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Opportunities and Challenges for Dietary Arsenic Intervention

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SUMMARY: The diet is emerging as the dominant source of arsenic exposure for most of the U.S. population. Despite this, limited regulatory efforts have been aimed at mitigating exposure, and the role of diet in arsenic exposure and disease processes remains understudied. In this brief, we discuss the evidence linking dietary arsenic intake to human disease and discuss challenges associated with exposure characterization and efforts to quantify risks. In light of these challenges, and in recognition of the potential longer-term process of establishing regulation, we introduce a framework for shorter-term interventions that employs a field-to-plate food supply chain model to identify monitoring, intervention, and communication opportunities as part of a multisector, multiagency, science-informed, public health systems approach to mitigation of dietary arsenic exposure. Such an approach is dependent on coordination across commodity producers, the food industry, nongovernmental organizations, health professionals, researchers, and the regulatory community. https://doi.org/10.1289/EHP3997

Background

Emerging data suggest that arsenic, even at relatively low levels of exposure, may affect human health, particularly during early life (NRC 2014). In consideration of this issue, regulatory efforts have been mobilized to address exposures, primarily from drinking water (Nachman et al. 2017). As successes are increasingly documented in these exposure-reduction efforts (Nigra et al. 2017; Welch et al. 2018), we view the diet as a driving source of exposure in populations with low drinking water arsenic. Despite its contributions to aggregate arsenic exposures, efforts to tackle arsenic in food have been relatively sparse. The Collaborative on Food with Arsenic and associated Risk and Regulation (C-FARR) brought arsenic and food scientists together with policy stakeholders for a workshop focusing on knowledge gaps and policy questions in recognition of this lagging focus. The resulting five papers address this issue from soil to plate to policy (Cubadda et al. 2017; Davis et al. 2017; Nachman et al. 2017; Punshon et al. 2017; Taylor et al. 2017). Moving beyond the C-FARR workshop, and considering scientific and policy hurdles, we discuss here an array of immediate-term opportunities that exist among multiple stakeholder groups to intervene on dietary arsenic exposures.

Arsenic exposure through drinking water has established health impacts (NRC 2014), and although existing science supports the assumption that effects will be similar from food, the role of diet in population arsenic exposures has been less studied. Most epidemiologic studies describing arsenic's effects have relied on drinking water concentrations or urine measurements as exposure measures, which are not designed to disentangle the role of dietary arsenic in the occurrence of disease (Nachman et al. 2017). Further, in comparison with drinking water, where arsenic occurs solely in inorganic forms, the species profile for

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food is complex, comprising inorganic arsenic (arsenite and arsenate) and more than 100 organic arsenic species that vary within and across foods (Cubadda et al. 2017). Although epidemiologic studies have provided clear evidence for the carcinogenicity of inorganic arsenic (iAs) and link it to myriad noncancer outcomes, our understanding of the chronic toxicity of organic species is emerging, further complicating characterization of dietary arsenic exposures (Taylor et al. 2017).

Although drinking water may be an easier medium for epidemiologists to use to examine arsenic exposure, it is not the dominant pathway for most of the U.S. population. An earlier assessment of public water in 25 states estimated that $<4\%$ of people were served by systems with arsenic concentrations >1 μg/L, and just over 1% were above the 10 μg/L U.S. EPA Maximum Contaminant Level (MCL) (Mushak et al. 2000). Since then, public water exposures have declined, following the implementation of the MCL (Nigra et al. 2017). Evaluations of modeled exposure across dietary and drinking water pathways suggest that in those with drinking water arsenic concentrations below the MCL, diet is responsible for the majority of both total and iAs intake (Kurzius-Spencer et al. 2014; Xue et al. 2010).

Despite the importance of the dietary pathway, sparse data exist about the role of dietary arsenic exposure in disease processes. Among these investigations, most have focused on rice, and very few have jointly considered drinking water exposures along with other potential dietary sources. Additional challenges in characterizing the role of diet include difficulty in separating out the effects of arsenic in the water used to cook rice in high water arsenic regions, estimating arsenic levels in rice and rice products and adjusting for the effects of dietary and other confounders (e.g., carbohydrate content of rice). To date, few studies raise the possibility of adverse health impacts of rice consumption among those with relatively low drinking water arsenic concentrations. These studies found a trend in cardiovascular disease risk with white (but not brown or overall) rice consumption in the prospective Nurses' Health Study among participants living in low arsenic regions (<3 μg/L), but not among those living in higher arsenic regions (Muraki et al. 2015). In Bangladesh, Melkonian et al. (2013) found a relationship between steamed rice consumption and premalignant and malignant skin lesions in both cross-sectional and prospective analyses of the Health Effects of Arsenic Longitudinal Study only among those with drinking water arsenic concentrations <100 μg/L. In the United States, an association between rice consumption and squamous cell carcinoma of the skin was observed in a population-based study, largely among those with tap water concentrations of arsenic <1 μg/L (Gossai et al. 2017). Using data from the Nurses' Health Study and the Health Professionals Follow-up Study, Zhang et al. (2016) found no significant increases in cancer risk from rice consumption but identified a borderline significant increased bladder cancer risk when comparing the highest rice-consumption group to the lowest; the study did not involve consideration of drinking water arsenic. Thus, although limited, epidemiologic evidence currently suggests that the effects of rice consumption may mirror those of arsenic in drinking water.

Dietary exposure characterization poses unique methodological challenges, as few studies describe distributions of arsenic across foods, and far fewer involve speciation (Cubadda et al. 2017). These data gaps complicate efforts to quantify dietary exposures and limit the ability to target foods for intervention based on their relative contributions to aggregate intake.

Though risks from food cannot be precisely quantified, existing evidence supports efforts to limit exposure wherever possible, especially for vulnerable populations (Naujokas et al. 2013). Despite the dominance of diet in population arsenic exposures, arsenic in food remains unregulated in the United States (Nachman et al. 2017). Under normal circumstances, regulatory agencies would be expected to play a key role in drafting enforceable interventions aimed at minimizing population exposures. In the case of arsenic, no enforceable regulatory standards exist for any foods, though the U.S. Food and Drug Administration (U.S. FDA) has proposed draft action levels and accompanying industry guidance for apple juice (U.S. FDA 2013) and infant rice cereal (U.S. FDA 2016). Legislative attempts to force stringent regulatory action (U.S. Congress 2012, 2015, 2017) have thus far been unsuccessful, though in its 2018 evaluation of U.S. FDA and U.S. Department of Agriculture (USDA) action on arsenic in rice, the U.S. Government Accountability Office (U.S. GAO) recommended FDA finalize its guidance on arsenic in infant rice cereal and called for improvements in interagency coordination on analytical methods and risk-assessment approaches for arsenic and other food contaminants (U.S. GAO 2018).

We previously described an approach that could be used to reduce dietary iAs exposure in the U.S. population. It employs existing monitoring data (and proposes newer data streams) to facilitate an iterative reevaluation of population dietary iAs exposures, and subsequently prioritizes specific foods for intervention, both in the form of measures to reduce arsenic concentrations in key foods (via action levels and regulatory standards to compel producer efforts to reduce arsenic content) and dietary advice when those reductions are more difficult (Nachman et al. 2017). If adequately protective standards are implemented and properly enforced (Signes-Pastor et al. 2017b), this type of holistic approach, which recognizes the pervasiveness of iAs in the food supply (Schoof et al. 1999), may hold promise for reducing population exposures. To complement this approach, especially in circumstances where regulatory action may occur more slowly (Krisberg 2017; Samet et al. 2017), other opportunities exist that can be implemented in the short term and may yield public health benefits stemming from arsenic exposure reductions.

Discussion

In the absence of regulations specific to arsenic in food, we argue that there are many opportunities for nonregulatory stakeholders to mitigate dietary exposures based on our current understanding of the food supply chain. Furthermore, we believe it is possible to reduce exposure to arsenic through control of source releases, and demonstration of ways to reduce the arsenic content of retail foods may pave the way for future regulatory changes at the federal level.

Figure 1 depicts intervention and monitoring points along the food supply that may be meaningfully employed by various stakeholders to reduce population dietary exposures. Given that rice has been the subject of considerable intervention research, we use it in demonstrating opportunities. We recognize, however, as we have previously specified (Nachman et al. 2017), that a coordinated, iterative monitoring intervention strategy that considers the contribution of all foods and beverages would begin to address the current needs of reducing exposure.

Rice cultivar selection and agronomic practices dominate as driving factors of grain arsenic concentrations (Norton et al. 2012; Yang et al. 2017). The influence of genetic variation on grain arsenic indicates that breeding low-arsenic rice cultivars is a viable approach and is currently underway (Norton et al. 2009). Manipulating flooding cycles in rice production, tied to sustainable agricultural practices for reducing water use, can also reduce grain arsenic (Li et al. 2009; Yang et al. 2017). Fertilization strategies, particularly using silicon, have potential as an effective strategy to reduce arsenic, and prevent certain plant diseases (e.g., straighthead disease in rice) (Limmer et al. 2018). Equally

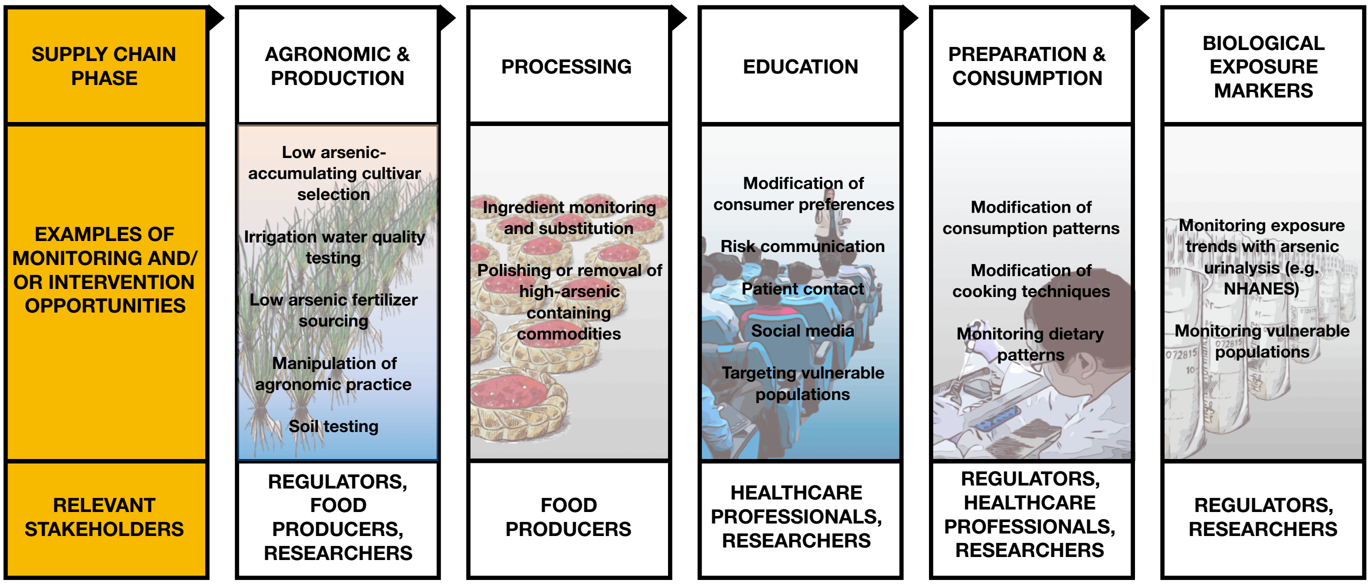

Figure 1. The food supply chain and opportunities for dietary arsenic exposure monitoring and intervention. A field-to-plate food supply chain model can aid in identifying monitoring, intervention and communication opportunities as part of a multisector, multiagency, science-informed, public health systems approach to mitigation of dietary arsenic exposure.

important to demonstrating efficacy of these approaches, is making them accessible and attractive to small scale rural farming operations; for example, re-using rice husk as a silicon fertilizer for rice paddy soils [shown to lower total and iAs (Penido et al. 2016; Seyfferth et al. 2016; Teasley et al. 2017)] has great potential because silicon fertilizers are too expensive to be implemented at many smallholding farms, and, if used, would potentially drive up the price of rice.

Recent Codex Alimentarius international food standards codes of practice (Codex 2017) lay out logical steps for the prevention and reduction of arsenic contamination in rice, grouped into: source-directed measures (determining that the arsenic concentrations of soils and irrigation water are not elevated before use; cognizance of proximity to point sources of arsenic contamination; avoiding use of arsenical pesticides and veterinary drugs, feed, soil amendments, and fertilizer), agricultural measures (use of alternative intermittent flooding strategies and low-arsenic cultivars), and monitoring and risk communication programs. Adherence to this code has the potential to dramatically reduce arsenic concentrations, particularly if food-product labeling were used to raise consumer awareness.

Recognizing that the arsenic content of many finished foods is dependent on the raw commodities that serve as ingredients, opportunities exist regarding both the selection of ingredients and quality assurance measures related to the arsenic concentrations of those constituents. For example, the replacement of high-fructose corn syrup with organic brown-rice syrup in products like toddler formula and energy bars (Jackson et al. 2012) and the use of the algae-derived gelatin substitute carrageenan in a variety of foods (Díaz et al. 2012; U.S. FDA 2017b) may contribute to dietary arsenic intake, although the health impacts of constituents require further testing. Currently, no programs exist to monitor the arsenic content of additives or ingredients, and recommended international standards for some of these inputs may not be based upon the most recent evidence (Food and Agriculture Organization 2001). Processor-level preventive actions, such as ingredient monitoring or ingredient substitution with others less likely to accumulate arsenic, may be beneficial.

Additional reductions may be achievable during food and ingredient processing by taking advantage of our understanding of the nature of iAs accumulation within commodities. For example, rice-processing procedures designed to remove the husk (which has been shown to accumulate iAs at levels as high as 1 ppm) and further polish the grain can achieve substantial iAs reductions (Carey et al. 2015; Meharg et al. 2008; Signes-Pastor et al. 2017a; Signes et al. 2008). Further, lower iAs content in rice-based products can be achieved by dilution of rice with other gluten-free grain (Carey et al. 2018).

In some instances when adequate exposure reduction cannot be accomplished by lowering the arsenic content of foods, alternative approaches to reduce dietary exposures may be warranted, such as modifying consumer preferences to influence purchasing behaviors (which would exert pressure on producers to address the arsenic content of their foods) (Nachman et al. 2017).

Interventions to communicate information on arsenic in food are somewhat limited and often rice-centric, though some helpful sources exist, including a comprehensive website focused on arsenic in rice and rice products by Consumer Reports (2015). The U.S. FDA (2017a) also maintains a communications and data-sharing website for arsenic in food. Research-based consumer education resources highlighting arsenic health risks and dietary (and other) exposure-reduction options are available online in a comprehensive website (Dartmouth College Superfund Research Program 2017) and an interactive graphic (Children's Environmental Health and Disease Prevention Research Center at Dartmouth 2016). Beyond these vetted resources, social media sites and blogs from gluten-free dietary information resources and Celiac disease organizations (e. g., Celiac Disease Found-ation 2017) also provide exposure-reduction resources. Research is needed to determine the effectiveness of these tools on individual behavior change and consumer decision-making. Additional communication efforts need to be tailored and targeted to populations at higher risk of adverse health effects from arsenic exposure, such as infants, children, and pregnant women, as well as to populations more highly exposed due to cultural preference and dietary restrictions (Lai et al. 2015).

Communication efforts successful in changing consumer behaviors may have collateral benefits along the food supply chain. Research published by Jackson et al. (2012) identifying elevated iAs in organic brown-rice syrup used in toddler formula resulted in a media cycle and public outcry that prompted some food manufacturers to take action to address arsenic in their products (Lundberg Family Farms 2016; Nature's One 2018), illustrating how media attention and consumer opinion can drive industry action to reduce arsenic content in food products even without regulation.

Recent research has highlighted post-retail opportunities for consumers to reduce the arsenic content of finished foods. Several studies have shown that some of the iAs content is readily leached from rice by washing and soaking, and even more can be removed by increasing the volume of cooking water that rice encounters, followed by draining off the excess iAs-containing water generated during cooking (Raab et al. 2009; Sengupta et al. 2006; Signes et al. 2008). To this end, a new rice cooking approach has been proposed based on a continual stream of percolating near-boiling water; when low-arsenic water has been used, this method has been demonstrated to remove $\sim 57\%$ of iAs from cooked rice at water-to-rice cooking ratio of 12:1, and a removal of $\sim 70\%$ of iAs with a ratio of 150:1 or higher in cooked rice bran (Signes-Pastor et al. 2017a). Proponents of this approach have suggested its feasibility both in industrial and domestic settings, and possibly even when low arsenic cooking water is not available by percolating freshly recycled distilled water (Carey et al. 2015). Such an approach may provide a near-term, suitable solution to mitigate high iAs levels in rice and rice bran, though further research is needed to assess potential loss of key vitamins and other water-soluble compounds that could be refortified if necessary.

Existing population-level health surveys, especially those that describe dietary patterns and collect biomarker data, can help target dietary interventions, and to a lesser extent, assist in evaluating existing exposure-reduction efforts. The What We Eat in America food survey, conducted as part of the National Health and Nutrition Examination Survey (USDA 2018), enables the characterization of dietary patterns across key population subgroups, including both vulnerable life stages regarding arsenic exposure and population subgroups with higher consumption of arsenic-accumulating foods. Urinary arsenic concentrations have been consistently related to rice consumption among populations throughout the world, and in both interventional and observational studies (Davis et al. 2017). These studies encompass populations of various ages, ranging from infancy and early childhood to pregnancy and later adulthood. Arsenic is known to pass through the placenta (e.g., Hall et al. 2007); in a prospective cohort study, intake of rice during pregnancy was related to arsenic concentration in infant toenails collected within a few months of birth (Davis et al. 2014), and a longitudinal study found an increase of infants' urinary arsenic during transition to solid food, including rice cereals, fruits, and vegetables (Signes-Pastor et al. 2018). Evaluations of arsenic biomarker trends among these subpopulations may allow for identification of interventions aimed at specific subpopulations or foods. Further, recent efforts to disentangle dietary from drinking water exposures within biomarker measurements may enhance sensitivity of evaluation of dietary interventions (Jones et al. 2016).

Conclusions

Dietary arsenic exposures are an increasingly recognized public health concern, and this concern calls for interventions to reduce exposure, especially to vulnerable populations, such as pregnant women, infants, and children. Regulatory advances will be essential for effective intervention to lower dietary arsenic exposure, but opportunities also exist for various stakeholders, including commodity producers, the food industry, physicians, and the public, to take steps along the supply chain. For instance, we have proposed a proactive scheme designed to compel the production of low-arsenic foods (Nachman et al. 2017). Such approaches require better monitoring efforts, such as those implemented in the Italian Total Diet Study (Cubadda et al. 2016), that employ the latest measurement techniques and push the field of practice forward. Moving further upstream, public health benefits may be derived from policies aimed at creating producer recommendations or setting production standards for soils and irrigation water.

Building upon GAO's (2018) recommendations of interagency coordination on arsenic in food, future regulatory policy interventions must consider the relative contributions of different dietary and other pathways to aggregate arsenic exposures. Further, enhanced efforts to monetize the avoidance of noncancer health outcomes (e.g., cardiovascular, developmental, and many others) associated with arsenic exposure would be of great value. The effect of reducing the occurrence of these outcomes was not quantitatively considered in the U.S. EPA's economic justification of the arsenic in drinking water rule (U.S. EPA 2000). An economic understanding of the public health benefits of preventing these outcomes would likely justify more stringent measures to reduce exposure.

An urgent component of moving regulatory policy forward is updating the iAs toxicological assessment. The EPA IRIS's endeavor to update its iAs risk assessment is currently underway but has yet to be finalized. GAO called for U.S. FDA to update its rice risk assessment (U.S. GAO 2018), however, such efforts may be redundant with, and less comprehensive than that of the EPA IRIS program. In its 2018 review of updates to the IRIS program, the National Research Council (NRC), expressed satisfaction with the program's adoption of systematic review methods in pursuit of hazard characterization and dose-response assessment (NRC 2018). With much effort already invested in the development of the iAs assessment, and ongoing coordination with the NRC, it is anticipated that the toxicity values produced by this effort will be key in informing future FDA rice (and other food) risk assessment endeavors. With these toxicity values, interventions will be able to set sights on risk-based exposure limits, rather than limiting efforts to general exposure reduction in the absence of any target based on actual dose–response relationships.

Certain gaps in understanding of the science exist that, if filled, would bolster policy efforts aimed at exposure reduction. Specifically, primary research, as well as systematic reviews and meta-analyses of "other priority outcomes" (e.g., diabetes, neurodevelopmental toxicity and immune effects) and "other endpoints to consider" (e.g., renal disease, liver and pancreatic cancer, and hypertension), as specified by the NRC (2014), are needed. In addition, research to better characterize life stage-specific windows of vulnerability to arsenic exposure, as well as their interactions with genetic factors, epigenetic alterations, and other contaminant exposures (Cardenas et al. 2015), as well as the timing of gene-expression changes (Wright and Christiani 2010) is warranted. Further, broadening consideration of arsenic to include oral exposure to organic arsenic species commonly found in foods (including methylated forms, arsenosugars, and arsenolipids) would be of value, especially for understanding dietary exposures. Focusing interventions narrowly on inorganic species may not account for the true health burdens resulting from exposure. Although uncertainty remains over population-wide health effects of dietary arsenic, focus on susceptible populations is critical. The mitigating role of nutrients involved in arsenic metabolism, such as folate and other B vitamins (Kurzius-Spencer et al. 2017; Spratlen et al. 2017) strongly suggests that susceptible populations will also include those with gastrointestinal disorders that inhibit the intestinal absorption of these vitamins, such as individuals with Celiac disease, a population with increased dietary arsenic exposure from the prevalence of a rice-based, gluten-free diet (Bulka et al. 2017; Punshon and Jackson 2018).

Dietary arsenic exposure is an important public health challenge that contributes to population risk of a broad number of adverse health impacts. Current regulatory approaches for arsenic are limited, and the statutory basis for potential controls is fragmented across multiple agencies. As a result, the patchwork of state and federal efforts has had limited success in reducing dietary exposures and often results in mixed messages to consumers about risks. It is time to rethink our current approaches and develop a systems approach to dietary arsenic exposures — from source to ingestion. A renewed, inclusive approach to problem formulation, including the social and behavioral sciences (The National Academies 2018), can provide a renewed perspective on both efforts to characterize the scope of the problem and the most productive opportunities to intervene. Our greatest success in reducing dietary exposures can be achieved only by a multisector, multiagency, science-informed, public health systems approach coordinated across regulators and the industry (Burke et al. 2017). When those are not enough to ensure minimal arsenic contributions through diet, a well-informed public empowered to make the right food choices is essential.

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