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Role of complex organic arsenicals in food in aggregate exposure to arsenic☆

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ABSTRACT

For much of the world's population, food is the major source of exposure to arsenic. Exposure to this non-essential metalloid at relatively low levels may be linked to a wide range of adverse health effects. Thus, evaluating foods as sources of exposure to arsenic is important in assessing risk and developing strategies that protect public health. Although most emphasis has been placed on inorganic arsenic as human carcinogen and toxicant, an array of arsenic-containing species are found in plants and animals used as foods. Here, we 2evaluate the contribution of complex organic arsenicals (arsenosugars, arsenolipids, and trimethylarsonium compounds) that are found in foods and consider their origins, metabolism, and potential toxicity. Commonalities in the metabolism of arsenosugars and arsenolipids lead to the production of di-methylated arsenicals which are known to exert many toxic effects. Evaluating foods as sources of exposure to these complex organic arsenicals and understanding the formation of reactive metabolites may be critical in assessing their contribution to aggregate exposure to arsenic.

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Introduction

The biogeochemical cycling of arsenic involves chemical, physical, and biological processes that result in substantial fluxes of arsenic through the environment (Zhu et al., 2014). Some of this arsenic is incorporated into food and water sources, providing routes for human exposure to this toxic metalloid. In terms of risk to humans, most emphasis has been placed on the role of inorganic arsenic in drinking water as a source of exposure (Smith and Steinmaus, 2009; Bloom et al., 2014; Shankar et al., 2014; Tsuji et al., 2014; Karagas et al., 2015). However, absent a water supply contaminated with inorganic arsenic, the major source of exposure to arsenic for most individuals is through consumption of foods that contain the metalloid (Kurzius-Spencer et al., 2014; Wilson, 2015). Inorganic arsenic is classified as a Group 1 carcinogen in humans (IARC, 2004, 2012). Consumption of foods containing inorganic arsenic probably contributes to the global cancer burden (Oberoi et al., 2014). Thus, altered patterns of food use, particularly in vulnerable subpopulations such as infants, have been recommended as a strategy to reduce exposure to this metalloid (Gundert-Remy et al., 2015). Although emphasis has usually focused on exposure to inorganic arsenic from consumption of contaminated foodstuffs, widely consumed foods such as rice that can contain both inorganic and di-methylated arsenicals may be significant sources of exposure (Zhao et al., 2013; Wang et al., 2015b). The presence of inorganic and di-methylated arsenic in rice is an important public health issue. Rice is the staple food for over one-half of the world's population (Muthayya et al., 2014). In the U.S., rice consumption makes a significant contribution to arsenic exposure in children (Davis et al., 2012), raising special concerns about exposure in an age group that may be especially vulnerable to adverse health effects induced by inorganic arsenic or its metabolites.

Besides inorganic and methylated arsenicals present in foods, three additional classes of arsenicals that are present at high concentrations in foods may make significant contributions to aggregate exposure to arsenic. These classes are arsenosugars, arsenolipids, and tri-methylated arsonium compounds of which arsenobetaine is most abundant. Here, we follow the nomenclature used in an earlier study (Borak and Hosgood, 2007) and refer to these compounds as complex organic arsenicals. Representative structures of some of the complex organic arsenicals are shown in Fig. 1. Complex organic arsenicals are characterized by the presence of a di- or tri-methylated arsenic-containing moiety in aliphatic or aromatic molecule. As described below, methylated arsenic moieties in complex organic arsenicals are derived from enzymatically catalyzed reactions that convert inorganic arsenic to methylated products (Thomas et al., 2007; Thomas, 2015). Thus, there is a critical linkage between the methylation pathway that produces metabolites in which toxic potencies are determined by the oxidation state of arsenic (Styblo et al., 2000) and a series of reactions that incorporate methylated arsenicals into larger biomolecular structures.

Research over the last four decades has identified complex organic arsenicals in many foods. Studies of their fate after ingestion suggest that some of these compounds can be transformed into metabolites which may have biological effects. In recent years, improved analytical methods have made possible the characterization and quantitation of these molecules and their metabolites, creating opportunities to understand their roles in aggregate exposure to arsenic. In the following paragraphs, we first summarize current knowledge of the origin and fate of these complex organic arsenicals and then suggest future directions for research to understand their role in aggregate exposure to arsenic from dietary sources.

1. Arsenosugars

1.1. Origin and occurrence

Arsenosugars are a class of arsenic-containing carbohydrates in which a di- or tri-methylated arsenical is incorporated into a ribofuranoside which contains glycerol, phosphate, sulfate or a sulfonate. Originally these compounds were identified as water-soluble components of seaweeds (Edmonds and Francesconi, 1981). The pathway for the formation of arsenosugars has not been fully elucidated but the formation of arsenosugars has been linked to metabolic processes that transform inorganic arsenic into methylated species. The marine brown macroalga *Fucus serratus* was shown to convert arsenate to arsenosugars (Geiszinger et al., 2001). Freshwater unicellular green alga *Chlamydomonas reinhardtii* which was exposed to arsenate produced mono- and di-methylated

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