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Mitigating dietary arsenic exposure: Current status in the United States and recommendations for an improved path forward

Keeve E. Nachman [a,b,c,d,*], Gary L. Ginsberg [e], Mark D. Miller [f], Carolyn J. Murray [g,h], Anne E. Nigra [a], Claire B. Pendergrast [i]

[a] Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[b] Johns Hopkins Center for a Livable Future, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[c] Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[d] Johns Hopkins Risk Sciences and Public Policy Institute, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[e] Connecticut Department of Public Health, Hartford, CT, USA
[f] Western States Pediatric Environmental Health Specialty Unit, University of California, San Francisco, CA, USA
[g] Dartmouth Children's Environmental Health and Disease Prevention Research Center, Hanover, NH, USA
[h] Geisel School of Medicine at Dartmouth, Hanover, NH, USA
[i] Dartmouth Superfund Research Program, Hanover, NH, USA

HIGHLIGHTS

- Our assessment of regulatory oversight of dietary arsenic found that foods are addressed on individual bases, and not comprehensively.
- A process for prioritizing dietary inorganic arsenic exposures by different lifestages is proposed.
- A relative source contribution-based approach to setting criteria for arsenic in prioritized foods is recommended.

GRAPHICAL ABSTRACT

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ABSTRACT

Inorganic arsenic (iAs) is a well-characterized carcinogen, and recent epidemiologic studies have linked chronic exposures to non-cancer health outcomes, including cardiovascular disease, diabetes, skin lesions and respiratory disorders. Greater vulnerability has been demonstrated with early life exposure for health effects including lung and bladder cancer, immunotoxicity and neurodevelopment. Despite its well-known toxicity, there are important gaps in the regulatory oversight of iAs in food and in risk communication. This paper focuses on the US regulatory framework in relation to iAs in food and beverages. The state of existing regulatory agency toxicological assessments, monitoring efforts, standard setting, intervention policies and risk communication are explored. Regarding the approach for standard setting, risk-based evaluations of iAs in particular foods can be informative but are insufficient to create a numeric criterion, given current uncertainties in iAs toxicology and the degree to which traditional risk targets can be exceeded by dietary exposures. We describe a process for prioritizing dietary exposures for different lifestages and recommend a relative source contribution-based approach to setting criteria for arsenic in prioritized foods. Intervention strategies begin with an appropriately set criterion and a monitoring program that documents the degree to which this target is met for a particular food. This approach

* Corresponding author at: Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.
E-mail address: knachman@jhu.edu (K.E. Nachman).

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will promote improvements in food production to lower iAs contamination for those foods which initially do not meet the criterion. Risk communication improvements are recommended to ensure that the public has reliable information regarding sources and alternative dietary choices. A key recommendation is the consideration of meal frequency advice similar to what is currently done for contaminants in fish. Recent action level determinations by FDA for apple juice and infant rice cereal are evaluated and used as illustrations of how our recommended approach can further the goal of exposure mitigation from key sources of dietary iAs in the US.

1. Introduction

Inorganic arsenic (iAs) is a toxic metal that has been associated with numerous adverse outcomes in humans, including various cancers, cardiovascular disease, diabetes, respiratory disorders, skin lesions, immunotoxicity and neurodevelopmental effects in early life (National Research Council, 2014). While regulatory focus has historically been on controlling iAs in drinking water and soil, dietary sources predominate for many individuals (Kurzius-Spencer et al., 2014; Carlin et al., 2015). Given the variability in iAs content of foods and intra-population rates of consumption of iAs-containing foods, it can be challenging to single out individual food items for regulatory action and public education. Such efforts have also been hampered by the lack of consensus regarding the carcinogenic potency of iAs, and the risk of certain non-cancer outcomes at lower doses. Despite these difficulties, existing assessments converge on the possibility of elevated health risk and the need to consider mitigation strategies to limit iAs dietary exposure (Naujokas et al., 2013; Carlin et al., 2015).

In the US, few foods have been subjected to regulatory interventions aimed at reducing the public's iAs exposure, and consequently, the appropriate incentives are not in place to promote exposure mitigation at the level of food production. Consumers have been confronted with media reports about the presence of arsenic in food, most notably with respect to apple juice and rice (Consumer Reports, 2012a; Consumer Reports, 2012b). Currently available information does not give consumers enough information to make informed choices about arsenic in the diet (Lai et al., 2015). Taken together, the emerging evidence regarding iAs's association with myriad adverse outcomes combined with the importance of diet as a key exposure source underscore the need for regulatory oversight, mitigation strategies, and enhanced risk communication.

In this paper, we focus on the challenges and opportunities for improving the manner in which iAs in food is evaluated, monitored and controlled within the US regulatory framework, using recent action level determinations by the Food and Drug Administration (FDA) as case study examples. Our goals are to examine the adequacy of existing regulatory approaches and communication activities, to examine the utility of risk-based and alternative strategies for setting criteria for specific food items, and to recommend practical mitigation strategies that target the greatest sources of dietary iAs exposure.

This paper and the four others that accompany it (Cubadda et al., 2017; Davis et al., 2017; Punshon et al., 2017; Taylor et al., 2017) are products of the Collaborative on Food with Arsenic and Associated Risk and Regulation (C-FARR), a two-year effort led by the Dartmouth Superfund Research Program and Children's Environmental Health and Disease Prevention Research Center. The goal of C-FARR is to synthesize the current information pertaining to arsenic from soil to plate, based on key questions and knowledge gaps identified by policy stakeholders and scientists from interdisciplinary backgrounds, to inform future regulatory and policy decisions affecting dietary arsenic exposure.

2. Defining the scope of the problem

2.1. Arsenic exposures and health effects

Unlike many other chemicals, the majority of evidence of adverse health outcomes for arsenic comes from studies of human populations instead of laboratory animal studies. A wealth of epidemiologic evidence supports the notion that chronic ingestion of iAs in water can elicit adverse health outcomes in exposed populations (National Research Council, 2014; Carlin et al., 2015). The National Academy of Sciences (NAS) Committee on Inorganic Arsenic provided a state of the evidence review of iAs to assist the EPA's Integrated Risk Information System (IRIS) in developing a toxicological assessment for iAs (National Research Council, 2014). The Committee developed a three-tier hierarchy of health endpoints based upon whether evidence of a causal relationship with iAs has been demonstrated. The first tier (causality well documented) included lung, skin and bladder cancers, ischemic heart disease, and skin lesions. The second tier, termed priority endpoints (well defined, but evidence still emerging), included prostate and renal cancers, diabetes, non-malignant respiratory disease, infant morbidity, neurodevelopmental toxicity, and immune effects. The final tier included health effects worthy of further consideration, but for which data are less well developed, included liver and pancreatic cancers, renal disease, hypertension, stroke and other pregnancy outcomes, such as fetal loss, stillbirth and neonatal mortality. The NAS Committee stated that for a number of these endpoints, the doses required to elicit adverse effects may be close to or even overlap with levels of current human exposure (NRC, 2014).

2.2. Vulnerable populations

Particular sub-populations may be at increased risk for health effects resulting from arsenic exposure. This may result from altered metabolism or underlying genetic risk factors, lifestages that represent developmental windows of unique sensitivity to iAs toxicity, and factors that may increase dietary exposure such as individual preferences, age group, cultural factors, and dietary restrictions (e.g., gluten-free or allergy). A European study found that dietary exposure was about 3 times as great for children under 3 years of age compared with adults (European Food Safety Authority, 2014). Certain ethnic groups may receive greater exposure as average rice consumption and urinary iAs were both higher in Asian/other, Mexican, and Black children than in white children age 6–17 according to NHANES 2003–2008 data (Lai et al., 2015). The fetus and young children may be at particular risk as a result of developing organ systems and expected years of life in which to develop cancer and other chronic outcomes (Miller et al., 2002).

The vulnerability from early life exposure is perhaps best exemplified by the dramatic increases in rates of death from bronchiectasis in Chile for those exposed to iAs in utero (standardized mortality ratio [SMR] of 12.4, CI 3.3–31.7) and/or postnatally (SMR 46.2, CI 21.1–87.7) (Smith et al., 2006). In a Chilean case control study, those exposed to moderately elevated levels of arsenic in utero or as children ($<100\ \mu g\ L^{-1}$ in water) had an increased bladder and lung cancer as adults despite exposures ending as much as 40 years earlier (Steinmaus et al., 2014).

The distribution of arsenic forms (MMA, iAs, DMA) excreted in urine have been used as a marker of an individual's ability to metabolize iAs via methylation (Marafante and Vahter, 1984). Inorganic arsenic is initially metabolized to MMA, an intermediate of substantial toxicity. In several studies, those who excreted a higher proportion of MMA in their urine had increased risk of lung, bladder and skin cancer suggesting that inadequate methylation capacity to DMA is a risk factor that