

# Seafood arsenic: Implications for human risk assessment

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## Abstract

Concerns about the adverse effects of chronic arsenic exposure have focused on contaminated drinking water and airborne workplace exposures; the risks of naturally occurring arsenic in foods have received less attention. About 90% of the arsenic in US diets comes from seafood, of which only a small proportion occurs in inorganic forms; the great majority consists of complex organic compounds that generally have been regarded as non-toxic. However, recent studies of seafood have documented formation of metabolites carcinogenic in some rodents. To calculate the risks of ingested seafood arsenic, therefore, it is necessary to identify the nature and quantity of arsenic species present and the metabolites formed by expected metabolic activities. We review the nature and quantities of the various arsenical compounds found in dietary seafood and discuss their metabolic processing and fate. Based on conservative dose estimates and the likelihood that arsenic's carcinogenic mechanisms follow sub-linear dose–response curves, we estimate a margin of exposure of at least  $10^3$ – $10^4$  between carcinogenic doses used in rodent studies and those expected after human consumption of large quantities of seafood.

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## 1. Introduction

The adverse effects of chronic arsenic exposure in humans have been the subject of long standing concerns. Historically such concerns focused primarily on environmental exposures from contaminated drinking water and airborne workplace exposures (WHO, 1981; American Conference of Governmental Industrial Hygienists, 2002; Mead, 2005). Recent regulatory efforts have mainly addressed those two important exposure routes (National Research Council, 2001; US Environmental Protection Agency, 2001; American Conference of Governmental Industrial Hygienists, 2002; IARC Working Group, 2004). By contrast, the toxicological significance of arsenic occurring naturally in foods has received less attention, but has generally been assumed to be insignificant. Researchers have only recently documented the individual levels of vari-

ous organic and inorganic arsenical compounds, rather than just total arsenic, in different food groups (Yost et al., 1998; Schoof et al., 1999a,b) and in daily diets by means of duplicate portion sampling (Robberecht et al., 2002). These studies indicate that arsenic is found routinely in most diets. For example, based on the Food and Drug Administration's 1982–1997 Total Diet Study (Adams et al., 1994; National Research Council, 1999), the estimated average daily dietary intake of arsenic by US adults is 25–75 µg/day.

The largest quantity of dietary arsenic, about 90% of the arsenic in US diets, comes from saltwater finfish and seafood (Adams et al., 1994). Only a small proportion of seafood-derived arsenic occurs in inorganic forms; the great majority of seafood arsenic consists of complex organic arsenical compounds. Thus, consumption of fish and seafood provides a relatively small share of dietary inorganic arsenic. By contrast, the most important dietary sources of inorganic arsenic include uncooked rice, grains and flour (Schoof et al., 1999a,b). In addition, significant amounts of inorganic arsenic are absorbed when rice, grains and other vegetables are cooked in arsenic-contaminated water.

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Accordingly, dietary arsenic can be categorized by arsenic type (e.g., organic vs. inorganic) and by source (e.g., seafood vs. rice and grains).

Despite high levels of total arsenic found in seafood, seafood ingestion has not been linked to arsenic toxicity in humans or other mammals (Edmonds and Francesconi, 1993). Such apparent inconsistency has led to considerable research aimed at understanding the biochemistry and metabolism of the arsenic compounds found in marine species. In pursuing those goals, some researchers have characterized the arsenical compounds found in marine species (Cullen and Reimer, 1989; Kaise and Fukui, 1992; Yamauchi et al., 1992; Ballin et al., 1994; Francesconi and Edmonds, 1998), while others have studied the forms and relative quantities of arsenical compounds excreted by seafood eaters in order to understand the metabolic consequences of seafood ingestion (Yamauchi et al., 1992; Le et al., 1994; Buchet et al., 1996; Heinrich-Ramm et al., 2001, 2002).

## 2. The origin of seafood arsenic

Arsenic is ubiquitous in open ocean seawater, where typical levels are 1–2  $\mu\text{g As/L}$  (Francesconi and Edmonds, 1998; WHO, 2001). Levels of arsenic are most constant in deep ocean waters, while levels in surface waters show seasonal variation (Cullen and Reimer, 1989). It is found mostly as inorganic arsenate (As[V]), particularly in deeper waters. Reduction and methylation by microorganisms occur in the more superficial photic zone, the ocean layer into which sufficient sunlight penetrates to support photosynthesis; levels of methylation correlate with photosynthetic activity (Andreae, 1979, 2005). Accordingly, in addition to As[V], surface waters contain small amounts of inorganic arsenite (As[III]), methyl arsonate (MA) and dimethyl arsinic acid (DMA). Deep-sea sediments may contain high concentrations of arsenic (Francesconi and Edmonds, 1994; Andreae, 2005), but such sediment-bound arsenic is “generally regarded as unavailable” to marine organisms (Francesconi and Edmonds, 1998).

Very little inorganic arsenic is taken up from sea water by most marine animals. To the contrary, marine animals accumulate arsenic primarily from their food, an accumulative process that reflects the sequence of metabolic transformations occurring as arsenic passes up the food chain (Sanders et al., 1989; Francesconi and Edmonds, 1994). That metabolic sequence, beginning with inorganic arsenate, leads to the accumulation by higher animal species of complex methylated compounds that they cannot directly synthesize from inorganic arsenic (Cullen and Reimer, 1989; Francesconi and Edmonds, 1994, 1998).

The sequence starts with phytoplankton (freely floating microscopic plants or algae) which readily take up arsenate from sea water via trans-membrane transport systems normally dedicated to the uptake of essential phosphate anions (Francesconi and Edmonds, 1998; Meharg and Hartley-Whitaker, 2002; Ullrich-Eberius et al., 2005). Following

uptake, algae rapidly detoxify arsenate by reduction and methylation, resulting in the formation of arsenic-containing sugars as well as minor amounts of DMA and other methylated arsenical compounds (Phillips, 1990; Tamaki and Frankenberger, 1992). Levels of arsenic are generally about 1000- to 10,000-fold greater in algae than in seawater, with levels differing across specific algal strains.

In marine animals, the predominant form of arsenic is arsenobetaine, a tri-methylated pentavalent (As[V]) compound first identified in 1977 (Edmonds et al., 1997). It is now recognized as nearly ubiquitous in the marine environment, particularly in finfish and seafood consumed by humans (Edmonds and Francesconi, 1988; Hanaoka et al., 1988; Cullen and Reimer, 1989) and accounts for virtually all of the water-soluble arsenic in such animals. There is sufficient evidence that higher marine animals do not synthesize arsenobetaine from arsenate, but the full details of its synthesis remain uncertain (Francesconi and Edmonds, 1994). It is likely that arsenosugars, released into ocean waters and sediment by the death and decay of algae, are transformed by microbial species to yield arsenobetaine or its precursors which are then ingested by marine animals (Edmonds and Francesconi, 1988; Francesconi and Edmonds, 1998; McSheehy et al., 2002). Experimental findings support the view that microbial species in seawater can transform MA and DMA, but not arsenate, into arsenobetaine (Cullen and Nelson, 1993; Cullen and Pergantis, 1993). It has also been proposed that some marine animals transform small amounts of arsenosugars into arsenobetaine (Edmonds and Francesconi, 1988; McSheehy et al., 2002).

In addition to arsenobetaine, other organic and inorganic arsenic compounds have been found in fish and marine animals that are common components of the human diet. The proportion of inorganic arsenic in those foods is generally low, less than 1–4% of total arsenic (Edmonds and Francesconi, 1993; National Research Council, 1999). Other organic arsenicals found in seafood include simple methylated compounds, particularly MA, DMA and trimethyl arsine oxide, and more complex organic compounds such as arsenocholine and arsenosugars. Their presence probably results from ingestion of algae containing such compounds as a consequence of algal transformation of arsenate. Tri-methylated arsenicals (e.g., trimethyl arsine oxide) are also formed via methylation of ingested arsenate by the microbial intestinal flora of fish and by post-mortem bacterial breakdown of arsenobetaine (Norin et al., 1985; Edmonds and Francesconi, 1988; Hanaoka et al., 1988; Hanaoka et al., 1992; Francesconi and Edmonds, 1994; Hanaoka et al., 1995). Arsenocholine, a key precursor of arsenobetaine (Christakopoulos et al., 1988), has only rarely been found at greater than trace levels in aquatic animals (Cullen and Reimer, 1989; Edmonds and Francesconi, 1993; Francesconi and Edmonds, 1994), suggesting that it exists mainly as a metabolic intermediary.

Arsenical compounds are not uniformly distributed throughout the tissues of marine animals. To the contrary, tissue levels of total arsenic and specific types of arsenic

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