

U.S. Food and Drug Administration

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

April 2016

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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/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or 100 parts per billion (ppb) action level for inorganic arsenic in infant rice cereals is identified in the FDA Draft Guidance for Industry entitled “Inorganic Arsenic in Rice Cereals for Infants: Action Level.”² FDA believes that the action level for inorganic arsenic in infant rice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.

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. These levels serve as guidance to FDA field staff. FDA will establish an action level, as opposed to a tolerance or regulatory limit (which must be established by rulemaking), 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, FDA will consider action levels, in addition to other factors, when considering whether to bring enforcement action in a particular case.

² Draft Guidance for Industry: Inorganic Arsenic in Rice Cereals for Infants: Action Level, online at <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm486305.htm>.

II. Background

Arsenic is an element that occurs in the environment from both natural and manmade 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. 2). Consumption of inorganic arsenic has been associated with cancer, skin lesions, cardiovascular disease, and diabetes in humans (Refs. 2-3). A report by the National Research Council (NRC) (Ref. 3) also listed adverse pregnancy outcomes and neurodevelopmental toxicity as adverse health effects of concern for inorganic arsenic. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) (Ref. 2), 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. 4) concluded that dietary exposure to inorganic arsenic should be reduced.

These findings support FDA initiatives to assess and reduce exposure to inorganic arsenic in food. For example, in July 2013, FDA issued a draft quantitative assessment of lifetime risk of certain cancers associated with exposure to inorganic arsenic in apple juice (Ref. 5) and draft guidance for industry with an action level for inorganic arsenic in apple juice of 10 µg/kg, or 10 ppb (Refs. 6-7). FDA also has conducted surveys of arsenic in other foods (Refs. 8-9), focusing primarily on rice and rice products. In April 2016, FDA released a risk assessment on arsenic in rice and rice products titled “Arsenic in Rice and Rice Products Risk Assessment Report” (Ref. 10). The risk assessment has undergone an informal federal interagency peer review and an external peer review and will now undergo public comment. FDA is using results from the risk assessment as part of its analysis to support the action level for inorganic arsenic in infant rice cereals. FDA has also released consumer advice on consumption of rice and rice products, see <http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm319870.htm>.

Inorganic arsenic exposure and children’s diets. Because it is in the 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. Rice 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

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, FDA is 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 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 arsenical monosodium methanearsenate (MSMA) for use on sod farms, golf courses, highway rights-of-way, and to control weeds in cotton fields, and to chromated copper arsenate for use by certified pesticide applicators using specialized high-pressure equipment in wood treatment facilities.

⁴ Organic in this sentence refers to arsenic molecules that contain carbon. Inorganic arsenic molecules do not contain carbon. This usage does not refer to organically grown food.

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potential for arsenic uptake (Ref. 10). Evidence from FDA’s Total Diet Study (Ref. 11) – 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. Follow-up sampling by FDA has also revealed significant levels of inorganic arsenic in rice and rice products, including infant rice cereals (Refs. 8-9). The 2011-2013 FDA survey (Ref. 8) 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. 10), 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 they consume more food relative to their body weight than do adults (Ref. 13). 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. 10). In addition, infants and children may be particularly susceptible to adverse neurodevelopmental effects of exposure to inorganic arsenic (Refs. 3, 10). FDA thinks that it is possible to reduce dietary exposure to inorganic arsenic from infant rice cereals through the industry’s use of current good manufacturing practices, in particular the selection of sources of rice or rice-derived ingredients with lower inorganic arsenic levels. Therefore, FDA is 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, 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, 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

⁵ The calculated percentages of inorganic arsenic from the 2011-2013 FDA survey (Ref. 8) can exceed 100 percent (e.g., the highest calculated percentage is 106 percent), because total arsenic and inorganic arsenic are measured separately, with different analytical methods.

⁶ Based on data from the U.S. National Health and Nutrition Examination Survey (NHANES), What We Eat In America (WWEIA), 2003-2010 (Ref. 12), 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.

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literature on the relationship between inorganic arsenic exposure and adverse effects in pregnancy, infancy, and early childhood⁷. 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 methyl mercury; 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. 3). 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. 4, Ref. 13). 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 2014⁸. Briefly, FDA used dietary intake data and data on inorganic arsenic concentrations (Refs. 8-9, also see footnote 8) to model exposure to inorganic arsenic from infant cereals and other foods, as well as to model possible reductions in exposure and risk that might occur when people 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, establishing a limit of 100 ppb 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 reduction cannot be quantified for non-cancer effects, these reductions in exposure would be expected to decrease neurodevelopmental effects in infants.

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. 15-16). The risk assessment 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 to brown-rice infant cereal consumption and an 18.8 percent reduction in lifetime cancer risk attributable to white-rice infant cereal consumption (see Risk Assessment, Table 5.6).

⁷ At this time, 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. 8) and 12 samples analyzed by Consumer Reports (Ref. 14). The 2014 dataset includes 76 samples analyzed by FDA (Ref. 9). See risk assessment (Ref. 10) for more information on these samples.

b. Achievability Assessment. To assess achievability, or manufacturers' ability to achieve hypothetical maximum limits for inorganic arsenic in infant rice cereals, FDA determined the percentage of infant rice cereal samples that met such limits. We used two data sets, 81 infant rice cereals sampled from 2011-2013 (Table 1) and 76 infant rice cereals sampled in 2014 (Table 2)⁹. 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 3). These data suggest that approximately 36 percent of infant rice cereal samples on the market in 2011-2013 could 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 4). These data suggest that approximately 47 percent of infant rice cereal samples on the market in 2014 could meet a 100 ppb hypothetical limit. The small increase in achievability (36 percent to 47 percent) from 2011-2013 to 2014 could be due to many factors, including chance. FDA believes that industry use of good manufacturing practices, in particular selective sourcing, 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. We request comments on the feasibility of achieving this level and on how the level might affect the availability of infant rice cereals in the marketplace.

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 proposing 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).

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 may cause neurodevelopmental effects, as well as increasing 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 proposed action level of 100 µg/kg or 100 ppb is intended to reduce the possible risks of neurodevelopmental and other health effects.

⁹ The method used by FDA for analyzing inorganic arsenic in rice is posted on the FDA website at <http://www.fda.gov/downloads/food/foodscienceresearch/laboratorymethods/ucm479987.pdf>.

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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 8,10

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 9

²sd, standard deviation

Table 3: Effects of proposed 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 8,10

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Table 4: Effects of proposed limits on inorganic arsenic based on infant rice cereals sampled in 2014: manufacturer achievability

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

¹iAs, inorganic arsenic

²Reference 9