as Wasserman et al. (2011)<br><br>Follow-up: Urine: Mean (SD) = 58.9 (51.5) Mean (SD), adjusted for creatinine = 130.8 (94.0) mg/g creatinine Blood: Mean (SD) = 4.4 (2.7) µg/L | At baseline, urinary arsenic adjusted for creatinine was significantly associated with decreases in IQ<br>Decreases in urinary arsenic concentrations at follow-up were associated with increases in working memory, but not with improvement in IQ | School grade at baseline, maternal intelligence, maternal age, HOME score, child's head circumference, plasma ferritin, and blood manganese |
| Rodrigues et al. 2016 | Cross-sectional | Bangladesh (Pabna and Sirajdikhan) | 524 | 20 to 40 months | BSID | Both areas tested several times: 1st trimester, 1 month, 12 months, 20-40 months Sirajdikhan: Median = 0.8 to 1.5 Pabna: Median = 26.5 to 31 | NA | Significant association between average water arsenic concentration and cognitive BSID score in area of high exposure, Pabna: β(SE) = -0.06 (0.03), p = 0.05<br>No association in low exposure area (potentially due to lead exposures)<br>No significant associations observed for motor BSID score in either location | Maternal age, maternal education, exposure to environmental tobacco smoke, child's sex, HOME score, maternal Raven score, and child's hematocrit levels |

## 5.2 Discussion of the Literature

Associations between arsenic exposures and decreased intelligence were observed in 11 of the 13 studies identified. The majority of studies were conducted in Bangladesh. Wasserman et al. (2004) found associations between IQ loss in 10 year olds and both water and urinary arsenic exposures, though the latter associations failed to reach significance. The decrements in IQ associated with water arsenic exposures were not negligible: concentrations of 10 and 50 µg/L were associated with decreases in IQ of 3.8 and 6.4 points, respectively (Wasserman et al., 2004). In a study of 6 year olds in the same region, Wasserman and colleagues again found associations between reduced intelligence and water arsenic exposures, though the magnitude of the association was smaller than that previously found in 10 year olds (Wasserman et al., 2007). Wasserman et al. (2011) found that blood and urinary arsenic (adjusted for creatinine) were associated with decreased IQ in 8-11 year olds; when follow-up testing was performed on these children approximately 2 years later, the authors found that the observed IQ decrements remained (Wasserman et al., 2016). That is, decreases in urinary arsenic concentrations at follow-up were not associated with improvements in intelligence; the effects of arsenic on neurodevelopment appear to be irreversible. Hamadani et al. (2011) followed a cohort of children from before birth to age 5 years. The authors concluded that there was an association between reduced IQ and urinary arsenic exposures during gestation and childhood, though the strongest association was observed when considering concurrent arsenic exposures (i.e., arsenic exposures measured at the same time as IQ testing) (Hamadani et al., 2011). Rodrigues et al. (2016) also found evidence of the neurodevelopmental effects of prenatal and early-life exposures to arsenic: high concentrations of water arsenic were associated with decreased cognition in 20-40 month olds.

In India, von Ehrenstein et al. (2007) found that urinary concentrations of arsenic were associated with small decreases in IQ. Wang et al. (2007) studied areas of China with high, medium and low concentrations of water arsenic, and found that children in the high exposure areas had, on average, IQ scores that were 10 points lower than those in the low exposure areas. Two studies in Mexico examined urinary arsenic concentrations and IQ, and found significant associations (Rocha-Amador et al., 2007; Rosado et al., 2007). Rocha-Amador et al. (2007) additionally investigated water arsenic exposures and found similar associations. Drawing upon several of the aforementioned studies, the meta-analysis conducted by Rodríguez-Barranco et al. (2013) estimated that a 50% increase in urinary arsenic concentrations would decrease IQ by -0.39 points in children aged 5-15. For water arsenic concentrations, there would be an estimated -0.56 point decrease in IQ given a 50% increase (Rodríguez-Barranco et al., 2013).

The two studies that did not find an association – Hamadani et al. (2010) and Tofail et al. (2009) – were conducted in younger populations. Hamadani et al. (2010) failed to find any associations between prenatal or early childhood water arsenic exposures and intelligence. Similarly, Tofail et al. (2009) did not find any associations between prenatal exposures and performance on several cognitive tests at age 7 months. However, as noted above, several studies have found evidence of these exposures and decreased intelligence (Hamadani et al., 2011; Rodrigues et al., 2016). In addition, the inconsistent findings in younger populations may be explained by the difficulties inherent in neurodevelopmental testing of younger children. It is also possible that there is a latency period between exposures to arsenic and its neurodevelopmental effects, or that exposure duration is critical to these effects.

The only included study conducted in a U.S. population is by Wasserman et al. (2014), who found significant decreases in IQ of approximately 5-6 points when comparing children with water arsenic concentrations ≥ 5 µg/L to those with concentrations < 5 µg/L. The authors report that when water arsenic concentrations were treated as a continuous variable, the relationship with decreases in IQ scores remained. However, the authors did not observe a consistent dose-response relationship between water arsenic and IQ (Wasserman et al., 2014). This could be due to a variety of reasons, including a smaller sample size in each of the exposure groups.

Considered as a whole, the literature provides consistent evidence of a relationship between exposures to arsenic and adverse neurodevelopmental effects. As stated above, uncertainties remain regarding the impact of timing of arsenic exposures on this association, especially in regards to early-life exposures. A limitation of the existing body of literature is that the majority of studies have been conducted in Bangladesh. This has necessitated translation and cultural adaptation of intelligence tests commonly used in scientific research (e.g., the Wechsler Intelligence Scale for Children), which were developed for use in U.S. children. The studies we identified provide few details on how these intelligence tests were adapted for Bangladeshi children. Additionally, these modified tests have not been subject to extensive validation, as the original tests were. However, Wasserman et al. (2014) found evidence of decreases in IQ points based on a sample of U.S. children exposed to arsenic in drinking water, which provides evidence that these studies can inform the risk in U.S. children. Further research on early-life exposures to arsenic, as well as in U.S. populations, would help elucidate the relationship between arsenic and neurodevelopment. The Wasserman et al. (2016) study in Bangladesh, which suggests that adverse neurodevelopmental effects are irreversible, highlights the importance of this endpoint.

# 6. Estimating IQ Losses in Children Based on Exposures to Arsenic

As previously stated, FDA recently conducted a scientific literature review and concluded that there is an association between arsenic exposures and IQ loss (FDA, 2016c). Despite this, FDA also determined that there were insufficient data to quantitatively describe the association (FDA, 2016c). While there are currently not enough data to identify a specific critical window of vulnerability of arsenic exposure, the existing evidence suggests the neurological deficits may be long-lasting or irreversible. Given the importance of this endpoint, we explored the feasibility of evaluating IQ loss based on current evidence. We performed a search of the grey literature to determine whether the endpoint of adverse neurodevelopmental effects has previously been used in rulemakings to set a standard for arsenic. We identified an approach used by the California Environmental Protection Agency (CalEPA) in 2008 to derive a Reference Exposure Level (REL) for inhalation of arsenic. Drawing upon the CalEPA (2008) method, the Massachusetts Department of Environmental Protection (MassDEP) also chose to set reference levels for arsenic exposures based on neurodevelopmental effects (MassDEP, 2011). As previously mentioned, Tsuji et al. (2015) developed a reference dose for the neurodevelopmental effects of arsenic. Based on this precedent, as well as our examination of the literature, we believe that there are sufficient data to quantify the association between arsenic exposures and IQ loss in children.

We acknowledge that uncertainties remain in establishing a quantitative relationship between arsenic in infant cereal and IQ loss, especially in regard to the timing of exposure. Some epidemiological studies have failed to find an association between prenatal or early-life exposures to arsenic and IQ scores in early childhood (Hamadani et al., 2010; Tofail et al., 2009). However, NAS posits that "this either suggests a latent period for arsenic exposure in utero or suggests that subtle effects of arsenic exposure cannot be detected in the relatively insensitive psychometric tests used in toddlers and can be adequately assessed only at higher ages" (NAS, 2013, p. 41). In addition, animal studies provide evidence for an association between early-life exposures to arsenic and neurodevelopment: studies in rats have found that these exposures are associated with decreased performance on cognitive tasks and changes in neural pathways involved in learning and memory (NAS, 2013). However, because of the inconsistent findings for early-life exposures, we examine the neurodevelopmental effects of arsenic exposures from infant rice cereal in the context of overall arsenic exposures during childhood (from ages 0 to 6 years old), where the evidence of the relationship is currently strongest. While our IQ loss results should be interpreted in light of these uncertainties, we believe that it is important to conduct a quantitative analysis, given widespread exposures to arsenic in U.S. children and the irreversible nature of its neurodevelopmental effects (Wasserman et al., 2016).

In Section 6.1, we present our selected concentration-response functions, which we use in Section 6.2 to estimate avoided IQ loss from decreased arsenic exposures from infant rice cereal in individual children (6.2.1) and nationwide (6.2.2). Section 6.2.2 also provides national-level estimates of the monetary benefits associated with decreasing arsenic exposures from infant rice cereal. In Section 6.3, we additionally present estimates assuming decreased arsenic exposures from all rice and rice products throughout childhood, not just from decreased arsenic in infant rice cereal during infancy. Section 6.4 provides further discussion of the uncertainties in our IQ loss methodologies and estimates.

## 6.1 Selection of Concentration-Response Functions

For the purposes of the evaluation presented in this report, we focus on studies that will allow us to monetize the benefits of reductions in arsenic exposure. From the 13 studies displayed in Table 10, we excluded 10 studies that did not meet our criteria. Our focus is on the endpoint of full-scale IQ, and therefore we excluded the four studies that did not use a psychological test specifically designed to measure this endpoint (Tofail et al., 2009; Hamadani et al., 2010; Rodrigues et al., 2016; Rosado et al., 2007). Selecting full-scale IQ as our endpoint (hereafter referred to simply as IQ) allowed us to develop a range of comparable estimates and to estimate monetary savings associated with reduced exposures to arsenic. We additionally excluded Wasserman et al. (2011, 2016) because these studies only presented estimates using blood arsenic and urinary arsenic adjusted for creatinine. We currently do not have methods from the peer reviewed literature for adjusting our dose estimates to these biomarkers. Although Wasserman et al. (2014) was the only study conducted in the U.S., it was excluded from our analysis as the results presented in the paper did not show a consistent dose-response relationship. We excluded Wang et al. (2007) because it only presented a categorical analysis of high, medium, and low exposure areas. The Rocha-Amador et al. (2007) study was excluded due to methodological issues; the authors concluded that fluoride is a more potent neurotoxicant than arsenic, but did not control for fluoride exposures in their arsenic regression models. Lastly, we excluded von Ehrenstein et al. (2009) because the authors note that their continuous concentration-response function was attenuated by outliers with high exposures; since we are interested in relatively low levels of arsenic exposures, we concluded that this function was not appropriate for our analyses. Although the meta-analysis from Rodríguez-Barranco et al. (2013) presents strong evidence for the risk of arsenic exposures, we were unable to include this paper because the authors did not present betas for their analysis. Instead, the authors report the results of their analysis as a pooled result for IQ loss based on a 50% increase in arsenic exposure.

We include concentration-response functions based on primary findings from the three remaining studies (Hamadani et al., 2011; Wasserman et al., 2004, 2007). In addition to the primary log-linear function from Hamadani et al. (2011), we also include a linear function reported in the study. This is because Tsuji et al. (2015) used the linear function from this study for verbal IQ to derive an RfD for neurodevelopmental effects (although few details of this function are presented in Hamadani et al. [2011]). We also include a linear slope based on Wasserman et al. (2004) and the CalEPA (2008) approach, which we refer to in subsequent sections as the Wasserman et al. (2004) linear extrapolation. Table 11 presents the concentration-response functions for arsenic exposures and IQ that we selected to estimate IQ changes. Our sources are described in further detail in the subsections below.

**Table 11. Concentration-Response Functions for Arsenic Exposures and IQ Loss Used to Estimate IQ Changes**

| Concentration-Response Function | Type of Arsenic Measure | Relationship Between Arsenic and IQ | Derivation |
|---|---|---|---|
| Hamadani et al. (2011) Log-linear | Urinary | Log-linear relationship<br>Beta of -1.4 | Original research by Hamadani et al. (2011) |
| Hamadani et al. (2011) Linear | Urinary | Linear relationship<br>0.9 IQ points lost per 100 µg/L of arsenic in the urine | Original research by Hamadani et al. (2011) with dose conversions based on Tsuji et al. (2015) |
| Wasserman et al. (2004) Quadratic | Water | Quadratic relationship<br>$y = y_0 + ax + bx^2$<br>$y_0 = 0$<br>a = -0.443<br>b = 0.0063 | Original research by Wasserman et al. (2004), and CalEPA (2008) Appendix D1 p.113 |
| Wasserman et al. (2004) Linear Extrapolation | Water | Linear relationship<br>1-point IQ loss per 2.27 µg/L of arsenic in drinking water | Based on the study by Wasserman et al. (2004) and methods used in CalEPA (2008) and MassDEP (2011) |
| Wasserman et al. (2007) | Water | Log-linear relationship<br>Beta of -1.06 | Original research by Wasserman et al. (2007) |

For the concentration-response functions based on urinary arsenic concentrations, we converted the arsenic intakes assumed from dietary exposures to urinary arsenic concentrations using the conversion equation from Tsuji et al. (2015), as described previously in Section 4.2.2. Detailed summaries of the studies and documents that form the basis of these concentration-response functions are provided in Sections 6.1.1 to 6.1.4. Additional studies from our literature search that were excluded from our analyses are described in detail in Appendix B.

### 6.1.1 Hamadani et al. (2011)

In their paper, "Critical Windows of Exposure for Arsenic-Associated Impairment of Cognitive Function in Preschool Girls and Boys: A Population-Based Cohort Study," Hamadani et al. (2011) aimed to assess cognitive and language development in 5-year-old children in relation to prenatal and postnatal arsenic exposures. The study was conducted as part of a population-based longitudinal study of a nutritional intervention in Matlab, Bangladesh. Urine samples were collected from mothers in early and late gestation and from children at 1.5 and 5 years of age, and were analyzed for the different arsenic metabolites. Hamadani et al. (2011) adapted a version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) for use in Bangladeshi children. To assess the association between arsenic and neurodevelopment, the researchers used analysis of variance (ANOVA) tests to analyze differences between quartiles of exposure and performed multivariable-adjusted regression analyses. Potential confounders included sex, home observation for measurement of environment (HOME) score (a measure of the quality of the home environment), mother's IQ, housing, gestational age, weight-for-age scores, and number of children in the household.

The majority of children participating in the study (around 1,700 total) were underweight or stunted. Children had median urinary arsenic concentrations of 34 µg/L and 51 µg/L at 1.5 and 5 years, respectively. Results of the ANOVA tests showed significant group differences and linear trends in full-scale IQ, performance IQ, and verbal IQ for each arsenic quartile. Multivariable regression analyses showed effects of sex and interactions between sex and urinary arsenic concentrations. When analyzing effects for girls and boys separately, Hamadani et al. (2011) found significant negative associations between full-scale IQ and verbal IQ in girls, and no statistically significant associations for boys. Concurrent urinary arsenic levels in girls showed stronger associations with IQ [verbal IQ: $\beta = -2.4$ (95% CI: -3.8, -1.1); full-scale IQ: $\beta = -1.4$ (95% CI: -2.7, -0.1)] than prenatal measurements or those taken at 1.5 years of age. In addition to the log-linear regression models, Hamadani et al. (2011) also presented low-dose linear relationships for the association, although they did not provide details for the derivation of these linear functions. The researchers estimated a 2.6 verbal IQ point loss and a 0.9 point IQ loss per 100 µg/L increase in urinary arsenic levels in 5-year-old girls. The researchers concluded that there is an association between early-life arsenic exposures and neurodevelopment, and noted that the finding of sex-related differences requires confirmation in future studies.

We used two concentration-response functions from Hamadani et al. (2011). We first selected the log-linear function for IQ ($\beta = -1.4$). Since the linear relationship for the association between arsenic exposures and verbal IQ was used in Tsuji et al. (2015) as the basis for the RfD for neurodevelopmental effects, we also investigated the linear relationship for IQ and arsenic of 0.9 points IQ lost per 100 µg/L increase in urinary arsenic.

### 6.1.2 Wasserman et al. (2004)

In their paper "Water Arsenic Exposure and Children's Intellectual Function in Araihazar, Bangladesh," Wasserman et al. (2004) conducted a cross-sectional study to investigate the association between arsenic exposure and reduced intellectual function in Bangladesh, while considering the effects of co-exposures to manganese. Children aged 10 years old (n = 201) of parents enrolled in a cohort study by the same authors were recruited into the study. Wasserman et al. (2004) measured total urinary arsenic concentrations and concentrations of arsenic and manganese in home water supplies. Children completed a version of the Wechsler Intelligence Scales for Children, adapted for use in Bangladesh. Regression analyses were used to examine the effects of arsenic, manganese, and co-exposures, using both continuous and categorical exposure variables. Covariates included measures of parental education and intelligence, markers of socioeconomic status, and body size measurements.

Children in the study came from families with low educational levels and had body size measurements corresponding to approximately the 4$^{th}$ percentile of children in the United States. The mean water and urinary arsenic concentrations were 117.8 µg/L and 116.6 µg/L, respectively. After adjustment for covariates, water arsenic concentrations explained approximately 4% of the variance in children's IQ scores. Wasserman et al. (2004) found a dose-dependent relationship between water arsenic concentrations and intellectual function: exposures in the highest quartile of exposure (>50 µg/L), as compared to the lowest (<5.5 µg/L), were associated with a 7.8 point reduction in full-scale IQ. In the continuous analyses, water supplies with an arsenic concentration of 10 and 50 µg/L were linked to an estimated 3.8 and 6.4 point loss in full-scale IQ, respectively. Water manganese concentrations were not significantly associated with reductions in intellectual function after

adjustment for water arsenic and other cofounders. Although there was a negative association between total urinary arsenic concentrations and intellectual function, it failed to reach statistical significance. Wasserman et al. (2004) concluded that arsenic exposures are linked to deficits in intellectual function, with a stronger association observed for water than urinary arsenic.

### 6.1.3 California Environmental Protection Agency (2008) and Massachusetts Department of Environmental Protection (2011)

CalEPA developed a chronic Reference Exposure Level (REL) for inorganic arsenic using the endpoint of adverse neurodevelopmental effects in children. The chronic REL is "a concentration at which adverse noncancer health effects would not be expected from chronic exposures" (CalEPA, 2008, p. 35). CalEPA determined that physiologically based pharmacokinetic (PBPK) modeling was not appropriate for use in developing the REL, as the modes of action and internal dosimetry of inorganic arsenic are not well understood. Instead, CalEPA used data from a 2004 study by Wasserman et al. (summarized in Section 6.1.1) to derive a value for the REL. In the Wasserman et al. (2004) study, the association between water arsenic concentration and IQ point loss was described by a quadratic model with a low slope dose of 0.44 points per µg/L. CalEPA considered the loss of 1 IQ point to be a minimal adverse effect level. The water arsenic concentration from Wasserman et al. (2004) associated with a 1-point loss in IQ (and thus considered a lowest observed adverse effect level, or LOAEL) is 1/0.44 = 2.27 µg/L. CalEPA assumed a daily water intake of 1 L and complete gastrointestinal absorption, translating this to a daily arsenic intake of 2.3 µg/day.

Since 10-year-old males (i.e., the population studied in the 2004 Wasserman et al. study) inhale approximately 9.9 $m^3$/day and absorb approximately 50% of arsenic via the inhalation route, the water arsenic LOAEL corresponds with a concentration of inorganic arsenic in air of 0.46 µg/$m^3$. CalEPA chose to apply an uncertainty factor of 10 for inter-individual variation because the Wasserman et al. (2004) study was limited to a specific population and an uncertainty factor of 3 for use of a LOAEL, which resulted in an REL of 0.015 µg/$m^3$ for inorganic arsenic in air.

CalEPA's chronic REL approach also serves as the basis for MassDEP's development of a Threshold Effects Exposure Limit (TEL) for inhalation of inorganic arsenic. TELs are intended to protect sensitive populations from adverse health effects over a lifetime of continuous exposure. MassDEP used the air arsenic concentration value of 0.015 µg/$m^3$ from CalEPA, along with the assumption of a relative source contribution from air of 20%, to calculate a TEL of 0.003 µg/$m^3$ (MassDEP, 2011).

We use the point of departure CalEPA estimated at a 1-point IQ loss from the Wasserman et al. (2004) paper and use this as a point of departure for a low-dose linear slope[8] in our calculations below. We refer to this function as the Wasserman et al. (2004) linear extrapolation.

[8] This follows a method that has precedent in the risk assessment literature. We assume the point of departure chosen by CalEPA (2.3 µg/day) as analogous to the benchmark dose (BMD), and the loss of 1 IQ point the benchmark response (BMR). We then follow the method described in conceptual model 3 of the National Research Council's *Science and Decisions:* "the following approximation can be used: *SlopeBMD* = BMR/BMD, which corresponds to the slope of the line connecting (BMD, BMR) and (0,0)" (National Research Council, 2009, p.171).

### 6.1.4 Wasserman et al. (2007)

In their 2007 paper, "Water Arsenic Exposure and Intellectual Function in 6-Year-Old Children in Araihazar, Bangladesh," Wasserman and colleagues aimed to investigate the association between arsenic and IQ in a younger population than previously examined in their 2004 paper. The authors conducted a cross-sectional study of 301 children aged 6 years old, whose parents were participating in a cohort study of the health effects of arsenic in Araihazar, Bangladesh. Arsenic exposures were assessed by analyzing water arsenic concentrations in the wells of each child's home, as well as via urinary arsenic measurements. The authors also measured water manganese concentrations and children's blood lead levels. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI), as adapted for use in Bangladeshi children, was used to assess intelligence. Wasserman et al. (2007) first developed a linear regression model of all covariates significantly associated with IQ, then examined the incremental association of continuous, log-transformed arsenic exposures. Covariates included in the model were maternal education, maternal intelligence, HOME score, school attendance, height, head circumference, and water manganese. Analyses were also conducted using quartiles of water arsenic concentrations.

Water arsenic concentrations had a mean of 120.1 µg/L, similar to the Wasserman et al. (2004) study, and ranged from 0.10 to 864 µg/L. Urinary arsenic concentrations had a mean of 110.7 µg/L and were significantly correlated with water arsenic ($r = 0.31$, $p < 0.0001$). After adjustment for confounders, the association between water arsenic and IQ loss just failed to reach significance ($\beta = -1.06$, $p < 0.07$), with water arsenic explaining 0.72% of the variance in IQ. Analyzed as quartiles, water arsenic displayed a dose dependent relationship with full-scale IQ: compared to those in the lowest quartile, children in the highest quartile of water arsenic had marginally significantly lower IQ scores ($\beta = -5.70$, $p < 0.06$). Although urinary arsenic showed a trend in the expected direction, it was not significantly associated with reduced IQ ($\beta = -1.78$, $p = 0.17$). The magnitude of the association between deficits in IQ and arsenic exposures in 6 year olds in this study was smaller than that previously observed in 10 year olds (Wasserman et al., 2004). While this may reflect the shorter duration of exposure, the authors noted that there had been extensive labeling of wells, as well as health education programs, which likely reduced drinking water consumption from the most contaminated wells. Another possible explanation for the smaller effect observed in younger children is that IQ tests tend to be less stable and reliable than those conducted at earlier ages. The authors concluded that there is evidence of the neurotoxicity of arsenic in younger age groups than previously studied.

## 6.2 Estimates of Avoided IQ Loss Associated with Reductions in Arsenic Exposures from Infant Rice Cereal

We used our arsenic exposure estimates, along with the concentration-response functions in Section 6.1, to estimate avoided IQ loss given reductions in arsenic intake from infant rice cereal, both per individual child and on the national level (presented in Sections 6.2.1 and 6.2.2, respectively). For our analyses on the national level, we also provide estimates of the monetary benefits associated with avoided IQ loss.

As previously stated, because of the uncertainties inherent in estimating IQ loss based solely on exposures during the first year of life, we chose to investigate changes in arsenic exposures from infant rice cereal by considering overall exposure in 0 to 6 year olds from rice. To do so, we added infant rice cereal exposure scenarios from the ages of 0 to 1 year old to average exposures from rice and rice products in 1 to 6 year olds. That is, in our analyses, we varied arsenic exposures from the ages of 0 to 1 year old, but kept those from 1 to 6 years old constant at average levels. We then predicted avoided IQ loss using the combined averages of exposures during ages 0 to 6 years old.

For the concentration-response functions based on urinary arsenic exposures, we modified the input values for Tsuji et al.'s (2015) dose conversion equation to match our population of interest, 0 to 6 year olds. Table 12 displays these modified input values.

**Table 12. Input Values Used to Convert Arsenic Dose to Urinary Arsenic Concentration**

| Parameter | Value | Derivation |
|---|---|---|
| Urinary excretion rate (L/day) | 0.33 | Weighted average of urinary excretion rate for 0 to 6 year olds from Walker and Griffin (1998) |
| Fraction of oral dose excreted in urine | 0.8 | Midpoint of estimated range of 0.7-0.9 from study of recovery of arsenic in urine and feces after intravenous dosing and oral dosing in water (Freeman et al., 1995; Roberts et al., 2002, 2007) |
| Body mass (kg) for 0-6 year olds | 17.4 | Estimate of the mean body weight of 0 to 6 year olds in the U.S. based on body weights in the *Exposure Factors Handbook* (EPA, 2011a) |

### 6.2.1 Individual-Level Estimates

To estimate avoided IQ loss associated with infant rice cereal consumption or concentration, we used the same arsenic exposure scenarios and sets of assumptions – based on FDA (2016c) and Shibata et al. (2016) – as previously described in Section 4.1. Table 13 and Table 14 show our estimates of avoided IQ loss using our selected concentration-response functions and the arsenic dose estimates displayed in Tables 7 and 8, respectively.

**Table 13. Estimates of Avoided Losses in Full-Scale IQ Associated with Changes in Arsenic Exposures in Infants, Using FDA's (2016c) Assumptions**

| Source | Type of Arsenic Measure | Implement FDA's Proposed Standard of 100 ppb Arsenic in Infant Rice Cereal | | Implement Alternate Standard of 50 ppb Arsenic in Infant Rice Cereal | | Reduce Infant Rice Cereal Consumption (3 Servings to 1 Serving per Day) | Replace Infant Rice Cereal (3 Servings to 0 Serving per Day) |
|---|---|---|---|---|---|---|---|
| | | High Consumer | Average Consumer | High Consumer | Average Consumer | | |
| Hamadani et al. (2011) Log-linear | Urinary | 0.16 | 0.07 | 0.80 | 0.33 | 0.44 | 0.72 |
| Hamadani et al. (2011) Linear | Urinary | 0.00 | 0.00 | 0.02 | 0.01 | 0.01 | 0.01 |
| Wasserman et al. (2004) Quadratic | Water | 0.03 | 0.01 | 0.14 | 0.05 | 0.07 | 0.11 |
| Wasserman et al. (2004) Linear Extrapolation | Water | 0.03 | 0.01 | 0.13 | 0.04 | 0.07 | 0.11 |
| Wasserman et al. (2007) | Water | 0.12 | 0.06 | 0.61 | 0.25 | 0.33 | 0.54 |
| Mean | | 0.07 | 0.03 | 0.34 | 0.14 | 0.18 | 0.30 |
| Median | | 0.03 | 0.01 | 0.14 | 0.05 | 0.07 | 0.11 |

**Table 14. Estimates of Avoided Losses in Full-Scale IQ Associated with Changes in Arsenic Exposures in Infants, Using Shibata et al.'s (2016) Assumptions**

| Source | Type of Arsenic Measure | Implement FDA's Proposed Standard of 100 ppb Arsenic in Infant Rice Cereal | | Implement Alternate Standard of 50 ppb Arsenic in Infant Rice Cereal | | Reduce Infant Rice Cereal Consumption (3 Servings to 1 Serving per Day) | Replace Infant Rice Cereal (3 Servings to 0 Serving per Day) |
|---|---|---|---|---|---|---|---|
| | | High Consumer | Average Consumer | High Consumer | Average Consumer | | |
| Hamadani et al. (2011) Log-linear | Urinary | 0.21 | 0.11 | 1.14 | 0.51 | 0.61 | 1.06 |
| Hamadani et al. (2011) Linear | Urinary | 0.01 | 0.00 | 0.03 | 0.01 | 0.02 | 0.03 |
| Wasserman et al. (2004) Quadratic | Water | 0.07 | 0.02 | 0.27 | 0.09 | 0.15 | 0.22 |
| Wasserman et al. (2004) Linear Extrapolation | Water | 0.07 | 0.02 | 0.27 | 0.09 | 0.15 | 0.22 |
| Wasserman et al. (2007) | Water | 0.16 | 0.08 | 0.86 | 0.39 | 0.46 | 0.80 |
| Mean | | 0.10 | 0.05 | 0.51 | 0.22 | 0.28 | 0.47 |
| Median | | 0.07 | 0.02 | 0.27 | 0.09 | 0.15 | 0.22 |

Table 13 and Table 14 show that our estimates of avoided IQ loss associated with decreased arsenic intake from infant rice cereal range from a mean of 0.03 to 0.47, depending on the exposure scenario, exposure assumptions and the approach used to estimate IQ losses. The assumptions based on Shibata et al. (2016) result in approximately twice the avoided IQ loss as those from FDA (2016c). The proposed FDA standard of 100 ppb results in the smallest avoided IQ losses; for average consumers, our estimates of avoided IQ loss are 0.00 to 0.11 IQ points. Implementing a lower standard of 50 ppb would result in IQ point savings in the average consumer of 0.01 to 0.51 points. Similarly, greater IQ point savings would also be observed in high consumers if FDA implemented a lower standard. Our results suggest that reducing infant rice cereal consumption or switching to alternate grains would also be effective ways to avoid IQ loss. High consumers could preserve up to approximately a half an IQ point by switching from consuming infant rice cereal at today's arsenic concentrations to only consuming alternate grains.

### 6.2.2 Nationwide Estimates

To estimate avoided IQ loss on the national level, we used the FDA's estimate of the average amount of infant rice cereal consumed daily on a per capita basis (across both consumers and nonconsumers), 0.664 µg/kg bw/day. We investigated the nationwide impact of three scenarios of reduced arsenic intake: implementing the FDA standard for arsenic in infant rice cereal of 100 ppb, implementing an alternative standard of 50 ppb, or switching to an alternate grain (such as oatmeal) with an arsenic concentration of 15 ppb or of 0 ppb. In all scenarios, benefits were calculated by comparing IQ loss to that expected given the current concentration of arsenic in infant rice cereals, 103.9 ppb. Based on census data, we estimated the number of children aged 0-6 years old in the United States to be 27,989,207 (U.S. Census Bureau, 2015).

Table 15Table 12 shows the avoided IQ loss in a hypothetical child consuming the average per capita amount of infant rice cereal each day. Table 16 displays avoided IQ loss on the national level per year under each scenario of decreased arsenic intake from infant rice cereal.

**Table 15. Estimates of Per Capita Avoided IQ Loss Associated with Decreased Arsenic Intake from Infant Rice Cereal**

| Concentration-Response Function | Avoided IQ Loss per Child Given Change to Specified Arsenic Concentration | | | |
|---|---|---|---|---|
| | 83.5 ppb (Mean Under Proposed FDA Standard of 100 ppb) | 20.8 ppb (Mean Under Alternate Standard of 50 ppb) | 15 ppb (Switch to Alternate Grain) | 0 ppb (Switch to Hypothetical Alternate) |
| Hamadani et al. (2011) Log-linear | 0.05 | 0.23 | 0.25 | 0.30 |
| Hamadani et al. (2011) Linear | 0.001 | 0.003 | 0.003 | 0.004 |
| Wasserman et al. (2004) Quadratic | 0.01 | 0.03 | 0.03 | 0.03 |
| Wasserman et al. (2004) Linear Extrapolation | 0.01 | 0.03 | 0.03 | 0.03 |
| Wasserman et al. (2007) | 0.04 | 0.17 | 0.19 | 0.22 |

**Table 16. Estimates of Annual Avoided IQ Loss Nationwide Associated with Decreased Arsenic Intake from Infant Rice Cereal**

| Concentration-Response Function | Avoided IQ Loss Nationwide Given Change to Specified Arsenic Concentration | | | |
|---|---|---|---|---|
| | 83.5 ppb (Mean Under Proposed FDA Standard of 100 ppb) | 20.8 ppb (Mean Under Alternate Standard of 50 ppb) | 15 ppb (Switch to Alternate Grain) | 0 ppb (Switch to Hypothetical Alternate) |
| Hamadani et al. (2011) Log-linear | 1,491,000 | 6,466,000 | 6,959,000 | 8,266,000 |
| Hamadani et al. (2011) Linear | 21,000 | 84,000 | 90,000 | 105,000 |
| Wasserman et al. (2004) Quadratic | 177,000 | 722,000 | 772,000 | 903,000 |
| Wasserman et al. (2004) Linear Extrapolation | 179,000 | 731,000 | 782,000 | 914,000 |
| Wasserman et al. (2007) | 1,129,000 | 4,895,000 | 5,269,000 | 6,259,000 |

Note: Results are rounded to the nearest 1,000.

We used EPA's recent estimate of the dollar value per IQ point (U.S. EPA, 2011b) to estimate the monetary benefits associated with our estimates of avoided IQ loss. The dollar value per IQ point is based on the change in lifetime earnings associated with an additional IQ point and additionally takes into account the costs of education (U.S. EPA, 2011b). We updated the EPA estimates to 2015 dollars using a 3% discount rate. Our lower-bound estimate of the value per IQ point was $9,421 and our upper-bound estimate was $13,943 based on the range used in EPA's analysis. It is important to note, however, that these estimates do not take into account the health and social impacts of reductions in IQ, and thus may underestimate the true value of an IQ point. Table 17 shows our estimates of the annual monetary benefits associated with decreased arsenic intake from infant rice cereal in U.S. children.

**Table 17. Estimated Annual Benefits Nationwide Associated with Decreased Arsenic Intake from Infant Rice Cereal**

| Concentration-Response Function | Estimated Value of Avoided IQ Loss Nationwide (in Billions) Given Change to Specified Arsenic Concentration | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 83.5 ppb (Mean Under Proposed FDA Standard of 100 ppb) | | 20.8 ppb (Mean Under Alternate Standard of 50 ppb) | | 15 ppb (Switch to Alternate Grain) | | 0 ppb (Switch to Hypothetical Alternate) | |
| | Low | High | Low | High | Low | High | Low | High |
| Hamadani et al. (2011) Log-linear | $2.01 | $2.97 | $8.70 | $12.88 | $9.37 | $13.86 | $11.13 | $16.47 |
| Hamadani et al. (2011) Linear | $0.03 | $0.04 | $0.11 | $0.17 | $0.12 | $0.18 | $0.14 | $0.21 |
| Wasserman et al. (2004) Quadratic | $0.24 | $0.35 | $0.97 | $1.44 | $1.04 | $1.54 | $1.21 | $1.80 |

| Concentration-Response Function | Estimated Value of Avoided IQ Loss Nationwide (in Billions) Given Change to Specified Arsenic Concentration | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 83.5 ppb (Mean Under Proposed FDA Standard of 100 ppb) | | 20.8 ppb (Mean Under Alternate Standard of 50 ppb) | | 15 ppb (Switch to Alternate Grain) | | 0 ppb (Switch to Hypothetical Alternate) | |
| | Low | High | Low | High | Low | High | Low | High |
| Wasserman et al. (2004) Linear Extrapolation | $0.24 | $0.36 | $0.98 | $1.46 | $1.05 | $1.56 | $1.23 | $1.82 |
| Wasserman et al. (2007) | $1.52 | $2.25 | $6.59 | $9.75 | $7.09 | $10.50 | $8.42 | $12.47 |
| Overall Minimum | $0.03 | | $0.11 | | $0.12 | | $0.14 | |
| Overall Maximum | $2.97 | | $12.88 | | $13.86 | | $16.47 | |

## 6.3 Estimates of Avoided IQ Loss Associated with Reductions in Arsenic Exposures from Rice and Rice Products

Infant rice cereal is not the only source of exposure to arsenic in a child's diet. Arsenic is also prevalent in rice and a variety of other rice products consumed by U.S. children. Additionally, arsenic may be present in other foods, drinking water, or other media such as contaminated soil. To investigate the potential impact of implementing FDA standards for arsenic in rice and rice products, rather than infant rice cereal only, we additionally present IQ loss and valuation estimates for children aged 0-6 years old that take into account decreased arsenic intake from other rice products. In children aged 0-6 years old, the mean per capita amount of rice (including rice flour) consumed is 0.556 g/kg bw/d, based on NHANES 2003-2010 data (FDA, 2016c). The mean concentration of inorganic arsenic in all rice is 96 ppb (FDA, 2016c). For consistency with our estimates in Section 6.2.2, we assumed a decrease in inorganic arsenic concentrations to either 15 ppb or 0 ppb.

Table 18 presents our estimates of IQ loss on a per capita basis, while Table 19 shows the total IQ loss per year nationwide. Table 20 provides valuation estimates for avoided IQ loss associated with decreased arsenic intake from rice and rice products.

**Table 18. Estimated Avoided IQ Loss per Child Associated with Decreased Arsenic Intake from Rice and Rice Products**

| Concentration-Response Function | Avoided IQ Loss per Child given Switch to Alternate Food at Specified Arsenic Concentration | |
|---|---|---|
| | 15 ppb | 0 ppb* |
| Hamadani et al. (2011) Log-linear | 2.60 | - |
| Hamadani et al. (2011) Linear | 0.02 | 0.02 |
| Wasserman et al. (2004) Quadratic | 0.28 | 0.33 |

| Concentration-Response Function | Avoided IQ Loss per Child given Switch to Alternate Food at Specified Arsenic Concentration | |
|---|---|---|
| | 15 ppb | 0 ppb* |
| Wasserman et al. (2004) Linear Extrapolation | 0.28 | 0.33 |
| Wasserman et al. (2007) | 1.97 | - |

*Log-linear functions cannot be used when assuming an arsenic concentration of 0, as the natural log of 0 is undefined.

**Table 19. Estimated Annual Avoided IQ Loss Nationwide Associated with Decreased Arsenic Intake from Rice and Rice Products**

| Concentration-Response Function | Avoided IQ Loss in 0 to 6 Year Olds Nationwide given Switch to Alternate Food at Specified Arsenic Concentration | |
|---|---|---|
| | 15 ppb | 0 ppb* |
| Hamadani et al. (2011) Log-linear | 72,739,000 | - |
| Hamadani et al. (2011) Linear | 479,000 | 567,000 |
| Wasserman et al. (2004) Quadratic | 7,737,000 | 9,186,000 |
| Wasserman et al. (2004) Linear Extrapolation | 7,781,000 | 9,222,000 |
| Wasserman et al. (2007) | 55,074,000 | - |

Note: Results are rounded to the nearest 1,000.
*Log-linear functions cannot be used when assuming an arsenic concentration of 0, as the natural log of 0 is undefined.

**Table 20. Estimated Annual Benefits Nationwide Associated with Decreased Arsenic Intake from Rice and Rice Products**

| Concentration-Response Function | Estimated Value of Avoided IQ Loss Nationwide (in Billions) Given Change to Specified Arsenic Concentration | | | |
|---|---|---|---|---|
| | 15 ppb As | | 0 ppb As* | |
| | Low Estimate | High Estimate | Low Estimate | High Estimate |
| Hamadani et al. (2011) Log-linear | $97.90 | $144.89 | - | - |
| Hamadani et al. (2011) Linear | $0.64 | $0.95 | $0.76 | $1.13 |
| Wasserman et al. (2004) Quadratic | $10.41 | $15.41 | $12.36 | $18.30 |
| Wasserman et al. (2004) Linear Extrapolation | $10.47 | $15.50 | $12.41 | $18.37 |
| Wasserman et al. (2007) | $74.13 | $109.70 | - | - |

*Log-linear functions cannot be used when assuming an arsenic concentration of 0, as the natural log of 0 is undefined.

As shown in Table 18, our estimates of avoided IQ loss per child vary widely, from 0.02 to 2.60 given a switch to an alternate food with 15 ppb arsenic. Across the population of children in the United States, these IQ losses add up to approximately 7.7 million to 72.7 million avoided IQ points lost (Table 19) and $0.6 to $144.9 billion in economic savings (Table 20).

## 6.4 Discussion of IQ Loss Methodologies and Estimates

Our estimates of IQ loss vary widely based on the approach used to quantify the relationship between arsenic exposures and IQ losses. Since we are examining arsenic intake levels that are below the levels observed in any of the primary studies of arsenic and IQ loss, we need to extrapolate their results to our lower levels. However, uncertainty remains as to what type of function (e.g., log-linear, linear) best describes the relationship between arsenic exposure and IQ loss, particularly at these lower levels of exposure.

Our estimates based on betas for the log-linear relationship between arsenic exposures and IQ from Hamadani et al. (2011) and Wasserman et al. (2007) may potentially overestimate the IQ losses in the lowest-dose regions. This is because, in the low-dose region (where our dietary exposures fall), the log-linear function has a steeper slope. This relationship is not unique to the arsenic literature; the use of log-linear functions relating children's blood lead levels and IQ loss is frequently found in the epidemiological literature. In the case of lead, which has a deeper literature from which to draw conclusions, it is thought that the log-linear relationship may accurately describe the relationship between lead and IQ loss. As stated in Hornung and Lanphear (2014), "collectively, the evidence that lead and some other environmental toxicants exhibit a supralinear relationship indicates that we can dramatically reduce morbidity from many prevalent chronic diseases that afflict industrialized populations" (p. 2). Therefore, it is also possible that using a linear slope in the low-dose region may underestimate the true effect. We included the linear function from Hamadani et al. (2011) because Tsuji et al. (2015) chose the linear verbal IQ slope (which showed a greater effect than full-scale IQ) from this paper as the basis for their RfD for neurodevelopmental effects, as described in Section 4.2.2. However, it should be noted that the primary results reported by Hamadani et al. (2011) were the log-linear regression analyses. Additionally, as previously stated, it is unclear how the linear relationship was derived because the details of the regression and model fit are not included in the original paper.

Because the shape of the dose-response curve is unknown in the lower-dose region, it is difficult to predict if the log-linear functions may overestimate IQ loss at the lower doses observed from infant cereal consumption. We highlight the results of the IQ loss estimates from the Wasserman et al. (2004) paper, given the precedent of its use to inform both the CalEPA and MassDEP regulatory limits. Additionally, these estimates are within the range of our upper- (log-linear Hamadani et al., 2011) and lower-bound (linear Hamadani et al., 2011) estimates for IQ loss. We used both the Wasserman et al. (2004) quadratic relationship (as described in more detail by CalEPA) directly, and a linear slope extrapolated from a point of departure of a 1-point loss in IQ. Both estimates are very similar, indicating that this function may be estimating IQ loss appropriately in the exposure ranges of arsenic in our cereal data. An additional uncertainty in our analysis arises because we are considering arsenic exposures from only one source. A full exposure analysis that includes additional foods and pathways may shift the arsenic exposure profiles of children further up the dose-response curve.

Additional uncertainties in our IQ loss estimates are a consequence of limitations in the body of literature on the association between arsenic and adverse neurodevelopmental effects. All the epidemiological studies used in deriving the various approaches were conducted in non-U.S. populations, and exposures to arsenic in these populations tend to be higher than those observed in the United States. In addition, studies using non-U.S. populations have necessitated the development of IQ tests that have been culturally adapted for these populations; however, the process for adapting

and validating these IQ tests is often not clearly described in the published studies. Additionally, children in Bangladesh tend to have poorer nutrition and lower educational status. Thus, results of these studies may not be directly generalizable to our population of U.S. infants and children.

The studies that form the basis of our concentration-response functions are in populations whose primary exposure to arsenic is from contaminated drinking water, though they potentially also have exposure from contaminated rice or other sources. Our estimates of the association between IQ and arsenic are either based on urinary arsenic concentrations or water arsenic concentrations, measured concurrently with the IQ test. We assume that drinking water exposures to arsenic are relatively constant throughout the lifetime of the populations studied, which means that these concurrent measures are reflective of average lifetime exposures to arsenic in the children examined. However, this assumption introduces an additional uncertainty into our analysis. Studies that measure urinary arsenic provide a representation of total arsenic exposure, but uncertainty is introduced by estimating arsenic dose based on urinary arsenic concentrations. It should be noted that our estimates are based on the method published in Tsuji et al. (2015).

Additionally, we performed searches of the literature to confirm that the parameters used in the equation to convert urinary arsenic to dose are reasonable. Another uncertainty arises from our assumption that total urinary arsenic concentrations are attributable to inorganic arsenic exposures only (i.e., not also organic forms of arsenic). In the Hamadani et al. (2011) study, the authors examined the association between neurodevelopment and total urinary arsenic (comprised of inorganic arsenic, MMA, and DMA). We assume that the measured MMA and DMA are a result of metabolism of inorganic arsenic, rather than direct ingestion of MMA and DMA. However, this is a reasonable assumption because Bangladeshi populations consume very little seafood, which is the most common dietary source of these organic forms (Wasserman et al., 2004).

Uncertainties also remain regarding the most important timeframe of exposure to arsenic for IQ loss (e.g., prenatal, infancy, or throughout childhood). It is difficult to parse out the contributions of exposures to arsenic throughout childhood on decreased IQ based on the available evidence. We also applied our concentration-response functions to infants only (i.e., we did not consider results in the context of exposures during ages 0 to 6 years old) and found that our IQ loss estimates were higher than those presented here. That is, using infant exposures directly in the concentration-response functions as a concurrent measure would result in larger estimated IQ loss. This is because infants have lower body weights, and thus higher arsenic intakes on a body-weight basis (i.e., in µg/kg bw/day). If the critical window of exposure to arsenic is during infancy, we may be underestimating IQ loss. Our methods for estimating IQ loss are thus conservative.

For the above reasons, we consider our IQ loss estimates to be preliminary results and note that they contain high levels of uncertainty. Nonetheless, our IQ loss estimates suggest that the deficits in IQ associated with exposures to arsenic in infants as a result of infant rice cereal consumption are not negligible. Even the lowest IQ loss estimates generated by the linear function from Hamadani et al. (2011) are not minimal when considered on a population basis (i.e., summed across the entire U.S. population of infants). According to the IQ loss estimates from Wasserman et al. (2004), a nationwide switch to an alternate infant food with 0 ppb arsenic would result in avoided IQ losses of approximately 1 million points per year and $1.2 to $1.8 billion in additional annual earnings.

# 7. Conclusions

Our analyses of arsenic exposures from infant rice cereal during the first year of life suggest that these exposures are not insignificant, and may place infants at risk for adverse health effects. During our search for estimates of daily exposures to arsenic from infant rice cereal, we identified sources other than the FDA (2016c) risk assessment, such as Shibata et al. (2016), that estimated higher arsenic exposures from infant rice cereal than FDA. We noted that the assumptions used in Shibata et al. (2016) regarding the number of tablespoons consumed per serving were similar to those used in the FDA (2016c) risk assessment. However, the FDA (2016c) risk assessment uses the assumption of 2.5 grams of infant rice cereal per tablespoon, while the Shibata et al. (2016) study assumes 4.6 grams per tablespoon, resulting in higher arsenic exposure estimates. Based on our examination of the nutrition facts of popular brands, we concluded that the assumption from Shibata et al. (2016) is more in line with products currently available on the U.S. market. Our arsenic exposure estimates based on the Shibata et al. (2016) assumptions are approximately twice as large as those based on the FDA (2016c) assumptions. FDA's quantitative assessment of the cancer risks of arsenic in infant rice cereal (FDA, 2016c) was listed as one of the reasons for setting the proposed new standard at 100 ppb. Modifying the exposure assumptions in the FDA analysis may thus result in more health-protective estimates.

Drawing upon the methods used in FDA (2016c) and Shibata et al. (2016), we estimated that high consumers of infant rice cereal (i.e., infants eating three servings per day) eating products currently on the U.S. market would have a daily arsenic intake of 0.35-0.67 µg/kg bw/day. Both the IRIS RfD and the ATSDR MRL for inorganic arsenic, which are based on skin changes and possible vascular complications, are set at 0.3 µg/kg bw/day. Thus, our exposure estimates indicate that infants may be at risk for these adverse health effects. Additionally, per the Tsuji et al. (2015) lower-bound estimate for an RfD for the neurodevelopmental effects of arsenic (0.4 µg/kg bw/day), high consumers of infant rice cereal may also be at risk for this endpoint. Even in average consumers of infant rice cereal (i.e., one serving per day), our estimates of arsenic intakes (0.15 to 0.29 µg/kg bw/day) leave little room for exposures to arsenic from other sources. Arsenic may also be found in drinking water, as well as dietary sources such as infant rice snacks and apple juice.

We also assessed various scenarios of reduced arsenic concentrations and reduced consumption of infant rice cereal. Our analyses suggest that implementation of the proposed new FDA standard for arsenic in infant rice cereal would only result in minimal decreases in arsenic exposures to infants. We demonstrated that one alternate limit of 50 ppb (which FDA [2016c] associates with an average arsenic concentration in rice cereal of 20.8 ppb) would result in far greater decreases in exposures, as would reducing or replacing infant rice cereal consumption with an alternate food. However, our analysis is aimed at illustrating the benefits of reducing arsenic exposure, rather than suggesting what a regulatory limit should be. We did not quantify all potential neurological endpoints, or other adverse effects associated with arsenic.

Although we note that our IQ loss estimates are preliminary and there are limitations inherent in our methodologies, our results suggest that the IQ losses associated with infant rice cereal consumption are not negligible when considered on a nationwide basis. Across the U.S. population of infants, we estimate that replacement of infant rice cereal with an alternate infant food not containing arsenic would result in approximately $1.2 to $1.8 billion in additional annual earnings by avoiding IQ losses of almost 1 million points per year. Further benefits could be realized by decreasing arsenic exposures

throughout childhood. We estimate that, across the U.S. population of children aged 0 to 6 years old, replacing all rice and rice products with alternate foods containing no arsenic would result in avoided IQ losses of more than 9 million points per year and approximately $12 to $18 billion in additional annual earnings. Additionally, our IQ valuation estimates show that even minimal IQ losses can also have significant economic impacts when summed across the entire population of infants in the United States. It is important to note that, although we selected the endpoint of IQ to enable monetization of benefits, there may be additional neurodevelopmental or other health endpoints that are more sensitive to changes in arsenic exposures. For example, Hamadani et al. (2011) found evidence of a steeper relationship between arsenic exposures and verbal IQ loss than full-scale IQ loss.

As noted above, our exposure and IQ loss estimates must be considered in light of the fact that they are not estimates of complete arsenic exposures in infants; infants are also exposed to arsenic in other dietary sources. Additionally, although we modeled high consumers of infant rice cereal in our analyses, we acknowledge that these estimates may not have captured the highest consumers, such as various ethnic groups or those with special dietary considerations. Data on infant rice cereal consumption in these populations are lacking, though there is evidence to suggest that they may face even higher exposures. For example, Munera-Picazo et al. (2014a) found that children under 5 years old with celiac disease had an inorganic arsenic intake that was a full order of magnitude higher than the mean daily inorganic arsenic intake from FDA's risk assessment report (FDA, 2016c).

Taken together, our arsenic exposure and IQ loss estimates suggest that arsenic in infant rice cereal poses health risks to infants. Findings of the recent study by Wasserman et al. (2016), which showed that IQ deficits in children persisted after 2 years, suggest that IQ loss is irreversible; avoiding exposures to arsenic from infant rice cereal and other dietary sources is both prudent and essential. We therefore recommend limiting consumption of infant rice cereal during infancy, and of rice and other rice-based products throughout childhood. However, it should be noted that concentrations of arsenic, other heavy metals such as lead, and other neurotoxins have not been well characterized for alternative infant foods. Further research is needed to determine what alternatives might be most appropriate. Additionally, our research on arsenic concentrations, as well as independent testing by HBBF, shows that large variation can exist between different brands of the same types of infant foods. We recommend feeding infants a varied diet that contains diverse grains and other foods, such as fruits and vegetables, in order to limit the risk of any one particular exposure (e.g., arsenic from infant rice cereal).

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# Appendix A: Review of the Literature on the Health Effects of DMA Exposures

While inorganic arsenic is considered to be the most toxic form of arsenic, other forms may also have similar adverse health effects. In its 2016 risk assessment, FDA concluded that, although DMA is present in infant rice cereals at relatively high levels, exposure to DMA at these levels is unlikely to pose a health concern. We reviewed toxicological evidence on the health effects of DMA to assess whether DMA in infant rice cereal may pose a health concern for infants.

FDA's decision not to regulate DMA in infant rice cereal appears to be primarily based on animal neurotoxicity studies and the Minimal Risk Level for exposure to DMA developed by ATSDR. Studies of chronic dietary exposures to DMA did not find any clinical signs of neurotoxicity or brain lesions in rats or mice at doses of 7.8 mg/kg bw/day and 94 mg/kg bw/day, respectively (ATSDR, 2007), even though the DMA levels studied were far higher than those that would be observed in dietary exposures to humans (FDA, 2016c). FDA conducted a literature search to identify existing standards for oral exposures to DMA, which yielded only ATSDR's MRL for chronic oral exposures to DMA of 0.02 mg/kg bw/day (FDA, 2016c). The MRL for DMA was based on a study of exposures to mice by Arnold et al. (2006), which found a LOAEL of 7.8 mg/kg bw/day associated with changes to cells in the urinary bladder in females. The MRL of 0.02 mg/kg bw/day was derived from a $BMDL_{10}$ of 1.80 mg/kg bw/day associated with a 10% extra risk of change from the control, along with uncertainty factors of 10 for extrapolation from animals to humans and 10 for human variability. In its 2016 risk assessment, FDA noted that its estimates of mean per capita exposures to DMA from rice or infant rice cereal exposures, which ranged from 43.5 to 74.1 ng/kg bw/day, only constituted a maximum of 0.4% of the MRL and thus are not likely to pose a health concern (FDA, 2016c).

When evaluating the health effects literature for DMA, it is important to note that determining its toxicity is difficult for a number of reasons. In humans, exposures to the different forms of arsenic commonly occur in combination, making it difficult to parse out the health effects of DMA versus cumulative arsenic exposures. For example, exposures to arsenic from consumption to rice often include inorganic forms ($As^{III}$ and $As^{V}$) as well as DMA (Williams et al., 2005; FDA, 2016b). Although laboratory studies of animal exposures to different forms of arsenic can, in theory, help to elucidate the health effects of each form in humans, there are significant differences in arsenic metabolism and distribution between species; because of these differences, it is difficult to determine which species provide the most suitable model for humans (U.S. EPA, 2010). In addition, the health effects of DMA vary based on whether it is in its trivalent or pentavalent form. The trivalent form of DMA, which is formed as an intermediate during metabolism of inorganic arsenic, is highly toxic and reactive; it is thought to contribute to the adverse human health effects of inorganic arsenic (U.S. EPA, 2010). However, the form of DMA found in rice is pentavalent (Williams et al., 2005). Thus, in the remainder of this report, we are referring only to the pentavalent form in our discussion of DMA.

The human health toxicity of a chemical is partially determined by its absorption, distribution, metabolism, and excretion. Following ingestion exposures, DMA appears to be well absorbed into the bloodstream in humans (approximately 75-85%, similar to inorganic arsenic) and is thus distributed throughout the body (U.S. EPA, 2010). However, studies of arsenic metabolites in blood have shown that DMA has a substantially shorter half-life in blood, and thus constitutes a lower proportion of total arsenic concentrations in blood than inorganic arsenic and MMA (National Academy of Sciences

[NAS], 2013). In addition, DMA undergoes minimal or no metabolism in humans (as well as in the majority of animal models) and is excreted rapidly in the urine (Cohen et al., 2006). Buchet et al. (1981) found that 75% of a single oral dose of DMA to human volunteers was excreted in urine as unchanged DMA within 4 days. Methylated forms of arsenic such as DMA are easier for the human body to excrete, as the ultimate metabolism of inorganic arsenic to DMA is considered to be a detoxification reaction to facilitate excretion (Cohen et al., 2006).

Studies of DMA exposures in animals have found evidence of non-cancer adverse health effects related to kidney and bladder function, as well as fetal development (ATSDR, 2007; EFSA, 2009). The urinary system appears to be the most sensitive target for exposures to DMA (ATSDR, 2007). As noted above, the MRL for chronic DMA exposures is based on adverse effects in the bladder. The renal effects of DMA exposures have been observed in rats and mice at high doses of 5 to 57 mg/kg bw/day in intermediate duration studies and of 3.1 mg/kg bw/day in chronic duration studies (ATSDR, 2007). While there has been limited research into the effects of early-life exposures to DMA, it has been shown to be easily transferable both from the mother to the fetus via the placenta, and via the blood-brain barrier in infants (EFSA, 2009). Developmental toxicology studies have shown that maternal toxicity and fetal death occur at high levels of exposure to DMA (EFSA, 2009).

Evidence on the carcinogenicity of DMA is mixed. Prior research has found that DMA exposure is associated with bladder cancer in rats, but has not been linked to any type of cancer in mice (ATSDR, 2007). In their 2006 paper "Methylated Arsenicals: The Implications of Metabolism and Carcinogenicity Studies in Rodents to Human Risk Assessment," Cohen et al. considered these results in light of the aforementioned issues related to interspecies differences in arsenic toxicity. The distribution and metabolism of arsenic is significantly different in rats and in humans and other animals. Rats undergo extensive metabolism of DMA to trimethylarsine oxide (TMAO), which constitutes more than half of the total arsenic in urine detected after administration of DMA in rats. In contrast, TMAO is not detectable in the vast majority of human urine samples (Cohen et al., 2006). While TMAO itself is not highly toxic, it is formed via a process that results in formation of trivalent DMA as a metabolic intermediate. Therefore, it is doubtful whether the carcinogenicity of DMA in rats is relevant to the risks of DMA exposure in humans (Cohen et al., 2006).

The adverse health effects of exposures to DMA observed in animal studies have all been observed at much higher doses of DMA than would reasonably be expected from dietary exposures in humans. In addition, the majority of adverse health effects associated with DMA have been observed in rats, which metabolize DMA very differently from humans. However, the overall health effects literature on DMA is currently lacking studies on early-life exposures and epidemiological studies in humans. Since DMA is a prevalent contaminant in rice, we therefore caution that further study is necessary to determine its safety for infants.

# Appendix B: Additional Studies on the Association between Arsenic Exposures and IQ Loss

In this section, we provide detailed summaries of studies on the association between arsenic and neurodevelopment that we reviewed but did not include in our quantitative analyses of IQ loss.

## Hamadani et al. (2010)

The 2010 study by Hamadani et al., "Pre- and postnatal arsenic exposure and child development at 18 months of age: a cohort study in rural Bangladesh," aimed to investigate the association between arsenic exposures and neurodevelopment in early childhood. Hamadani et al. (2010) opted to test children at 18 months, since neurodevelopmental tests at this age tend to be more predictive of intelligence than those conducted earlier in life (e.g., at 7 months as in a previous study conducted by the authors, Tofail et al. (2009)). Children (n = 2112) were recruited from a study of maternal nutrient supplementation during pregnancy in Bangladesh. Urinary arsenic concentrations were measured in the mother at 8 and 30 weeks of gestation, as well as in the child at 18 months of age. ANOVA tests were used to analyze differences in neurodevelopmental measures by urinary arsenic quartiles. Regression analyses were conducted with adjustment for age, sex, HOME score, assets, housing, mother's education, mother's BMI, gestational age, number of children in the household, birth length, head circumference, weight-for-height z-score, and tester. The authors also examined the possible effects of arsenic metabolism in children by entering DMA into the regression analysis for urinary arsenic at 18 months, and stratifying children based on percentage of MMA.

Median urinary arsenic concentrations in mothers (mean of gestation weeks 8 and 30) and children in the study were 96.3 µg/L and 34.6 µg/L, respectively. ANOVA tests showed significant differences in neurodevelopmental testing scores by quartile of both maternal and child urinary arsenic. However, after controlling for confounders, no significant differences in neurodevelopmental scores were found when comparing the highest and lowest quartiles of arsenic exposures. Similarly, the regression analyses did not show any significant associations between arsenic and any of the neurodevelopmental tests. No effect of arsenic metabolism was found. Hamadani et al. (2010) noted that these results were contrary to expectations; it is possible that the effects of arsenic on neurodevelopment exhibit later on in life, or that exposure duration is critical to these effects.

## Rocha-Amador et al. (2007)

In their 2007 paper, "Decreased intelligence in children and exposure to fluoride and arsenic in drinking water", Rocha-Amador et al. (2007) aimed to examine the effects of fluoride and arsenic on IQ. The authors selected children aged 6 to 10 years old (n = 308) from three areas of Mexico (Moctezuma, Salitral, and 5 de Febrero) with varying levels of the two contaminants. IQ was assessed using the Mexican version of the Wechsler Intelligence Scale for Children Revised. Levels of both contaminants were measured in water and arsenic. Children's blood lead levels were also measured. The multiple linear regression model for log-transformed arsenic was adjusted for the following variables: blood lead, mother's education, socioeconomic status, height-for-age z-score, and transferrin saturation. Two communities had high levels of water arsenic: Salitral and 5 de Febrero had means of 169 and 194 µg/L, respectively. The final community, Moctezuma, had a significantly lower mean of 5.8 µg/L. Water fluoride levels followed the same pattern as water arsenic. However, urinary arsenic levels in 5 de Febrero (i.e., the community with the highest water arsenic

contamination) were lower than those in Salitral, due to use of bottled water by residents. After adjustment for confounders, both water and urinary arsenic showed significant negative associations with IQ ($\beta$ = -6.15 and -5.72, respectively, $p < 0.001$). The observed negative associations were greater when considering fluoride exposures. Rocha-Amador et al. (2007) concluded that both fluoride and arsenic may be associated with decreases in IQ in children.

### Rodrigues et al. (2016)

In their study "Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water," Rodrigues et al. (2016) aimed to investigate the relationship between exposures to arsenic, manganese and lead, both independently and in combination, and deficits in intellectual function in Bangladeshi children. The authors recruited 524 participants enrolled in a prospective birth cohort study from two regions of Bangladesh, Pabna, and Sirajikhan. At age 20-40 months, children completed a version of the Bayley Scales of Infant and Toddler Development, which was adapted for use in Bangladesh. Water samples were obtained from infant's homes at age 1 month, 12 months, and 20-40 months and analyzed for arsenic and manganese; due to high correlation between the water concentrations at different time points, only the concurrent measurements were used in the final analyses. Blood lead levels were also measured at age 20-40 months. Linear regression models were used to examine the association between log-transformed water arsenic and manganese concentrations and children's Bayley scores. Generalized additive models were also used to determine whether additional terms (e.g., quadratic) should be included in the regression models to improve fit. Covariates included in the model were maternal demographics (age, education, and intelligence), sex, tobacco smoke exposure, HOME score, and child hematocrit levels.

Children participating in the study had a mean age of 2.3 years. Although children in the two regions had similar demographics on the whole, there were significant differences in body size measurements, premature birth, and exposure to tobacco smoke. Median water arsenic concentrations were higher, and median manganese and lead water concentrations lower, in Pabna than in Sirajdikhan. The generalized additive models showed that the association between water arsenic concentrations and Bayley scores was linear. In Pabna, the region with higher arsenic concentrations, there was a significant negative association between exposures and scores on the Bayley scale ($\beta$ = -0.06, SE = 0.03). This association was not observed in Sirajdikhan, where 81% of samples were below 50 µg/L. Similarly, significant associations between lead exposures and intellectual deficits were only observed in Sirajdikhan, which had higher water lead concentrations. No significant associations were observed between intellectual function and manganese exposures in either region. Rodrigues et al. (2016) found some evidence to suggest an interaction between arsenic and lead exposures, with lead exposures exacerbating the negative effects of arsenic exposures. To investigate the effect of timing of arsenic exposures, the authors analyzed associations between Bayley scores and water concentrations collected during the first trimester and 1 month post-partum in Pabna. Significant associations were observed for first trimester, but not for 1 month post-partum, exposures; this may be because the majority of children in the study were breastfed. Rodrigues et al. (2016) concluded that, when exposure to lead is lower, arsenic exposures are associated with decreased intellectual functioning.

### Rodríguez-Barranco et al. (2013)

In their 2013 paper "Association of arsenic, cadmium, and manganese exposure with neurodevelopment and behavioral disorders in children: A systematic review and meta-analysis," Rodríguez-Barranco et al. reviewed the literature on arsenic exposures and neurodevelopmental outcomes in children and performed meta-analyses of the identified studies. The authors included original research articles of prenatal or postnatal exposures in study populations up to 16 years of age, resulting in a total of 15 studies on arsenic and neurodevelopment. Each included study was assessed for quality using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement by von Elm et al. (2008). Rodríguez-Barranco et al. (2013) rated the studies as low, medium, or high quality according to the number of STROBE methodological criteria (nine in total) that were met. All included studies that used any type of Wechsler IQ measurement scale and linear regression techniques were also included in the meta-analyses. Since the studies used different transformations of the arsenic exposure variable (i.e., natural log, log base 10, or none), each effect estimate was recalculated for the meta-analyses to express a relative change in exposures. Rodríguez-Barranco et al. (2013) selected the change as a 50% increase in the arsenic exposure variable, either arsenic water concentrations or urinary arsenic concentrations.

Out of the 15 studies reviewed, a significant association between arsenic exposures and impaired cognitive function in children was found in 13 studies. Deficits in verbal, performance, and full-scale IQ were most commonly observed. The authors conducted two meta-analyses, using urinary arsenic levels (six studies total) and water arsenic concentrations (four studies). Rodríguez-Barranco et al. (2013) found that a 50% increase in urinary arsenic levels was associated with a decrease in full-scale IQ of -0.39 points and a decrease in verbal IQ of -0.26 points in children aged 5-15. For water arsenic concentrations, a 50% increase was associated with a -0.56 point decrease in full-scale IQ. Water arsenic concentrations were also associated with a -0.33 point decrease in performance IQ, but no statistically significant associations were observed for verbal IQ.

### Rosado et al. (2007)

Rosado et al. (2007) investigated the effects of exposures to arsenic on cognitive function in a cohort of Mexican schoolchildren aged 6-7 years old. Children (n = 602) recruited into the study lived near the site of a metallurgic smelter with known contamination by toxicants such as lead and arsenic. Urinary arsenic (speciated, MMA, and DMA) and blood lead measurements were obtained. Children completed an array of cognitive testing measures to evaluate memory, attention, problem solving, and vocabulary processes. Intelligence was assessed using several subscales of the Wechsler Intelligence Scale for Children-Revised Mexican Version, as well as other tests such as the Peabody Picture Vocabulary Test. Regression models were adjusted for confounders that were significantly associated with children's test scores: children's age, children's sex, mother's school education, hemoglobin, and blood lead. Stratified analyses were also performed to assess children with urinary arsenic levels $\leq 50$ µg/L and $> 50$ µg/L, and to investigate sex differences in the association.

The mean urinary arsenic concentration of children in the study was 58 µg/L. In the continuous and stratified analyses, urinary arsenic concentrations were associated with several tests of intelligence. When results were stratified by gender, the authors found that several cognitive tests were only negatively associated with urinary arsenic in boys, but not girls. The authors hypothesized that this finding was a result of the higher urinary arsenic concentrations observed in boys. Rosado et al.

(2007) concluded that arsenic exposures were associated with decrements in intellectual function, and that this association was independent of any neurodevelopmental effects of lead.

### Tofail et al. (2009)

Tofail et al.'s 2009 paper, "Effect of Arsenic Exposure during Pregnancy on Infant Development at 7 Months in Rural Matlab, Bangladesh," aimed to prospectively examine the effects of prenatal arsenic exposures on neurodevelopment in early childhood. Women were recruited from a cohort study on the effects of micronutrient supplementation during pregnancy. Urinary arsenic samples were collected from women (n = 1799) during early and late gestation ($8^{th}$ and $30^{th}$ gestation week, respectively). Neurodevelopment in offspring at 7 months of age was assessed using the Bayley Scales of Infant Development, which evaluates cognitive and motor function, as well as two problem solving tests designed to assess cognition. Tofail et al. (2009) first examined differences in scores by arsenic quartile using ANOVA tests. Regression models were then constructed for each outcome, controlling for age, mother's and father's education, housing, assets, income, mother's BMI, parity, gestational age, and child's birth length, head circumference and length z-scores at age 7 months.

Median urinary arsenic concentrations at gestation week 8 and 30 were 81 µg/L and 84 µg/L, respectively. No significant differences in any outcome were found when maternal urinary arsenic concentrations were analyzed by quartile. Similarly, none of the regression analyses for urinary arsenic concentrations and neurodevelopmental outcomes showed significant associations. Tofail et al. (2009) concluded that there was not an association between arsenic exposures and the neurodevelopmental functions examined, but noted that it is possible that other outcomes may be impacted, or that there may be a longer latency period between exposures and effects than examined in their study.

### Von Ehrenstein et al. (2007)

In von Ehrenstein et al.'s 2007 paper, "Children's Intellectual Function in Relation to Arsenic Exposure," the authors aimed to examine the association between IQ loss and arsenic exposures in utero and during childhood. Children (n = 351) aged 5-15 years old were recruited from an area of India with known arsenic exposures. These children were born to mothers in a cohort study of chronic respiratory disease, who were classified as having high or low exposure to arsenic based on water arsenic concentrations (>400 µg/L and <50 µg/L, respectively). Since there is no IQ test intended specifically for use in Indian children, the authors selected appropriate tests based on consultation with local investigators: the Wechsler Intelligence Scale for Children, the Raven Colored Progressive Matrices test, the Total Sentence Recall test, and the Purdue pegboard test. In addition to completing the IQ test, children provided urinary samples for arsenic testing and were examined for arsenic-induced skin lesions. Arsenic exposure was also assessed by water well concentrations: the authors measured arsenic in all wells used during the children's lifetime for a period of 6 months or more. From these exposure histories, the authors calculated lifetime average and peak arsenic exposure. In utero exposures were also assessed based on mother's exposure during pregnancy. In the statistical analyses, arsenic exposures were examined as continuous and categorical variables. To calculate a full-scale IQ measure, von Ehrenstein et al. (2007) summed the z-scores of verbal and performance tests. Linear regression models were adjusted for age, sex, BMI, maternal and paternal education, father's occupation, mother's age, type of house building material, and number of rooms in the house.

The mean peak and average water arsenic concentrations were 147 and 59 µg/L, respectively. Urinary arsenic concentrations had a mean of 78 µg/L and were slightly higher in boys than girls. No consistent dose-response relationships were found for the association between performance in the cognitive tests and any of the water arsenic measures. Full-scale IQ scores decreased with increasing tertile of urinary arsenic exposure ($p = 0.05$), though this relationship was attenuated when urinary arsenic concentrations were analyzed as a continuous variable. Per every 100 µg/L increase in urinary arsenic concentrations, von Ehrenstein et al. (2007) found a 0.07 point decrease in full-scale IQ. The authors noted that analyses using continuous urinary arsenic were heavily skewed by a few extremely high measurements. Von Ehrenstein et al. (2007) concluded that urinary arsenic concentrations better reflect exposure from all sources of arsenic (i.e., from food and drinking water) and are associated with small decrements in cognitive function.

### Wang et al. (2007)

In their 2007 paper "Arsenic and Fluoride Exposure in Drinking Water: Children's IQ and Growth in Shanyin County, Shanxi Province, China," Wang et al. examined children (n = 720) living in areas of China with varying levels of exposure to arsenic and fluoride. Areas were classified as high arsenic-low fluoride, medium arsenic-low fluoride, high fluoride-low arsenic or control (low arsenic and low fluoride). Children in these groups were similar to each other in terms of average age (approximately 10 years old), income, and parental education. IQ was measured via a modified form of the Raven's test, standardized for use in rural Chinese children. The authors performed unadjusted regression analyses, as the groups did not show significant differences in the aforementioned potential confounders.

Mean drinking water arsenic concentrations in the high and medium arsenic groups were 190 µg/L and 142 µg/L, respectively. The authors found that children in the control group had a mean IQ score of 105 points. IQ scores were significantly lower in the medium arsenic group (mean of 101, $p < 0.05$) and the high arsenic group (mean of 95, $p < 0.01$). Compared to the control group, the high fluoride group also had significantly lower IQ, though the magnitude of the observed deficits was greater for arsenic then fluoride. Wang et al. (2007) concluded that arsenic has adverse effects on children's IQ.

### Wasserman et al. (2011)

Wasserman et al.'s 2011 paper, "Arsenic and manganese exposure and children's intellectual function," aimed to investigate the potential interaction effects of arsenic and manganese exposure on children's neurodevelopment. The authors recruited Bangladeshi children (n = 299) aged 8-11 years old from four areas with varying levels of drinking water contaminants: high arsenic-high manganese, high arsenic-low manganese, low arsenic-high manganese, and low arsenic-low manganese; high arsenic and manganese concentrations were defined as >10 µg/L and >500 µg/L, respectively. In all participants, arsenic was additionally measured in urine and blood. Blood measurements of manganese, lead and selenium were also collected. IQ was assessed using the Wechsler Intelligence Scale for Children, adapted for use in Bangladesh. Log-linear regression analyses for IQ and blood arsenic and manganese were conducted, adjusted for head circumference, maternal age, maternal intelligence, school attendance, ferritin and arsenic-manganese interaction. Models for urinary arsenic and manganese, adjusted and unadjusted for creatinine, and for water arsenic and manganese were also constructed.

Mean urinary concentrations in the low arsenic groups were approximately 50 µg/L, whereas in the high groups mean urinary arsenic levels were approximately 106 µg/L. Urinary arsenic adjusted for creatinine showed a negative relationship with IQ, but neither water nor unadjusted urinary arsenic showed an association. Compared to the lowest quartile of blood arsenic, children in the highest quartile of blood arsenic had a mean IQ score that was 6.19 points lower. No interactions between arsenic and manganese were found, though manganese exposures were independently associated with decreased IQ. Wasserman et al. (2011) concluded that their study provides evidence of an association between arsenic and reduced intellectual function, though the association was attenuated at the low levels of arsenic observed.

### Wasserman et al. (2014)

In their study "A Cross-Sectional Study of Well Water Arsenic and Child IQ in Maine Schoolchildren," Wasserman et al. (2014) investigated the relationship between arsenic and intellectual deficits in U.S. children. The authors aimed to reduce the uncertainty of generalizing from prior findings in Bangladeshi children, who differ from U.S. children in exposure levels and other sample characteristics (e.g., nutritional and educational status). The researchers recruited children from elementary schools in three areas of Maine with reported high levels of arsenic in the water, resulting in a sample of 272 children. During home visits, Wasserman et al. (2014) collected children's toenail samples and water samples. IQ was assessed using a version of the Wechsler Intelligence Scales for Children. Linear regression analyses were conducted to assess the association between children's IQ and water arsenic concentrations, both as a continuous and categorical measure (four categories studied: <5; ≥5 to <10; ≥10 to <20; and >20). Wasserman et al. (2014) assessed unadjusted and adjusted (for maternal education and intelligence, number of children in the household, school district, and HOME score) models.

Children participating in the study were primarily white and of medium socioeconomic status, with a mean age of approximately 10 years. The average water arsenic concentration was 9.88 µg/L, with nearly a third of samples exceeding EPA's limit of 10 µg/L. In the adjusted model, Wasserman et al. (2014) found that children consuming water with arsenic concentrations ≥ 5 µg/L had significant deficits in several measures of IQ – full-scale, working memory, verbal comprehension, and perceptual reasoning – as compared to children with water arsenic < 5 µg/L. However, no consistent dose-response relationship was found for water arsenic levels > 5 µg/L. On average, water arsenic levels explained 2-3% of the variance in children's IQ scores. Using a cutpoint for water arsenic concentrations of 5 µg/L, children in the high exposure group had an estimated 6.09 point decrease in full-scale IQ, 4.97 point decrease in perceptual reasoning, 6.22 point decrease in verbal comprehension, and 4.88 point decrease in working memory as compared to children in the low exposure group. Although water arsenic and toenail arsenic levels were significantly correlated, no significant association between toenail arsenic and children's IQ was observed. Wasserman et al. (2014) concluded that water arsenic levels ≥ 5 µg/L, which are commonly observed in the U.S., may be associated with intellectual deficits.

### Wasserman et al. (2016)

Wasserman et al.'s (2016) study, "Child Intelligence and Reductions in Water Arsenic and Manganese: A Two-Year Follow-up Study in Bangladesh," aimed to investigate whether reductions in drinking water exposures to arsenic in Bangladesh would be associated with improved intellectual function in children. The researchers recruited children who had participated in their 2011 study on

the association between arsenic exposures and intelligence. After the previous study was conducted, new community wells were installed to provide a safer drinking water source for children who had been ingesting well water with arsenic concentrations > 50 µg/L. Installation of the new wells occurred approximately a year after the IQ tests were initially administered, and the follow-up testing occurred approximately 2.79 years after initial testing. Wasserman et al. (2016) analyzed children's total urinary arsenic concentrations and blood arsenic concentrations. In order to enable comparison of initial and follow-up IQ scores, raw scores on the Wechsler Intelligence Scale for Children were converted to standardized scores, which take age into account. Linear regression models were used to examine the associations between changes in arsenic biomarkers (creatinine-adjusted urinary arsenic and blood arsenic) and changes in IQ scores (full-scale IQ and the verbal comprehension, perceptual reasoning, working memory, and processing speed indices). The models were adjusted for maternal IQ, maternal age, HOME score, school grade, head circumference, and plasma ferritin.

Children participating in the follow-up study (n = 296) had mean urinary arsenic concentrations of 58.9 µg/L and mean blood arsenic concentrations of 4.4 µg/L. Arsenic exposures were lower at follow-up than in the 2011 study, with an average decrease in urinary arsenic concentration of 19.81 µg/L. The largest reductions in arsenic exposures were observed in children who were previously most highly exposed (water arsenic concentrations > 10 µg/L). Baseline creatinine-adjusted urinary arsenic concentrations were significantly associated with full-scale IQ and all measured indices, apart from perceptual reasoning. Adjusting for confounders and baseline working memory scores, changes in creatinine-adjusted urinary arsenic were significantly associated with changes in working memory scores at follow-up. Working memory scores increased by 0.91 points (95% confidence interval: 0.15, 1.67) for every 100 µg/L decrease in creatinine-adjusted urinary arsenic concentrations. However, decreases in arsenic exposures were not significantly associated with increases in full-scale IQ or any other indices. Similar patterns were observed in analyses using blood arsenic concentrations. Wasserman et al. (2016) concluded that installation of low-arsenic water wells successfully reduced arsenic exposures, and that reductions in arsenic exposures are not associated with significant improvements in IQ in the short term (i.e., in the 2-year follow-up period).