

U.S. Food and Drug Administration

Supporting Document for Action Level for Arsenic in Apple Juice

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I. Introduction

The purpose of this document is to present the background and rationale for FDA's action level for inorganic arsenic in apple juice. The 10 micrograms/kilogram ($\mu\text{g}/\text{kg}$) or 10 parts per billion (ppb) action level for inorganic arsenic in apple juice is identified in the FDA Guidance for Industry entitled "Arsenic in Apple Juice: Action Level." FDA considers the action level for inorganic arsenic to be achievable and protective of public health.

II. Background

Arsenic is an element that occurs in the environment from both natural and anthropogenic 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). Arsenic is found in both inorganic and organic 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, developmental effects, cardiovascular disease, neurotoxicity, and diabetes in humans (Ref. 2). In recent assessments, the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) (Ref. 2), which includes participation by U.S. FDA scientists, concluded that food can be a major contributor to inorganic arsenic exposure, and the European Food Safety Authority (EFSA) (Ref. 3) concluded that dietary exposure to inorganic arsenic should be reduced. These findings suggest a need to reduce exposure to inorganic arsenic from food.

Apple juice is one source of exposure to inorganic arsenic from food. Apple juice is a greater potential source of dietary inorganic arsenic exposure to children than to adults, because children's dietary patterns are often less varied than those of adults, and they consume more apple juice relative to their body weight than do adults (Ref. 4).

FDA has conducted routine surveillance for arsenic in apple juice since 1991, and has recently increased its surveillance efforts. The surveillance results are discussed in this supporting document and the associated risk assessment document (Ref. 5). Total arsenic levels in apple juice samples have routinely been below 10 ppb; for example, more than 95 percent of total arsenic levels in a set of 94 apple juice samples collected at retail as part of a fiscal year 2011 assignment were below 10 ppb (see Ref. 6 and Section V below). The remaining four samples in that assignment with total arsenic levels above 10 ppb had inorganic arsenic levels below 10 ppb. However, FDA has identified apple juice samples with inorganic arsenic levels above 10 ppb in previous years (Ref. 7). FDA considers that it is possible to further reduce public exposure to inorganic arsenic from apple juice in general, and specifically from apple juice that currently may contain inorganic arsenic at levels above 10 ppb. Therefore, FDA is issuing draft guidance on an action level for inorganic arsenic in apple juice.

III. Overview of FDA Activities Addressing Arsenic in Apple Juice and Other Foods

a. Fruit Juice Surveillance. FDA has been routinely monitoring arsenic in apple juice for many years through its [Total Diet Study \(TDS\)](http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm)¹ and the Toxic Elements in Food and Foodware, and Radionuclides in [Food Program \(TEP\)](http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm2006907.htm)². The TDS is a market basket study in which about 280 table-ready foods representative of the U.S. diet are screened four times a year for levels of pesticide residues, industrial chemicals, radionuclides, nutrients, and toxic elements, including arsenic. The TEP is a targeted monitoring program that monitors levels of certain toxic elements, including arsenic, in foods and foodware. Foods selected for analysis are typically known or suspected sources of toxic

¹ <http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/default.htm>

² <http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm2006907.htm>

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elements in the diet. Surveillance results for arsenic in apple juice are discussed in Section V below.

FDA also conducts targeted screening of juice imports through its import alert program. [Import alert 20-05](#)³ covers surveillance of heavy metals, including arsenic, in fruit juices and fruit juice concentrates. The import alert allows FDA District Offices to detain, without physical examination, certain imported fruit juices and fruit juice concentrates from specified firms. As of June 2013, the import alert included firms from Argentina for arsenic in apple juice and apple juice concentrate, and firms from China for inorganic arsenic in pear juice and pear juice concentrate. The import alert also advises FDA Districts that surveillance of heavy metal levels in fruit juices and fruit juice concentrates from all countries is warranted. In July 2011, FDA issued an import bulletin to significantly increase the number of imported juice products sampled and analyzed for arsenic under the TEP.

FDA also recently increased collection and analysis of ready-to-drink juice samples purchased domestically. FDA issued an assignment in October 2011 resulting in the collection of 94 baby food and general consumption apple juice samples from retail establishments across the country. The results of this assignment are discussed in Section V below. FDA issued a separate assignment in December 2011 to analyze 150 ready-to-drink juices other than apple juice, such as grape and pear juice. These assignments were intended to collect more data on the prevalence of arsenic in fruit juices and to increase understanding of the forms of arsenic (arsenic species) found in different juices. FDA is considering what further actions, if any, are needed for fruit juices other than apple juice.

b. 2008 Hazard Assessment. In 2008, [FDA established a level of concern](#)⁴ of 23 ppb for inorganic arsenic in single-strength (ready to drink) apple juice as part of a hazard assessment. This level of concern was based on non-cancer endpoints, such as cardiovascular and dermatological effects, that could occur with consumption of higher levels of arsenic over a limited period of time (short term, not lifetime). Juice samples, if found to contain 23 ppb or more total arsenic, were to be speciated to determine the level of inorganic arsenic. For samples containing over 23 ppb inorganic arsenic, FDA considered the level, along with other factors, to determine whether regulatory action was indicated. FDA also identified a level of concern of 23 ppb for [inorganic arsenic in pear juice in 2008](#)⁵.

c. Risk Assessment for Arsenic in Apple Juice. In 2011, FDA initiated a quantitative risk assessment for arsenic based on childhood, chronic and lifetime exposure and cancer endpoints. The risk assessment has undergone [peer review](#)⁶ and is available on the FDA website, along with the peer review report. FDA is using results from the quantitative risk assessment as part of its analysis to support the action level for inorganic arsenic in

³ http://www.accessdata.fda.gov/cms_ia/importalert_56.html

⁴ <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm277681.htm>

⁵ <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm277676.htm>

⁶ <http://www.fda.gov/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/ucm079120.htm>

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apple juice in the [new draft guidance](#)⁷. More information on the results of the risk assessment is provided in Section VI below.

d. Other Foods. FDA also has taken, or is planning to take, the following actions on arsenic in other foods:

- 1. Bottled water:** FDA established an allowable level for arsenic in bottled water of 10 ppb (0.010 mg/l) in 2005 (70 Fed. Reg. 33694, June 9, 2005), consistent with section 410 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 349). FDA evaluated and adopted the maximum contaminant level of 10 ppb for arsenic in bottled water, the same level established by the U.S. Environmental Protection Agency (EPA) in 2002 for arsenic in public drinking water.
- 2. Poultry:** 3-Nitro® (roxarsone) is an approved animal drug that contains an organic form of arsenic. In response to scientific reports that the organic arsenic in roxarsone could be converted into inorganic arsenic in roxarsone-treated chickens, FDA scientists developed an analytical method capable of detecting very low levels of inorganic arsenic in edible tissue. In 2011, FDA scientists reported finding increased levels of inorganic arsenic in the livers of chickens treated with 3-Nitro®. In response, Alpharma, a subsidiary of Pfizer, Inc., voluntarily suspended sales of 3-Nitro® in the United States in 2011. More information on these actions can be found on the [FDA website](#)⁸.
- 3. Rice and rice products:** Compared with other plant foods, rice has relatively higher levels of total and inorganic arsenic. Rice can be a major source of inorganic arsenic in the diet, particularly for consumers who eat large amounts of rice (Ref. 2). FDA has been surveying total and inorganic arsenic levels in rice and rice products in the United States to help establish dietary exposure levels for the U.S. population⁹. FDA will consider what further actions, if any, are needed for rice after reviewing the survey results.

FDA may sample foods for a contaminant or take enforcement actions when contamination may pose a health hazard. Under section 402(a)(1) of the FD&C Act (21 U.S.C. 342(a)(1)), a food is deemed to be adulterated if the food bears or contains any poisonous or deleterious substance which may render it injurious to health, and for

⁷ <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ChemicalContaminantsMetalsNaturalToxinsPesticides/ucm360020.htm>

⁸ <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm257540.htm>.

Consistent with 21 CFR 109.6, the risk of arsenic residues in apple juice has been evaluated in the context of setting an action level to reduce exposure to arsenic in apple juice due to the presence of arsenic in the environment that is unavoidable. The risk of arsenic residues in edible tissues resulting from the use of a new animal drug is evaluated under a different regulatory framework (see 21 U.S.C. 360b). No residue of carcinogenic concern of a new animal drug may be present in the edible tissues of, or foods yielded from, treated animals (section 512(d)(1)(I) of the FD&C Act (21 U.S.C. 360b(d)(1)(I))). The carcinogenic risk of animal drug residues is evaluated solely to determine the sensitivity of the regulatory method that must be used to detect no residues in food from animals treated with the new animal drug (21 CFR 500 subpart E). Therefore, the risk assessment conducted for roxarsone in poultry is not comparable to the risk assessment for arsenic in apple juice.

⁹ <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm319870.htm>

substances that are not added substances, if the quantity of the substance ordinarily renders the food injurious to health.

IV. Health Effects

Inorganic arsenic, the sum of arsenite (As^{+3}) and arsenate (As^{+5}), is generally considered more toxic than organic arsenic, and some organic species in food (such as arsenobetaine, commonly found in seafood) are considered nontoxic (Ref. 3). Short-term exposure to high levels of inorganic arsenic can cause gastrointestinal, cardiovascular, hematological, renal, and neurological effects in humans (Refs. 1-2). Chronic exposure to inorganic arsenic has been associated with cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes in humans (Refs. 2-3).

Evidence for arsenic-induced cancer in humans is based on epidemiological studies of oral arsenic exposure, primarily through inorganic arsenic in drinking water (Refs. 3, 8-9). Most notably, oral inorganic arsenic exposure has been linked to human skin, urinary tract, and lung cancers (Refs. 1-3). Although high doses of arsenic can affect multiple systems, cancer is the primary concern associated with chronic exposure. Thus cancer—specifically lung and urinary tract cancer—is the endpoint of concern used in recently published risk assessments (Refs. 2-3), and in FDA’s risk assessment (Ref. 5).

Several organic arsenic species have been found at low levels in apple juice (dimethylarsinic acid, DMA^{V} , and monomethylarsonic acid, MMA^{V}). These species have demonstrated toxicity in animal studies (Ref. 3). DMA^{V} is a known carcinogen in rat studies, but these findings may not be relevant to humans because of metabolic differences between rats and humans (Refs. 2-3).

V. Arsenic Sources, Analytical Methodology, and Data on Arsenic in Juice

a. Potential Sources of Arsenic in Apple Juice and Potential Control Points. FDA does not have any specific data on sources of arsenic in apple juice sold in the United States. Possible sources include processing aids, prior use of arsenic-based pesticides on land currently used for apple orchards, current use of arsenic-based pesticides in other countries, naturally high levels of arsenic in soil or water, and atmospheric deposition from industrial activities. It may be possible in some cases for manufacturers who have found inorganic arsenic in sources of apples or apple juice concentrate to reduce or limit inorganic arsenic in apple juice by choosing sources of apples or apple juice concentrate with lower inorganic arsenic levels or no detectable inorganic arsenic. Another potential source of inorganic arsenic in apple juice is water used by manufacturers to dilute concentrate to prepare ready-to-drink juice. Municipal water supplies in the U.S. are required to meet a maximum contaminant level of 10 ppb arsenic established by the U.S. EPA. Well water from areas of the U.S. with naturally high arsenic levels in groundwater could contain higher levels of arsenic. It may be possible in some cases for manufacturers who have found arsenic in water used to dilute concentrate to reduce or

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limit levels of inorganic arsenic in ready-to-drink apple juice by examining and controlling arsenic levels in water used for dilution of juice concentrate.

b. Analytical Methodology. FDA scientists use an inductively coupled mass spectrometry (ICPMS) method for total arsenic¹⁰ and a high performance liquid chromatography-inductively coupled mass spectrometry (HPLC-ICPMS) method for speciation analysis¹¹. Measurement of total arsenic is considered simpler and easier to perform than speciation analysis, in which the inorganic and organic forms of arsenic present in a sample are identified and quantified. Also, based on FDA experience, total arsenic analysis is more sensitive at low levels of arsenic (<10 ppb) present in most juice samples than is speciation analysis. Therefore, in the past, FDA has screened apple juice samples for total arsenic, and then speciated samples with elevated total arsenic to determine inorganic arsenic levels. FDA intends to continue this practice with the new action level.

c. Data on Arsenic Levels and Arsenic Species in Apple Juice. As noted above, FDA has surveyed arsenic levels in apple juice historically, and the agency has recently initiated new surveys to enhance its database on arsenic levels in apple juice (Refs. 6-7). The combined surveys include samples containing juice intended for sale in the United States from Argentina, Brazil, China, Chile, Mexico, South Africa, Turkey, and the United States. The resulting data set (253 samples) shows total arsenic levels in single-strength apple juice ranging from nondetect to 45 ppb. More than 90 percent of the samples are at or below 10 ppb total arsenic.

FDA recently reported speciation results for 94 retail apple juice samples collected in FY11 (Ref. 6). Of the 94 samples, 90 had total arsenic levels of 10 ppb or less; the other four samples had total arsenic levels ranging from 11 to 36 ppb. All samples had inorganic arsenic levels below 10 ppb. Only three of the 94 samples had levels of MMA^V or DMA^V above trace amounts (i.e., above 2 ppb, Ref. 6). Because the vast majority of samples contained nondetectable or trace levels of the MMA^V and DMA^V species of organic arsenic, and because inorganic arsenic is considered more toxic than organic arsenic (see Section IV), FDA concluded that the action level for arsenic in apple juice should be based on inorganic arsenic.

VI. Risk Assessment and Achievability Assessment Results

a. Risk Assessment. To facilitate development of an action level for inorganic arsenic in apple juice, FDA conducted a quantitative assessment of the risk for cancer associated with exposure to inorganic arsenic in apple juice. Detailed information on the risk assessment process can be found in the risk assessment document (Ref. 5). Briefly, FDA used data on lung and urinary tract cancer cases from a Taiwanese population exposed to

¹⁰Analysis of Foods for As, Cd, Cr, Hg and Pb by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS), <http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/Metals/UCM272693.pdf>.

¹¹High Performance Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometric Determination of Four Arsenic Species in Fruit Juice (Elemental Analysis Manual: Section 4.10), <http://www.fda.gov/Food/FoodScienceResearch/LaboratoryMethods/ucm219640.htm>.

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high levels of inorganic arsenic in drinking water (Ref. 8-9) to develop a dose-response model for inorganic arsenic and cancer. To model consumption, FDA used data from the National Health and Nutrition Examination Survey to estimate apple juice consumption rates for children (ages 0-6) and for all persons (for ages 0-50 and for lifetime), both for average consumption and for high consumption (three times average consumption). FDA then modeled arsenic concentrations in apple juice from FDA sampling data. For the purpose of evaluating potential guidance values for inorganic arsenic in apple juice, FDA determined that the most appropriate data set was 94 ready-to-drink (not concentrate) apple juice samples collected at retail as part of an assignment in FY 2011. The most realistic juice model estimated average inorganic arsenic concentrations in juice assuming that one of three hypothetical maximum limits (3, 5, and 10 ppb) was in place, and juices with arsenic concentrations exceeding these maximum limits were eliminated from the food supply. Finally, the dose-response model was used to model disease rates based on the estimated average inorganic arsenic concentrations in apple juice.

Based on FDA FY11 sampling data and assuming chronic exposure (0-50 years), the modeled urinary tract and lung cancer disease rates at the hypothetical maximum limits ranged from 2.5 to 8.0 cases per million people for the average consumer and 7.7 to 24.9 cases per million people for high-level consumers (see Ref. 5 and Table 1 in this supporting document). Comparison of risk estimates between lifetime exposure and childhood exposure indicate that much of the risk is incurred during childhood because the majority of exposure is achieved during childhood (Ref. 5).

b. Achievability Assessment. To assess achievability, or manufacturers' ability to achieve the hypothetical limits on inorganic arsenic, FDA determined the percentage of apple juice samples surveyed in 2011 that fell at or below such limits. Table 1 illustrates that 31, 54, and 100 percent of the FY11 samples respectively fell at or below the modeled limits of 3, 5, and 10 ppb inorganic arsenic. These data suggest that it would be difficult for manufacturers to achieve action levels of 3 or 5 ppb inorganic arsenic, since only 31 percent of samples fell at or below 3 ppb and only 54 percent of samples fell at or below 5 ppb. It appears much more likely that manufacturers could achieve an action level of 10 µg/kg or 10 ppb inorganic arsenic, since 100 percent of the FY11 samples fell at or below the limit of 10 µg/kg or 10 ppb. Because samples have been identified in previous years as containing inorganic arsenic above 10 ppb (Ref. 7), the 10 µg/kg or 10 ppb limit will reduce public exposure to inorganic arsenic from apple juice that may contain inorganic arsenic at levels above 10 µg/kg or 10 ppb in the future.

VII. Conclusion

FDA previously identified 23 ppb as the level of concern for inorganic arsenic in apple juice for the purpose of a hazard assessment based on short term exposure and non-cancer endpoints. Based on a new quantitative risk assessment using chronic exposure (0-50 years) and cancer endpoints, as well as considerations including new data on total and inorganic arsenic levels and manufacturer achievability, FDA is setting an action level for inorganic arsenic in single-strength apple juice of 10 µg/kg or 10 ppb. The action level of

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10 µg/kg or 10 ppb, based on chronic exposure, will be protective against adverse effects associated with short term exposure that were the basis for the level of concern of 23 ppb.

FDA has concluded that it is appropriate to set an action level for inorganic arsenic because FDA sampling data show that inorganic arsenic is the main form of arsenic in apple juice and because inorganic arsenic is considered more toxic than organic arsenic. FDA will continue its current practice of screening apple juice samples for total arsenic, prior to speciating for inorganic arsenic in samples with total arsenic levels above 10 µg/kg or 10 ppb.

FDA has concluded that a level of 10 µg/kg or 10 ppb inorganic arsenic is achievable under good manufacturing practices based on evaluation of recent FDA data on arsenic levels in apple juice samples purchased at retail. FDA also has concluded that an action level of 10 µg/kg or 10 ppb is adequate to protect the public health based on its risk assessment.

VIII. 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. 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 http://whqlibdoc.who.int/trs/WHO_TRS_959_eng.pdf.
3. 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>.
4. National Research Council (NRC), 1993, Pesticides in the Diets of Infants and Children, National Academy Press, Washington, D.C.
5. U.S. FDA, 2013, A Quantitative Assessment of Inorganic Arsenic in Apple Juice. <http://www.fda.gov/downloads/Food/FoodScienceResearch/RiskSafetyAssessment/UCM360016.pdf>
6. U.S. FDA, 2011a, Results of Arsenic Analysis in Single-Strength Apple Juice, 2011 (ORA Sampling Assignment 2011102701), December 16, 2011 update, accessed online at <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm283725.htm>.
7. U.S. FDA, 2011b, Arsenic in Apple Juice Analytical Results, 2005-2011 Toxic Elements Food and Foodware Program, December 16, 2011 update, accessed online at <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm273328.htm>.

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8. 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.

9. 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. Effects of three proposed limits on arsenic in apple juice: modeled disease rates and manufacturer achievability¹²

Limit (inorganic arsenic, ppb)	Average inorganic arsenic level in juices below specified limit ¹³	Disease rates ¹⁴ based on average juice consumption ¹⁵	Disease rates based on three times average juice consumption (high consumer)	Percentage of 94 FY11 samples with inorganic arsenic levels at or below specified limit ¹⁶
3	1.4	2.5 (0.0, 6.8)	7.7 (0.0, 20.3)	31 %
5	2.7	4.8 (0.0, 12.8)	14.9 (0.1, 38.5)	54 %
10	4.4	8.0 (0.0, 21.3)	24.9 (0.2, 63.8)	100 %

¹² Disease rates for total lung and urinary tract cancer are from A Quantitative Assessment of Inorganic Arsenic in Apple Juice (Ref. 5). Disease rates are based on chronic (0-50 years) exposure. Arsenic levels are based on FY11 retail apple juice data (Ref. 6).

¹³ Average residue level based on 94 samples. For the purpose of calculating average levels, levels below 1 or the level of quantitation were assumed to be 1.4 ppb.

¹⁴ Number of cases per million. Numbers in parentheses represent lower and upper bounds.

¹⁵ Average juice consumption: 4.1 g juice/kg bw/day for children aged 0-6 years; 0.83 g juice/kg bw/day for all persons aged 0-50; 0.62 g juice/kg bw/day for all persons.

¹⁶ Percentages calculated by dividing the number of samples with inorganic arsenic levels at or below the proposed limit by 94 total number of samples.