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Arsenic species in seafood: Origin and human health implications*

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Abstract: The presence of arsenic in marine samples was first reported over 100 years ago, and shortly thereafter it was shown that common seafood such as fish, crustaceans, and molluscs contained arsenic at exceedingly high concentrations. It was noted at the time that this seafood arsenic was probably present as an organically bound species because the concentrations were so high that if the arsenic had been present as an inorganic species it would certainly have been toxic to the humans consuming seafood. Investigations in the late 1970s identified the major form of seafood arsenic as arsenobetaine [$(CH_3)_3As^+CH_2COO^-$], a harmless organoarsenic compound which, following ingestion by humans, is rapidly excreted in the urine. Since that work, however, over 50 additional arsenic species have been identified in marine organisms, including many important food products. For most of these arsenic compounds, the human toxicology remains unknown. The current status of arsenic in seafood will be discussed in terms of the possible origin of these compounds and the implications of their presence in our foods.

Keywords: arsenic; arsenic in seafood; arsenobetaine; arsenolipids; arsenosugars; arsenate; dimethylarsinate.

INTRODUCTION

Although it had been known since the early 1900s that marine samples contained a high arsenic content, the first systematic investigation of this phenomenon in seafood was made in the 1920s, and it was to be another 50 years before the unknown arsenic compound in lobster was identified as arsenobetaine [1]. Subsequent toxicological testing indicated that arsenobetaine was completely harmless and its occurrence in seafood presented no human health concerns.

Since the identification of arsenobetaine, over 50 additional arsenic compounds have been reported in marine organisms, many of which serve as common types of seafood. The arsenic compounds of most significance, either because they occur at high levels (e.g., arsenosugars) or because they have toxic properties (e.g., arsenate) or are important metabolites (e.g., dimethylarsinate), are shown in Fig. 1. The levels of arsenic in marine organisms can vary widely, but most samples fall within the range of about 5–100 μg As g^{-1} dry mass. Terrestrial foods, in contrast, almost invariably have low levels of arsenic with most samples having less than 0.05 μg As/g dry mass [2]. There are exceptions, however: rice, for example, can typically contain about 0.1–0.4 μg As g^{-1} [3,4].

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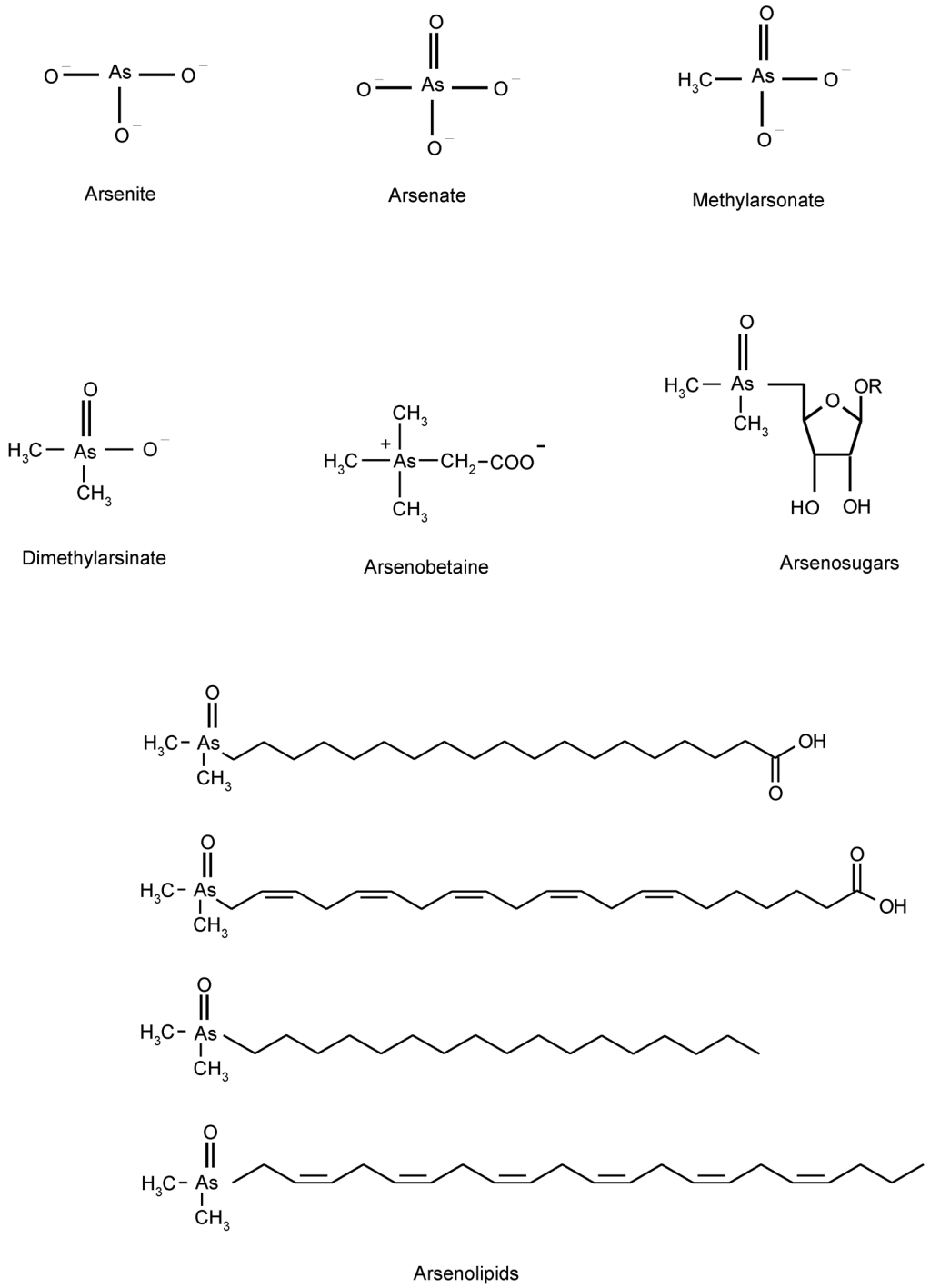

Fig. 1 Structures of arsenic species especially relevant to the occurrence and metabolism of arsenic in seafood.

Despite the many advances made in the area of naturally occurring arsenic compounds, we still do not have a good understanding of the biological chemistry of arsenic or the significance of its presence in our foods. This general theme will be pursued in the following review. In particular, arsenic in marine organisms and seafood will be discussed through a series of questions: (i) How does it get there?; (ii) Why does it stay?; (iii) What does it do?; and (iv) What should we do about it?

HOW DOES IT GET THERE?

Perhaps the key to understanding how arsenic finishes up in marine organisms lies in the similarities between the chemistry of arsenic and its fellow group 15 members, phosphorus and nitrogen. In normal seawater of pH 8.1, arsenic exits primarily as arsenate, or, more precisely, as the diprotonated oxo-anion $[H_2AsO_4]^-$ (pK_{2a} = 6.8, ionic radius 0.248 nm) [5]. A major seawater nutrient is phosphate, which at pH 8.1 also exists as the diprotonated oxo-anion $[H_2PO_4]^-$ (pK_{2a} = 7.2, ionic radius 0.238 nm). Marine algae have membrane transport systems to take up the essential phosphate from seawater, but these systems are insufficiently selective to discriminate against the structurally similar arsenate species. The result is easy access for arsenic into the algal cell. Within the cell, arsenate is again mistaken for phosphate leading to disruption (decoupling) of oxidative phosphorylation processes with resultant toxic effects [6]. To alleviate the potential toxicity of arsenate, algae have developed a process of converting it to arsenosugars by successive oxidative alkylation steps. These steps can be followed by growing algae in water with different arsenic concentrations, and monitoring the arsenic species by high-performance liquid chromatography (HPLC)/mass spectrometry in the algae with time. A clear example of this detoxification process was reported for the brown alga *Fucus serratus* by Geiszinger et al. [7]. Their data, which relate specifically to water-soluble arsenicals, show that at low arsenic exposure (20 μg As l^{-1}) the alga takes up arsenate readily and converts it efficiently to arsenosugars, and that intermediates in the scheme do not accumulate to a significant degree. At higher exposure, however, a build-up of the intermediates methylarsonate and dimethylarsinate was observed, while at the highest exposure (100 μg As l^{-1}), the alkylation/detoxification pathway was overloaded, and the toxic arsenite species accumulated to levels fatal to the alga.

Although most work on arsenic since the 1980s has focused on water-soluble species, some of the early interesting results in the field came from examination of the lipid-soluble arsenicals. Lunde in 1968 was the first to report that fish contained appreciable levels of lipid-soluble arsenic [8]. Benson and co-workers, however, were the first to investigate its formation in algae using a biochemical approach beginning with radiolabeled arsenate [9,10]. Their approach was similar to that employed in the classic studies with algae and radiolabeled $^{14}CO_2$ which had been applied 30 years earlier to unravel the carbon path in photosynthesis, the so-called Calvin cycle or the Calvin–Benson–Bassham cycle [11]. By running radio-chromatograms of extracts from the alga at various times, Benson and co-workers [9] were able to show that arsenate was taken up by the algae and that the first biotransformation intermediates were actually lipid-soluble arsenic species. Two of these arsenolipids then converted to water-soluble compounds, which, based on results from later work, were almost certainly arsenosugars [1,7]. One major type of lipid arsenic formed by the algae, however, showed quite different properties and remained unidentified (see below).

WHY DOES IT STAY?

Arsenobetaine is the most widespread and abundant of the organoarsenic compounds found in marine animals. It has also been reported in algae, but generally as a minor constituent [12,13]. Despite the fact that arsenobetaine was the first organoarsenic compound identified in seafood (in lobster in 1977), its biosynthetic origin remains unknown. What is becoming clear though is that the dominance of arsenobetaine in marine animals is likely related to the similar chemistry of arsenic and nitrogen. Both these group 15 elements form betaines. In the case of nitrogen, an abundant biologically important betaine is

glycine betaine [$(CH_3)_3N^+CH_2COO^-$], which serves as an osmolyte protecting osmoconforming organisms from changes in the salinity of their ambient water [14]. Thus, when salinity is high the cell actively takes up small charged organic molecules, including glycine betaine, to counteract osmotic pressure differences within and outside the cell. These compounds are favored over inorganic ions because at high concentrations they are less damaging to proteins in the cell. Arsenobetaine is structurally very similar to glycine betaine; it thus seems possible that the cell is unable to distinguish between these ions and takes up arsenobetaine by the same transporter. There are two pieces of indirect evidence to support this hypothesis. First, mussels maintained in seawater of varying salinities show a marked decrease in their arsenic content at lower salinities [15]. Furthermore, the efficiency of uptake of arsenobetaine from seawater by these mussels decreases with increasing levels of glycine betaine—a result consistent with competitive uptake [16]. Second, fish of the same species taken from adjacent waters of varying salinities showed a clear direct relationship between arsenic content and salinity [17].

Definitive evidence for arsenobetaine's behavior as an osmolyte has not yet been forthcoming. A recent study by Ressl et al. with the soil bacterium *Corynebacterium glutamicum*, however, has provided the opportunity to test this hypothesis [18]. Those authors reported the X-ray structure of the Na^+ coupled symporter BetP from *C. glutamicum*, which has a highly effective osmoregulated uptake system with claimed specificity for glycine betaine. It will be interesting to measure the selectivity for glycine betaine of this transporter when challenged with arsenobetaine.

WHAT DOES IT DO?

The fact that organoarsenic is found in marine organisms at high concentrations raises the possibility that it is actually of use to the organism. This could take two forms—incidental use or directed use. The first of these has already been mentioned, i.e., that the organism uses some compounds containing arsenic because they (by chance) mimic and provide the same service as other commonly used natural products (e.g., arsenobetaine for glycine betaine). The lower quantities of the arsenic compounds in organisms relative to the compounds they might mimic, however, suggests that such a role for arsenic is of little biological consequence for the organism. The possibility remains, of course, that the arsenic analog is very effective in its role, and that its presence even at modest concentrations might provide a decided advantage to the organism. There are no data so far to support this view.

Of more fundamental interest is that the organoarsenic compounds serve a particular role in the organism, and that their biosynthesis is directed by biochemical requirements of the organism. Although there are no data supporting this hypothesis, some recent studies on lipids and arsenic-containing lipids have at least revealed an experimental path to test such a hypothesis. Products derived from fatty fish, for example, cod liver oil, have high levels of arsenolipids. The compounds, the structures of which were first elucidated in 2008, comprise arsenic-containing fatty acids and their decarboxylated products [19,20]. These compounds appear to be arsenic analogs of lipid natural products present at high levels in fish (e.g., polyunsaturated fatty acids). The origin of the usual (non-arsenic) lipids in fish is clearly algae [21], and it appears likely that the arsenic lipids are also synthesized by algae. Based on the early work by Benson and co-workers [9], the formation of arsenolipids from arsenate in seawater was thought to be solely a detoxification process. A factor contributing to the uptake and transformation of arsenate, however, was low-phosphate waters [10]. A recent study has added considerable interest to this earlier observation. In 2009, De Mooy et al. reported that in low-phosphate waters some species of unicellular algae utilize nitrogen and sulfur, rather than phosphorus, in the biosynthesis of their membrane lipids [22]. This was thought to be a strategy to preserve phosphorus when the phosphate supply was limited. The work raises the possibility that arsenic is being used similarly in membranes, and that the arsenolipids result from directed synthesis by a process activated when phosphate levels are low. We are currently pursuing these aspects of arsenic biochemistry.

WHAT SHOULD WE DO ABOUT IT?

The natural occurrence of large amounts of arsenic in seafood in a variety of chemical forms has presented a considerable problem for health authorities in the food safety area [23]. It is a problem that has been, unwisely, ignored by most countries to the point where either no maximum permissible concentration has been set for arsenic or, where there is one, it serves no practical purpose because most seafood clearly exceed it sometimes by a factor of 100 or more [24]. It may be of interest to take a quick look at the early work on arsenic in seafood and see how the perception of this arsenic has changed over the years as we have learned more about the natural products chemistry of arsenic, its speciation, and the relative toxicity of the various arsenic species.

A quick look at the early work on arsenic in seafood

At the British Pharmaceutical conference in 1922, Jones reported arsenic concentrations of about 5–90 μg As g^{-1} dry mass in marine algae from British coastal waters [25]. He referred to this arsenic as "organic arsenic" and commented that its presence in pharmaceutical and food products derived from algae should cause no alarm because there had been no medical record of these products causing harm. Jones also made perceptive comments on the impracticality of the recommendation at that time that no item used in the preparation of a food product should contain more than "1.43 parts per million" of arsenic. He also remarked "…it is not sufficient to have a single standard for arsenic which is applied to everything that can be regarded as entering into the composition of food." These comments are still highly relevant today although they might now be voiced in terms of the importance of speciation in food legislation.

In 1925, Cox reported an improved method for measuring arsenic and provided data of arsenic concentrations in fish and in the urine of a person after eating fish [26]. He noted that the arsenic content of the urine sample was at a level normally associated with chronic arsenic poisoning. Preliminary attempts to identify the "seafood arsenic" were presented one year later by Chapman who noted that this arsenic was in an organic form and was evidently possessed of very slight toxic properties compared with inorganic arsenic [27]. This toxicological aspect was investigated in 1935 by Coulson et al. who performed experiments with rats fed inorganic arsenic and seafood arsenic (they used shrimp) and concluded that the seafood arsenic was nontoxic and rapidly excreted in the urine of the rat [28].

The view and general acceptance that organic arsenic, in seafood at least, was natural and nontoxic persisted until the 1970s. This was the time when the problem of mercury in fish was being aired in the press. The realization that most of the mercury in fish was present as organic mercury, and that this organic mercury (methyl mercury) was more toxic than inorganic mercury, heralded a new era in how environmental and food scientists viewed metal contamination and maximum permissible concentrations of metals in foods. It also led to a realization that more scientific information was needed regarding arsenic in seafood, and encouraged research in arsenic speciation analysis which has continued to the present.

The idea that elemental speciation data are needed to fully assess an element's environmental, biological, or toxicological role is now well accepted by the scientific community. The implementation of these ideas into food legislation, however, is a difficult task; the case of arsenic is particularly complex because it is present in foods in so many forms, and we lack information on the toxicity and metabolism of these arsenicals [23]. How should we best begin to address the problem? How can we painlessly introduce arsenic speciation data into the discussion of food legislation?

Goals and steps toward legislation of arsenic species in food

The toxicological risk of high inorganic arsenic concentrations in drinking water (>100 μg As l^{-1}) is well documented [29]. More recently, however, epidemiological evidence has been accumulating sug-

gesting human health effects at lower levels of exposure [30–32]. Studies at low exposures are inevitably susceptible to confounding factors, and different interpretations of the data are possible, as highlighted by the current lively debate on arsenic exposure and the incidence of type 2 diabetes mellitus in the United States [33,34]. Nevertheless, there is a growing perception that our exposure to inorganic arsenic is too high, and that the Provisional Tolerable Weekly Intake of inorganic arsenic, proposed as 15 $\mu g/kg^{-1}$ body mass in 1988 by the Joint FAO/WHO Expert Committee on Food Additives, should be reassessed. In this reassessment, the contribution from food should certainly be considered and will likely lead to legislation for arsenic content in food. In Europe, this process is already underway with The European Food Safety Authority recently issuing a scientific opinion on arsenic in food (<http://www.efsa.europa.eu/en/scdocs/scdoc/1351.htm>).

Future legislation concerning arsenic should be framed in a way to benefit both consumers and suppliers of food—to provide protection to consumers by preventing contaminated food entering the marketplace while facilitating easy access to the marketplace of foods that clearly do not present any toxic concern.

To begin the process, we need to collect relevant factual information in addition to formulating some reasonable assumptions. This might include the following: (i) inorganic arsenic is a known chronic toxic agent sometimes present at high concentrations in drinking water and in some foods; (ii) seafood has high arsenic content, most of which is organic; (iii) the major organoarsenic species in seafood are arsenobetaine, arsenosugars, and arsenolipids; (iv) arsenobetaine has been shown to be a harmless compound in various toxicity tests; (v) limited data so far on the toxicity of arsenosugars indicate low toxicity; and (vi) there are no data available for arsenolipids.

Speciation data on arsenic in seafood clearly demonstrate that the inorganic arsenic content is very low. For example, 30 species of fish collected in a French study contained from 0.005 to 0.073 μg As g^{-1} wet mass of inorganic arsenic while their total arsenic (mostly arsenobetaine) burden was usually at least 100-fold higher [35]. The situation for shellfish (molluscs and crustaceans) was similar to that for the fish, although the levels of inorganic arsenic were higher. These data are consistent with results from several earlier studies on arsenic in seafood reviewed in 1993 [24]. Importantly, the data show that there is no workable relationship between the total arsenic content (assume mainly arsenobetaine) and the content of inorganic arsenic in seafood samples. For this reason, it would not be sound to attempt to extract inorganic arsenic data from total arsenic data (read arsenobetaine) for seafood. The problems with earlier attempts to do this have been discussed [24]. Nevertheless, because there is an abundance of data on total arsenic content of seafood, but few data on the inorganic arsenic content, the temptation to take this "conversion factor" approach is ever present. The better approach is to obtain more speciation data that can identify possible problem samples in regard to inorganic arsenic content. It is interesting to note, however, that despite the considerable research activity in arsenic speciation analysis [36], and the pressing toxic issues related to inorganic arsenic, there is still no single commonly accepted way of determining inorganic arsenic in foods. Accordingly, there is an urgent need for a validated analytical method for inorganic arsenic and for the preparation of food reference materials certified for inorganic arsenic content.

But not all seafood contains only trace quantities of inorganic arsenic. There are some clear exceptions, the most dramatic example being the edible seaweed hijiki (*Hizikia fusiformis*) which consistently contains inorganic arsenic at levels of 60 $\mu g\ g^{-1}$ or more (UK Food Standards Agency, 2004; <http://www.food.gov.uk/multimedia/pdfs/arsenicseaweed.pdf>). Clearly, hijiki represents a special case: even moderate consumption of hijiki could make a considerable contribution to the Provisional Tolerable Weekly Intake for inorganic arsenic. At the very least, the public should be informed of the situation with hijiki, and advised to minimize their consumption of the product. There are also isolated examples of elevated inorganic arsenic in fish from Thailand [37] and mussels from Norway [38], but these data are exceptions to the normal pattern for fish and molluscan species.

Metabolic considerations

The above discussion is based on the assumption that all organic arsenic in seafood is harmless, and there are certainly no toxicological data to indicate otherwise. This appears to be a good starting point from which to begin to put speciation data into legislation for arsenic in foods. But, in time, more complex aspects of the metabolism of organoarsenic compounds and the toxicological consequences of this might also need to be addressed.

For arsenobetaine, the situation again is straightforward. All evidence to date indicates that although arsenobetaine is bioavailable to humans (i.e., it is taken up from the gut), it is not metabolized—it is quickly excreted unchanged in the urine and hence metabolic aspects need not be considered [24].

The situation with arsenosugars, however, is more complex. When humans consume arsenosugars, whether present in algae [39], mussels [40], or ingested as a pure synthesized compound [41,42], they metabolize the ingested arsenic to mainly dimethylarsinate which is then excreted in the urine. Interestingly, this is the same major metabolite produced from inorganic arsenic, and the intermediates produced *en route* to dimethylarsinate are thought to play a role in arsenic's mode of toxic action [43]. Thus, the possibility exists for inorganic arsenic and arsenosugars to have at least some common intermediate metabolites, in which case arsenosugars might also be capable of producing toxic effects. In this regard, it is worth noting that the contribution of dimethylarsinate in urine from consuming seafood relative to that obtained from inorganic arsenic in water can be considerable. For example, a meal of mussels (100 g with an arsenosugar content of 2 μg As g^{-1} wet mass) would be approximately equivalent, in terms of urine dimethylarsinate produced, to consuming about 20 l of water with the *maximum* (10 μg l^{-1}) permissible arsenic content (or about 200 l of water at the more usual arsenic concentration of 1 μg l^{-1}). Arsenolipids are also converted to dimethylarsinate by humans [44], so a similar concern might also be raised for these types of organoarsenic compound.

A final point concerning individual variability may also in future need to be considered when assessing the arsenic content in seafood. Individuals can vary a lot in the way they metabolize trace elements, and there is a growing body of data showing this effect also for arsenosugars [38,39]. In the most recent example with six volunteers who ingested an arsenosugar, four of them excreted >85 % of the arsenic in the urine within four days (mostly as dimethylarsinate), whereas the remaining two excreted less than 15 % of the ingested arsenic in the urine [45]. The fate of the missing arsenic is not yet known.

CONCLUDING COMMENTS

Some species of arsenic show structural similarities to certain biologically important forms of nitrogen and phosphorous, which probably facilitates arsenic's uptake and retention in marine organisms and explains the presence of high levels of organoarsenic species in many types of seafood. The human toxicology of most of the organoarsenic species remains to be investigated. Future legislation on permissible concentrations of arsenic in foods must include data on the type of arsenic species present and their metabolic and toxicological properties.

REFERENCES

1. K. A. Francesconi, J. S. Edmonds. *Adv. Inorg. Chem*. **44**, 147 (1997).
2. European Commission. Report of experts participating in Task 3.2.11, European Commission, Directorate-General Health and Consumer Protection, Reports on tasks for scientific co-operation (SCOOP) (2004).
3. P. N. Williams, A. H. Price, A. Raab, S. A. Hossain, J. Feldmann, A. A. Meharg. *Environ. Sci. Technol*. **39**, 5531 (2005).
4. S. Torres-Escribano, M. Leal, D. Velez, R. Montoro. *Environ. Sci. Technol*. **42**, 3867 (2008).
5. Y. Marcus. *Ion Properties*, p. 54, Marcel Dekker, New York (1997).

6. H. Dixon. *Adv. Inorg. Chem*. **44**, 191 (1997).
7. A. Geiszinger, W. Goessler, S. N. Pedersen, K. A. Francesconi. *Environ. Toxicol. Chem*. **20**, 2255 (2001).
8. G. Lunde. *J. Am. Oil Chem. Soc*. **45**, 331 (1968).
9. R. V. Cooney, R. O. Mumma, A. A. Benson. *Proc. Natl. Acad. Sci. USA* **75**, 4262 (1978).
10. A. A. Benson, R. E. Summons. *Science* **211**, 482 (1981).
11. A. A. Benson, J. A. Bassham, M. Calvin, T. C. Goodale, V. A. Haas, W. Stepka. *J. Am. Chem. Soc*. **72**, 1710 (1950).
12. V. Nischwitz, S. A. Pergantis. *Analyst* **130**, 1348 (2005).
13. M. Grotti, F. Soggia, C. Lagomarsino, W. Goessler, K. A. Francesconi. *Environ. Chem*. **5**, 171 (2008).
14. P. H. Yancey, M. E. Clark, S. C. Hand, R. D. Bowlus, G. N. Somero. *Science* **217**, 1214 (1982).
15. L. A. Clowes, K. A. Francesconi. *Comp. Biochem. Phys. C* **137**, 35 (2004).
16. J. Gailer, K. A. Francesconi, J. S. Edmonds, K. J. Irgolic. *Appl. Organomet. Chem.* **9**, 341 (1995).
17. E. H. Larsen, K. A. Francesconi. *J. Mar. Biol. Assoc. UK* **83**, 283 (2003).
18. S. Ressl, A. C. T. van Scheltinga, C. Vonrhein, V. Ott, C. Ziegler. *Nature* **458**, 47 (2009).
19. A. Rumpler, J. S. Edmonds, M. Katsu, K. B. Jensen, W. Goessler, G. Raber, H. Gunnlaugsdottir, K. A. Francesconi. *Angew. Chem., Int. Ed.* **47**, 2665 (2008).
20. M. S. Taleshi, K. B. Jensen, G. Raber, J. S. Edmonds, H. Gunnlaugsdottir, K. A. Francesconi. *Chem. Commun.* **39**, 4706 (2008).
21. J. K. Volkman, S. M. Barrett, S. I. Blackburn, M. P. Mansour, E. L. Sikes, F. Gelin. *Org. Geochem*. **29**, 1163 (1998).
22. B. A. S. Van Mooy, H. F. Fredricks, B. E. Pedler, S. T. Dyhrman, D. M. Karl, M. Koblizek, M. W. Lomas, T. J. Mincer, L. R. Moore, T. Moutin, M. S. Rappe, E. A. Webb. *Nature* **458**, 69 (2009).
23. K. A. Francesconi. *Analyst* **132**, 17 (2007).
24. J. S. Edmonds, K. A. Francesconi. *Mar. Poll. Bull*. **26**, 665 (1993).
25. J. Jones. *Year Book of Pharmacy, Transactions of the British Pharmaceutical Conference*, 22–24 July, C. H. Hampshire et al. (Eds.), p. 388, London (1922)
26. H. E. Cox. *Analyst* **50**, 3 (1925).
27. A. C. Chapman. *Analyst* **51**, 548 (1926).
28. E. A. Coulson, R. E. Remington, K. M. Lynch. *J. Nutr.* **10**, 255 (1935).
29. National Research Council. *Arsenic in Drinking Water*, National Academic Press, Washington, DC (2001).
30. A. Rahman, M. Vahter, A. H. Smith, B. Nermell, M. Yunus, S. El Arifeen, L. A. Persson, E. C. Ekstrom. *Am. J. Epidemiol*. **169**, 304 (2009).
31. M. R. Karagas, T. D. Tosteson, J. S. Morris, E. Demidenko, L. A. Mott, J. Heaney, A. Schned. *Cancer Causes Control* **15**, 465 (2004).
32. A. Navas-Acien, E. K. Silbergeld, R. Pastor-Barriuso, E. Guallar. *JAMA* **300**, 814 (2008).
33. C. Steinmaus, Y. Yuan, J. Liaw, A. H. Smith. *Epidemiology* **20**, 656 (2009).
34. A. Navas-Acien, E. K. Silbergeld, R. Pastor-Barriuso, E. Guallar. *Epidemiology* **20**, 668 (2009).
35. V. Sirot, T. Guérin, J.-L. Volatier, J.-C. Leblanc. *Sci. Total Environ*. **407**, 1875 (2009).
36. K. A. Francesconi, D. Kuehnelt. *Analyst* **129**, 373 (2004).
37. P. Jankong, C. Chalhoub, N. Kienzl, W. Goessler, K. A. Francesconi, P. Visoottiviseth. *Environ. Chem.* **4**, 11 (2007).
38. J. J. Sloth, K. Julshamn. *J. Agric. Food Chem*. **56**, 1269 (2008).
39. M. Ma, X. C. Le. *Clin. Chem*. **44**, 539 (1998).
40. V. W. M. Lai, Y. M. Sun, E. Ting, W. R. Cullen, K. J. Reimer. *Toxicol. Appl. Pharmacol*. **198**, 297 (2004).
41. K. A. Francesconi, R. Tanggaard, C. J. McKenzie, W. Goessler. *Clin. Chem.* **48**, 92 (2002).

42. R. Raml, W. Goessler, P. Traar, T. Ochi, K. A. Francesconi. *Chem. Res. Toxicol*. **18**, 1444 (2005).
43. M. Vahter. *Toxicology* **181/182**, 211 (2002).
44. E. Schmeisser, A. Rumpler, M. Kollroser, G. Rechberger, W. Goessler, K. A. Francesconi. *Angew. Chem., Int. Ed.* **45**, 150 (2006).
45. R. Raml, G. Raber, A. Rumpler, T. Bauernhofer, W. Goessler, K. A. Francesconi. *Chem. Res. Toxicol*. **22**, 1534 (2009).

