

U.S. Food and Drug Administration

Supporting Document for Action Level for Inorganic Arsenic in Rice Cereals for Infants

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I. Introduction

The purpose of this document is to present the background and rationale for FDA’s action level¹ for inorganic arsenic in rice cereals for infants (hereafter referred to as infant rice cereals). The 100 micrograms per kilogram ($\mu\text{g}/\text{kg}$) or 100 parts per billion (ppb) action level for inorganic arsenic in infant rice cereals is identified in the FDA Guidance for Industry entitled “Inorganic Arsenic in Rice Cereals for Infants: Action Level.”² FDA believes that the action level for inorganic arsenic in infant rice cereals will help protect public health by reducing infants’ dietary exposure to inorganic arsenic and is achievable with the use of current good manufacturing practices.

II. Background

Arsenic is an element that occurs in the environment from both natural and manmade

¹ Under 21 CFR 109.4, when certain conditions are met, FDA may establish an action level for an added poisonous or deleterious substance to define a level of contamination at which a food may be regarded as adulterated, within the meaning of section 402(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). These action levels serve as guidance to FDA field staff and industry. We will establish an action level, as opposed to a tolerance or regulatory limit (which must be established by rulemaking (21 CFR 109.4)), when technological or other changes that might affect the appropriateness of the tolerance are foreseeable in the near future (21 CFR 109.6(d)). Consistent with 21 CFR 109.6, we will consider action levels, in addition to other factors, when considering whether to bring enforcement action in a particular case.

² Guidance for Industry: Inorganic Arsenic in Rice Cereals for Infants: Action Level, online at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-action-level-inorganic-arsenic-rice-cereals-infants>

sources, including erosion of arsenic-containing rocks, volcanic eruptions, contamination from mining and smelting ores, and previous or current use of arsenic-containing pesticides (Ref. 1).³ Arsenic is found in both inorganic and organic⁴ forms (together referred to as total arsenic), and inorganic arsenic is generally considered more toxic than organic arsenic (Ref. 5). Consumption of inorganic arsenic has been associated with cancer, skin lesions, cardiovascular disease, and diabetes in humans (Refs. 5-6). A report by the National Research Council (NRC) (Ref. 6) also listed adverse pregnancy outcomes and neurodevelopmental toxicity as adverse health effects of concern for exposure to inorganic arsenic. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) (Ref. 5), which includes participation by FDA scientists, concluded that food can be a major contributor to inorganic arsenic exposure, and the European Food Safety Authority (EFSA) (Ref. 7) concluded that dietary exposure to inorganic arsenic should be reduced.

These findings support our initiatives to assess and reduce exposure to inorganic arsenic in food. For example, in July 2013, we announced the availability of a quantitative assessment of lifetime risk of certain cancers associated with exposure to inorganic arsenic in apple juice (Ref. 8) and draft guidance for industry with an action level for inorganic arsenic in apple juice (78 FR 42086). We also conducted surveys in 2013, 2016, and 2018 of arsenic in other foods (Refs. 9-11), focusing primarily on rice and rice products, and released consumer advice on consumption of rice and rice products, available online at <https://www.fda.gov/consumers/consumer-updates/consumers-seven-things-pregnant-women-and-parents-need-know-about-arsenic-rice-and-rice-cereal>. On April 6, 2016, we published in the *Federal Register* (81 FR 19976) a notice of availability for a draft guidance for industry entitled “Inorganic Arsenic in Rice Cereals for Infants: Action Level,” a supporting document entitled “Supporting Document for Action Level for Inorganic Arsenic in Rice Cereals for Infants,” and a risk assessment report entitled “Arsenic in Rice and Rice Products Risk Assessment: Report.” The risk assessment (Ref. 12) underwent an extensive peer review and received public comment. We are using results from the risk assessment as part of our analysis to support the action level for inorganic arsenic in infant rice cereals.

In 2018, the U.S. Government Accountability Office released a report on Federal Efforts to Manage the Risk of Arsenic in Rice (Ref. 13). The report recommended that the Commissioner of FDA should develop a timeline for finalizing the draft guidance on arsenic in infant rice cereal.

Exposure to inorganic arsenic in rice and rice products. Because it is in the

³ Generally, it is not possible for FDA to identify the specific source of any arsenic that may be found in a particular type of food, including infant rice cereals. Therefore, for purposes of this guidance, we are not distinguishing the presence of arsenic that may be due to prior pesticide use, such that the residues are pesticide chemical residues subject to a tolerance or tolerance exemption by the Environmental Protection Agency (EPA) under section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a)), or other environmental contamination. Our understanding from EPA information is that currently, arsenical pesticide use in the U.S. is limited to the organic arsenicals monosodium methanearsonate (MSMA) for use on sod farms, golf courses, highway rights-of-way, and to control weeds in cotton fields (Ref. 2) and 10,10'-Oxybisphenoxarsine (OBPA) to prevent microorganism growth in plastics and as a material preservative in adhesives and coatings (Ref. 3), and to chromated arsenicals for use by certified pesticide applicators using specialized high-pressure equipment in wood treatment facilities (Ref. 4).

⁴ Organic in this sentence refers to arsenic molecules that contain carbon. Inorganic arsenic molecules do not contain carbon. Use of the term “organic” here does not refer to organically grown food.

environment, inorganic arsenic is found in some foods. Rice and rice-based food products have higher levels of inorganic arsenic than do other foods tested by FDA, and given their widespread consumption, are a major food source of inorganic arsenic (Ref. 12). Rice also tends to have higher arsenic concentrations than other cereal crops (such as wheat and barley) because of its ability to take up arsenic from soil and water and because it is typically grown under flooded conditions, which increase the potential for arsenic uptake (Ref. 12). Evidence from FDA's Total Diet Study (Ref. 14) – an ongoing survey and analysis of the average American diet – revealed that total arsenic levels, although varying, tend to be higher in rice and rice products than in other foods. Our follow-up sampling has also revealed significant levels of inorganic arsenic in rice and rice products, including infant rice cereals (Refs. 9-11). The 2011-2013 FDA survey (Ref. 9) indicated that inorganic arsenic levels vary among and within different categories of rice grain (from 23 to 249 ppb). The percentage of inorganic arsenic varies among rice samples, with inorganic arsenic representing as little as 12 percent of total arsenic in some samples and up to 100 percent in other samples.⁵

Rice is commonly served to infants, primarily in the form of infant rice cereal (Ref. 12), which is the most commonly consumed infant instant cereal in the U.S.⁶ Rice and rice products are a greater potential source of dietary inorganic arsenic exposure for infants and children than for adults, because the dietary patterns of infants and children are often less varied than those of adults, and because infants and children consume more food relative to their body weight than do adults (Ref. 16). Therefore, elevated levels of inorganic arsenic in foods that infants eat, such as rice cereals, may represent a significant source of exposure for infants (Ref. 12). In addition, infants and children may be particularly susceptible to adverse neurodevelopmental effects of exposure to inorganic arsenic (Refs. 6, 12). It is possible to reduce dietary exposure to inorganic arsenic from infant rice cereals through industry's use of current good manufacturing practices, in particular selection of sources of rice or rice-derived ingredients with lower inorganic arsenic levels and testing these incoming rice and rice-derived ingredients for levels of inorganic arsenic. Using rice with lower levels of inorganic arsenic will result in lower levels of inorganic arsenic in the infant rice cereal because the main ingredient (rice) will have lower levels of inorganic arsenic. Therefore, we are issuing guidance on an action level for inorganic arsenic in infant rice cereals.

III. Risk Assessment and Achievability Assessment Results

a. Risk Assessment. FDA's risk assessment for inorganic arsenic in rice and rice products informs the development of an action level for inorganic arsenic in infant rice cereals. The risk assessment includes a qualitative component that addresses the risk of certain non-cancer adverse health effects to infants, to young children, and during pregnancy from dietary exposure to inorganic arsenic in rice and rice products. The risk assessment also includes a quantitative component that provides estimates of exposure to inorganic arsenic from rice and rice products and estimates of lifetime cancer risk from this exposure. Finally,

⁵ Although inorganic arsenic can never exceed 100% of total arsenic, the calculated percentages of inorganic arsenic from the 2011-2013 FDA survey (Ref. 9) can exceed 100 percent (e.g., the highest calculated percentage is 106 percent), because total arsenic and inorganic arsenic are measured separately, using different analytical methods, each with differing measurement uncertainty.

⁶ Based on data from the U.S. National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2010 (Ref. 15), the mean per capita daily intake of dry instant infant cereals (not containing fruit) for the first year of life is as follows: rice, 4.8 g/d; oatmeal 2.8 g/d; barley, 0.1 g/d; and mixed grains, 0.8 g/d.

the risk assessment estimates potential reductions in inorganic arsenic exposure and cancer risk from possible mitigation actions, including limiting the maximum level of inorganic arsenic in infant rice cereals.

The qualitative component of the risk assessment is of special significance for infants. For this component of the risk assessment, FDA conducted a systematic review of the scientific literature, examining published data up to February 2015, on the relationship between inorganic arsenic exposure and adverse effects in pregnancy, infancy, and early childhood.⁷ There is growing evidence from human and animal studies that suggests 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 [see Appendix 9.13, Risk Assessment]. Specifically, for infants and children, the risk assessment noted the following: children are particularly susceptible to neurotoxic effects from low-level exposure to lead and methylmercury; there are data suggesting that children may likewise be particularly susceptible to neurotoxic effects of inorganic arsenic, e.g., as manifested in intelligence test results in children. Animal studies have also demonstrated neurotoxicity (Ref. 6). Also, children three years and younger have the highest exposure to inorganic arsenic because they have 2-3-fold higher intakes of food on a per body mass basis as compared to adults (Ref. 7, 16). Therefore, a child's daily exposure to contaminants in food, such as inorganic arsenic in rice, could potentially be much higher than that of adults.

As noted above, infant rice cereal is a common food served to infants. The quantitative component of the risk assessment estimated reductions in concentrations of inorganic arsenic in infant rice cereals that could potentially occur if maximum levels were in place, based on the inorganic arsenic levels observed in infant rice cereals sampled from 2011-2013 and in 2014.⁸ Briefly, FDA used dietary intake data and data on inorganic arsenic concentrations (Refs. 9-10, also see footnote 8) to model baseline exposure to inorganic arsenic from infant cereals and other foods, as well as to model the potential reductions in exposure and risk that could occur if people were to change consumption patterns and reduce consumption of rice cereals and other rice products or when rice cereals with inorganic arsenic concentrations above possible limits are removed from the marketplace. As shown in Table 5.5 of the risk assessment, which models removal of rice cereals above 100 ppb inorganic arsenic from the marketplace, a 100 ppb limit could reduce the mean concentration of inorganic arsenic in brown-rice infant cereals from 119.0 ppb to 79.0 ppb and in white-rice infant cereals from 103.9 to 83.5 ppb. Although the risk assessment (Ref. 12) could not quantify non-cancer effects, the reductions in exposure would be expected to decrease potential neurodevelopmental effects in infants consuming rice cereal.

To examine cancer effects, FDA developed a dose-response model for inorganic arsenic and lung and bladder cancer, using data from a study of a Taiwanese population exposed to high levels of inorganic arsenic in drinking water (Refs. 18-19). The risk assessment

⁷ Based on the 2016 FDA risk assessment, the literature does not provide the data needed to conduct a quantitative assessment of non-cancer health effects associated with arsenic exposure *in utero*, through maternal intake, and during early childhood.

⁸ The 2011-2013 dataset used for the risk assessment and the achievability assessment includes 69 samples analyzed by FDA (Ref. 9) and 12 samples analyzed by Consumer Reports (Ref. 17). The 2014 dataset includes 76 samples analyzed by FDA (Ref. 10). See risk assessment (Ref. 12) for more information on these samples.

found that exposure to inorganic arsenic in rice and rice products may increase lung and bladder cancer cases in later life, whether exposure occurs only during infancy (through infant rice cereals) or throughout life. For cancer effects, establishing a 100 ppb limit would result in a 37 percent reduction in lifetime cancer risk attributable solely to brown-rice infant cereal consumption and an 18.8 percent reduction in lifetime cancer risk attributable solely to white-rice infant cereal consumption (see Risk Assessment, Table 5.6).⁹

b. Achievability Assessment. To assess achievability, or manufacturers' ability to achieve hypothetical maximum limits for inorganic arsenic in infant rice cereals (i.e., white-rice and brown-rice), FDA determined the percentage of infant rice cereal samples that met such limits. We used three data sets, 81 infant rice cereals sampled from 2011-2013 (Table 1), 76 infant rice cereals sampled in 2014 (Table 2), and 149 infant rice cereals sampled in 2018 (Table 3)¹⁰. For infant rice cereals from the 2011-2013 dataset, 20, 36, 62, and 84 percent of samples met the modeled limits of 75 ppb, 100 ppb, 125 ppb, and 150 ppb, respectively (Table 4). These data suggest that approximately 36 percent of infant rice cereal samples on the market in 2011-2013 would meet a 100 ppb hypothetical limit. For infant rice cereals from the 2014 dataset, 3, 47, 89 and 95 percent of samples met the modeled limits of 75 ppb, 100 ppb, 125 ppb, and 150 ppb, respectively (Table 5). These data suggest that approximately 47 percent of infant rice cereal samples on the market in 2014 would meet a 100 ppb hypothetical limit. For infant rice cereals from the 2018 dataset, 33, 76, 99, and 100 percent of samples met the modeled limits of 75 ppb, 100 ppb, 125 ppb, and 150 ppb, respectively (Table 6). The increase in achievability (36 percent to 76 percent) from 2011-2013 to 2018 could be due to many factors, including chance. However, data in Tables 1-3 indicate a downward shift over time in the distribution of inorganic arsenic concentrations in infant rice cereal samples on the U.S. market, with decreasing mean, 90th percentile, and maximum concentrations over the three sampling periods. These data demonstrate that alternate sources of rice are available to enable infant rice cereal manufacturers to supply the market and meet the action level. Thus, based on these data, FDA concludes that industry use of good manufacturing practices, such as selective sourcing of rice or rice-derived ingredients with lower levels of inorganic arsenic and testing these incoming rice and rice-derived ingredients for levels of inorganic arsenic could allow all manufacturers to achieve lower levels of inorganic arsenic in infant rice cereals, and specifically to achieve a 100 ppb action level for inorganic arsenic in infant rice cereal. Selective sourcing, i.e., buying rice from growers or mills with consistently lower levels of inorganic arsenic than in the general rice supply, will lower inorganic arsenic in infant rice cereals.

IV. Conclusion

Based on a risk assessment on arsenic in rice and rice products, as well as considerations including data on inorganic arsenic levels in infant rice cereals and manufacturer achievability, FDA is establishing an action level for inorganic arsenic in infant rice cereals of 100 µg/kg or 100 ppb. This guidance applies to all types of infant rice cereals (e.g., white-rice, brown-rice, organically grown, and conventionally grown).

⁹ The predicted total (bladder and lung) lifetime cancer risk attributable to inorganic arsenic for those < 1 year of age from consumption of infant white rice cereal is 1.6 cases per million and from consumption of infant brown rice cereal is 1.9 cases per million (based on per capita consumption) (see Risk Assessment, Table 5.1).

¹⁰ The method used by FDA for analyzing inorganic arsenic in rice is posted on the FDA website at <https://www.fda.gov/media/95197/download>.

FDA has concluded that it is appropriate to set an action level for inorganic arsenic in infant rice cereals. FDA surveillance has shown that rice and rice products contain inorganic arsenic at higher levels than other foods, and rice cereals are commonly consumed by infants as a significant part of their diet. FDA's risk assessment shows that inorganic arsenic exposure during fetal development, infancy, and childhood may contribute to neurodevelopmental effects, as well as increase lifetime cancer risk, and that establishing an action level will reduce inorganic arsenic exposure and risk.

FDA has concluded that a level of 100 µg/kg or 100 ppb inorganic arsenic in infant rice cereals is achievable under current good manufacturing practices, based on evaluation of recent FDA data on inorganic arsenic levels in infant rice cereals. The action level of 100 µg/kg or 100 ppb is intended to reduce the possible risks of neurodevelopmental and other health effects.

V. References

1. Agency for Toxic Substances and Disease Registry (ATSDR), 2007, Toxicological Profile for Arsenic, U.S. Department of Health and Human Services, Public Health Service, accessed online at <http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf>.
2. U.S. Environmental Protection Agency (EPA), 2018, Monosodium methanearsonate (MSMA), an Organic Arsenical, accessed online at <https://www.epa.gov/ingredients-used-pesticide-products/monosodium-methanearsonate-msma-organic-arsenical>.
3. U.S. EPA, 2012, OBPA Registration Review: 10,10'-Oxybisphenoxarsine, accessed online at <https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPP-2009-0618>.
4. U.S. EPA, 2016, Chromated Arsenicals Final Work Plan. Registration Review. Case Number 0132, accessed online at <https://www.regulations.gov/document?D=EPA-HQ-OPP-2015-0349-0005>.
5. WHO/FAO Joint Expert Committee on Food Additives (JECFA), 2010, Evaluation of Certain Contaminants in Food, 72nd Report of the World Health Organization/Food and Agriculture Organization of the United Nations Joint Expert Committee on Food Additives, accessed online at https://apps.who.int/iris/bitstream/handle/10665/44514/WHO_TRS_959_eng.pdf;jsessionid=9B941773BD2EBDEE5F7674F982732C60?sequence=1.
6. National Research Council of the National Academies (NRC), 2013, Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report. Accessed online at <http://www.nap.edu>.
7. European Food Safety Authority (EFSA), 2010, Scientific Opinion on Arsenic in Food, EFSA Journal 2009, 7(10): 1351, accessed online at <http://www.efsa.europa.eu/en/efsajournal/doc/1351.pdf>.

8. U.S. Food and Drug Administration (FDA), 2013a, A Quantitative Assessment of Inorganic Arsenic in Apple Juice, accessed online at <https://www.fda.gov/media/86075/download>.
9. U.S. FDA, 2013b, Analytical Results from Inorganic Arsenic in Rice and Rice Products Sampling, accessed online at <https://www.fda.gov/media/86074/download>.
10. U.S. FDA, 2016a, Analytical Results from Inorganic Arsenic in Rice Cereals for Infants, Non-rice Infant Cereal and Other Foods Commonly Eaten by Infants and Toddlers, accessed online at <https://www.fda.gov/food/cfsan-risk-safety-assessments/arsenic-rice-and-rice-products-risk-assessment>.
11. U.S. FDA, 2020, Analytical Results from Inorganic Arsenic in Rice Cereals for Infants, accessed online at <https://www.fda.gov/media/135552/download>.
12. U.S. FDA, 2016b, Arsenic in Rice and Rice Products Risk Assessment Report, accessed online at <https://www.fda.gov/media/96071/download>.
13. U.S. Government Accountability Office (GAO), 2018, Food Safety: Federal Efforts to Manage the Risk of Arsenic in Rice, accessed online at <https://www.gao.gov/assets/700/690701.pdf>.
14. U.S. FDA, 2016c, Total Diet Study, accessed online <https://www.fda.gov/food/science-research-food/total-diet-study>.
15. Centers for Disease Control and Prevention (CDC), 2013, National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2013, downloaded from <http://www.cdc.gov/nchs/nhanes.htm>.
16. National Research Council (NRC), 1993, Pesticides in the Diets of Infants and Children, National Academy Press, Washington, D.C.
17. Consumer Reports, 2012, Arsenic in Your Food. Retrieved from <https://www.consumerreports.org/cro/magazine/2012/11/arsenic-in-your-food/index.htm>.
18. Chen C-L, et al., 2010a, Arsenic in Drinking Water and Risk of Urinary Tract Cancer: A Follow-Up Study from Northeastern Taiwan. *Cancer Epidemiology, Biomarkers & Prevention*, 19(1):101–110.
19. Chen C-L, et al., 2010b, Ingested Arsenic, Characteristics of Well Water Consumption and Risk of Different Histological Types of Lung Cancer in Northeastern Taiwan. *Environmental Research*, 110(5):455–462.

Table 1: Inorganic arsenic levels in infant rice cereals sampled in 2011-2013¹

Food type	Number of samples	Mean (sd ²) (ppb)	90 th percentile	Range (ppb)
Infant rice cereals	81	116.7 (43.3)	183.4	39—254

¹References 9,12

²sd, standard deviation

Table 2: Inorganic arsenic levels in infant rice cereals sampled in 2014¹

Food type	Number of samples	Mean (sd ²) (ppb)	90 th percentile	Range (ppb)
Infant rice cereals	76	103.1 (24)	126.4	21—176

¹Reference 10

²sd, standard deviation

Table 3: Inorganic arsenic levels in infant rice cereals sampled in 2018¹

Food type	Number of samples	Mean (sd ²) (ppb)	90 th percentile	Range (ppb)
Infant rice cereals	149	85 (21)	107	22-142

¹Reference 11

²sd, standard deviation

Table 4: Effects of modeled limits on inorganic arsenic based on infant rice cereals sampled in 2011-2013: manufacturer achievability

Limit (iAs ¹ , ppb)	Percentage of samples with iAs levels ≤ specified limit (%) ²
75 ppb	20
100 ppb	36
125 ppb	62
150 ppb	84

¹iAs, inorganic arsenic

²References 9,12

Table 5: Effects of modeled limits on inorganic arsenic based on infant rice cereals sampled in 2014: manufacturer achievability

Limit (iAs ¹ , ppb)	Percentage of samples with iAs levels ≤ specified limit (%) ²
75 ppb	3
100 ppb	47
125 ppb	89
150 ppb	95

¹iAs, inorganic arsenic

²Reference 10

Table 6: Effects of modeled limits on inorganic arsenic based on infant rice cereals sampled in 2018: manufacturer achievability

Limit (iAs ¹ , ppb)	Percentage of samples with iAs levels ≤ specified limit (%) ²
75 ppb	33
100 ppb	76
125 ppb	99
150 ppb	100

¹iAs, inorganic arsenic

²Reference 11