

The organoarsenical inertness assumption is increasingly contested

Karen Pendergrass · ORCID 0000-0002-2348-7259 · Heavy Metal Index, Institute of Contaminant Standards

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CORRESPONDENCE

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Abstract

A foundational assumption in food-arsenic risk assessment holds that organoarsenical compounds — principally arsenobetaine, the dominant arsenic species in marine fish and shellfish — are metabolically inert in humans, pass through the body essentially unchanged, and pose no toxicological concern even at concentrations that would be alarming if the arsenic were inorganic. This assumption is the basis for a structural divide in how regulatory agencies treat arsenic in food: inorganic arsenic is regulated, characterized with dose-response relationships, and the subject of Closer to Zero initiatives and EU maximum levels; organic arsenic in seafood is largely excluded from risk characterisation on the grounds that it does not contribute to health risk. It is also the assumption that makes the distinction between inorganic arsenic (iAs) and total arsenic (tAs) meaningful in practice: a product reporting total arsenic at 200 ppb with 97 percent arsenobetaine is treated as fundamentally different from one at 200 ppb with 97 percent inorganic arsenic.

1 | Overview

Eight independent studies entered the wiki corpus across batches 9 through 11, published between 2023 and 2024, that collectively challenge one or more dimensions of the inertness assumption. No single paper refutes it definitively. Taken together, however, they establish that the assumption is being tested on three distinct evidentiary fronts simultaneously: the metabolism front (whether organoarsenicals are truly inert during digestion), the biomonitoring front (whether urinary metrics reliably distinguish organoarsenical metabolism from inorganic arsenic methylation), and the toxicity front (whether epidemiological endpoints associated with fish arsenic exposure remain below detection). The convergence of challenges across three independent research traditions, in multiple food matrices spanning seafood, fungi, and microalgae-derived ingredients, constitutes a synthesis-page-worthy finding that would not be visible from any single source page and has direct implications for how the wiki characterises arsenic in seafood-containing products.

2 | The biomonitoring confound

The standard approach to biomonitoring inorganic arsenic exposure in human populations uses the urinary ratio of dimethylarsinic acid (DMA) to inorganic metabolites as an index of methylation efficiency, with higher DMA fractions interpreted as efficient methylation and therefore lower retained iAs burden. Davydiuk et al. 2023 reviewed the evidence on a specific confound in this interpretation: arsenosugars and arsenolipids from seafood consumption are metabolised to DMA via a pathway that does not pass through the inorganic arsenic methylation sequence. The metabolic route from arsenosugars to DMA is independent of the route from inorganic arsenite and arsenate to DMA.

The practical consequence is that populations with high seafood intake will show elevated urinary DMA fractions not because they methylate inorganic arsenic efficiently, but because they are excreting DMA derived from arsenosugar catabolism. Studies using urinary %DMA as a methylation index in seafood-eating populations — a common design in Japanese, Korean, Taiwanese, and coastal South American biomonitoring cohorts — may systematically underestimate the inorganic arsenic exposure burden of those populations by attributing seafood-derived DMA to endogenous methylation capacity. Davydiuk 2023 documents multiple published biomonitoring studies where seafood consumption was not adequately controlled and DMA-based methylation efficiency indices were reported as though they measured only inorganic arsenic metabolism.

The implications run directly into the regulatory architecture. EFSA's 2021 chronic dietary iAs exposure assessment and EFSA's 2024 updated risk characterisation (both anchored to urinary biomonitoring data) estimate inorganic arsenic exposure partly through modelling that uses biomonitoring studies from European populations; the bias in those studies from seafood arsenosugars, while smaller in European than in Japanese populations, is not zero and is not corrected for. If the reference biomonitoring literature systematically underestimates inorganic arsenic exposure in fish-eating populations, the modelled exposure margins of the EFSA 2024 assessment may be slightly optimistic.

3 | Digestion-phase conversion of organic arsenicals

A separate challenge to the inertness assumption concerns whether organic arsenic forms survive gastrointestinal digestion intact. Liu et al. 2023 used a standardised in vitro gastrointestinal digestion protocol to characterise arsenic speciation in crab and scallop before and after simulated digestion. Organic arsenicals in both matrices underwent a 2-to-3-fold increase in the inorganic As(V) fraction following digestion, attributed to a pH-dependent free radical oxidation mechanism that becomes active under the acidic conditions of the stomach. The implication is that the speciation measured in the food at the moment of consumption — the

speciation that is used to classify a food as "predominantly organic arsenic and therefore low risk" — is not the speciation present at the point of intestinal absorption.

The magnitude of the in vitro conversion does not resolve how much inorganic arsenic is actually absorbed from a typical seafood portion. In vitro digestion models have well-documented limitations as proxies for in vivo absorption: they replicate pH, enzyme activity, and transit time imperfectly, and they do not account for intestinal re-speciation or transporter-mediated selectivity in absorption. The finding establishes that the assumption of speciation stability through digestion is not justified, and that the gap between food-measurement speciation and absorbed-fraction speciation has not been closed. It does not by itself establish the absorbed fraction of inorganic arsenic from seafood or its health relevance at typical dietary exposure levels.

4 | Epidemiological signal in a large prospective cohort

The strongest human-evidence challenge to the inertness assumption comes from a prospective cohort study, not from speciation biochemistry. Kagawa et al. 2023 reported on the J-MICC Daiko Study, a community-based cohort of 2,709 Japanese adults with measured serum arsenic levels and prospectively adjudicated hypertension outcomes. Serum total arsenic, which the authors estimate to be 98 percent arsenobetaine based on Japanese population speciation surveys, was associated with hypertension risk in a dose-dependent relationship that remained statistically significant after adjustment for fish consumption frequency, age, sex, body mass index, and other cardiovascular risk factors.

The finding is anomalous under the inertness assumption. If 98 percent of serum arsenic is arsenobetaine and arsenobetaine is biologically inert, serum total arsenic should be a proxy for fish consumption frequency rather than an independent vascular risk factor once fish consumption is controlled. Kagawa 2023 does control for fish consumption frequency, and the association persists. The authors discuss three possible interpretations: residual confounding by fish consumption constituents not captured by the frequency variable; a biological effect of arsenobetaine or one of its minor co-metabolites at concentrations typical of fish-eating populations; or misclassification of serum arsenic as predominantly arsenobetaine when inorganic arsenic makes up a larger fraction than population-average surveys suggest in this cohort.

The study does not discriminate among these interpretations, and none of the three is ruled out. What the study establishes is that a large, well-characterised prospective cohort provides an epidemiological signal for health risk at fish-arsenic exposure levels that the inertness assumption would predict are harmless. This is not the same as demonstrating arsenobetaine toxicity, but it is inconsistent with the assumption that organic arsenic from fish consumption is toxicologically invisible.

5 | Extension to fungi and microalgae-derived ingredients

The three papers above concern marine food matrices where arsenobetaine is the dominant species. Two papers from the same ingest period extend the concern about organoarsenical inertness assumptions into non-marine food categories that are increasingly relevant to supplement, functional-food, and protein-ingredient supply chains.

Raab et al. 2024 reported the first detection of AsSugPhytol, a lipophilic arsenosugar, in the green microalga *Chlamydomonas reinhardtii*, finding that 57 percent of total arsenic in this organism exists as arsenolipids. The significance is methodological and commercial simultaneously. Methodologically, standard acid digestion protocols for total arsenic determination may not quantitatively recover arsenolipid fractions depending on the lipid extraction efficiency of the preparation, meaning total-arsenic measurements in microalgae-derived

ingredients may underestimate recoverable arsenic. Commercially, the finding affects the risk characterisation of spirulina, chlorella, algae protein concentrates, and algae oil ingredients, which are increasingly present in protein powders, infant nutrition products, and functional foods. If a substantial fraction of total arsenic in a microalgae ingredient exists as arsenolipids whose toxicological behaviour is not established, and if those arsenolipids contribute to urinary DMA via the seafood-arsenosugar pathway documented by Davydiuk 2023, then a product formulated with algae protein and tested for total arsenic only may be carrying uncharacterised arsenic species with uncharacterised health implications.

Walenta et al. 2024 reported the discovery of a novel arsenobetaine amide in four mushroom species, an organoarsenical not previously observed in any organism. The finding extends the universe of dietary organoarsenicals beyond the marine and freshwater systems where they have been studied. It also reopens the question of whether arsenobetaine itself — identified and named for its structural relationship to the betaine compounds, and assumed inert on the basis of rat excretion studies conducted in the 1970s and 1980s — is the only bioactive species in its structural class, or whether arsenobetaine amide and similar congeners may have biological activity not yet studied.

Sim et al. 2024 validated an HPLC-ICP-MS method for iAs determination in seaweed and found that *Laminaria digitata* carries more than 50 percent of its total arsenic as inorganic arsenic. This is not an organoarsenical inertness finding in the same sense as the preceding papers — it is an occurrence finding showing that kelp-family seaweeds have a high iAs fraction by matrix, not by metabolic conversion. But it is relevant to the synthesis because it illustrates that the assumption that "seaweed arsenic is organic and therefore low risk" is demonstrably wrong for this commercially important algae genus, and the EU's 2023/915 regulation now sets specific iAs limits for seaweed products in recognition of this. The distinction between what a food matrix contains and what the default "it's organic" assumption implies is exactly the structure this synthesis addresses.

6 | The convergent point

Each paper challenges a different component of the received view. The Davydiuk review challenges biomonitoring reliability. The Liu digestion study challenges speciation stability through GI transit. The Kagawa cohort challenges epidemiological inertness in a dose-response framework. The Raab microalgae paper and Walenta mushroom paper challenge the assumption that organoarsenical diversity is limited to the well-characterised marine-fish suite. The Sim seaweed paper challenges the assumption that plant-derived seafood ingredients are low in inorganic arsenic.

Taken together, these papers do not add up to a refutation of the inertness assumption. Arsenobetaine is still the dominant arsenic species in marine fish. High fish consumption remains a net health benefit for most populations when weighed against omega-3 fatty acids, protein quality, and micronutrient content. Regulatory agencies have not moved to restrict arsenobetaine or to require seafood arsenic speciation under EU or US frameworks.

What the accumulation does support is a narrower claim: the inertness assumption is a working hypothesis that has been underexplored, that is now being tested with methods not available when the assumption was established, and that the results of those tests are not uniformly reassuring. The simple statement "organic arsenic from seafood is not a health concern" cannot be reproduced without qualification, because that statement is now inconsistent with the published literature. The qualified version — that arsenobetaine at typical dietary levels is not demonstrated to cause harm at the same exposure thresholds as inorganic arsenic, but that biomonitoring data confounded by arsenosugar metabolism and epidemiological signals at population-typical exposure levels warrant continued investigation — is the one the current evidence supports.

The analytical implication is specific. Products formulated with microalgae-derived ingredients (spirulina, chlorella, algae protein, algae oil) and tested only for total arsenic are not fully characterised under the current state of the evidence, because total-arsenic measurement does not resolve the arsenolipid and inorganic-arsenic fractions that the studies above show can be substantial and toxicologically uncharacterised in these matrices. The EU 2023/915 seaweed iAs limit is the regulatory leading edge of this change, and its implementation is a signal of whether the "organic arsenic" exemption is narrowing in regulatory frameworks.

7 | What this synthesis does not yet rest on

The most important gap is a controlled human in vivo feeding study directly measuring inorganic arsenic absorption from seafood. The Kagawa cohort provides an epidemiological signal but cannot distinguish arsenobetaine toxicity from confounding. The Liu digestion study provides a mechanism for in vitro As(V) generation but cannot establish the absorbed fraction in living subjects. Until an in vivo absorption study is conducted, the synthesis cannot state that arsenobetaine exposure contributes to inorganic arsenic body burden at measurable levels. The finding remains that the basis for assuming it does not is weaker than previously supposed.

The Raab microalgae finding should be treated as organism-specific until replicated in commercial spirulina or chlorella products. *Chlamydomonas reinhardtii* is a model organism with growth conditions (laboratory culture, defined media) that may not reproduce the arsenolipid profile of commercially cultivated microalgae. The prevalence and identity of arsenolipids in commercial algae-ingredient matrices is an active research gap.

The Kagawa cohort is Japanese. Arsenobetaine exposure from fish consumption is unusually high in Japanese adults relative to European or North American populations; the dose at which the epidemiological signal is detectable may not apply at lower seafood-consuming populations. Before extending the Kagawa finding to global recommendations, corroboration from a non-Japanese cohort with comparable arsenic speciation data would be necessary.

8 | Implications for downstream wiki pages

freshwater-fish should note in its arsenic coverage sub-block that biomonitoring studies from fish-eating populations that use urinary %DMA as a methylation index may underestimate inorganic arsenic exposure due to arsenosugar catabolism, and that total arsenic values in freshwater fish include both inorganic and organic fractions whose relative toxicological contributions are under active investigation.

shellfish and seaweed should each note that the "organic arsenic" classification does not settle questions about bioaccessibility after digestion (Liu 2023 mechanism) or, for seaweed, the iAs fraction itself (Sim 2024 finding that *Laminaria digitata* iAs exceeds 50 percent of tAs).

Any future ingredient page created for microalgae-derived products (spirulina, chlorella, algae protein) should carry a note in its arsenic coverage sub-block about arsenolipid fraction uncertainty and the Raab 2024 finding, rather than defaulting to "organic arsenic dominates, low risk."

arsenic should note in its speciation section that the assumption of organoarsenical inertness is under active challenge from multiple research directions, with citations to the anchor papers here. The section should be explicit that "total arsenic in seafood" is not equivalent to "inorganic arsenic in seafood" and also not equivalent to "harmless organic arsenic."

arsenic-speciation (when written) should reference the Davydiuk 2023 biomonitoring confound as a reason that speciated rather than total-arsenic testing is the preferred standard for seafood matrices in any context where the inorganic arsenic fraction is the health-relevant quantity.

For the app model, ingredients flagged as primarily organic arsenic sources (fish, shellfish) should not receive a zero-risk modifier based solely on the organic classification; the app should model them as "arsenic speciation incompletely characterised for this matrix" and output uncertainty flags rather than dismissals.

9 | Anchor sources

- Davydiuk et al. 2023. Critical review published 2023. Arsenosugars and arsenolipids from seafood catabolism produce urinary DMA independently of inorganic arsenic methylation efficiency, confounding biomonitoring studies that use urinary %DMA as an iAs methylation index in seafood-eating populations.
- Liu et al. 2023. In vitro gastrointestinal digestion study. Organic arsenicals in crab and scallop show a 2–3× increase in the inorganic As(V) fraction following simulated digestion via pH-dependent free radical oxidation. Speciation at consumption does not equal speciation at the point of absorption.
- Kagawa et al. 2023. J-MICC Daiko prospective cohort, n=2,709 Japanese adults. Serum total arsenic (98% arsenobetaine by population survey) is associated with dose-dependent hypertension risk after adjustment for fish consumption frequency and cardiovascular risk factors. Epidemiological signal anomalous under the inertness assumption.
- Raab et al. 2024. Analytical chemistry study of *Chlamydomonas reinhardtii*. First report of AsSugPhytol in any organism; 57% of total arsenic exists as arsenolipids. Implications for commercial microalgae-derived ingredients and standard total-arsenic measurement reliability.
- Walenta et al. 2024. LC-ICP-MS speciation study of four mushroom species. Discovery of a novel arsenobetaine amide species previously unreported in any organism; extends organoarsenical diversity to terrestrial fungi.
- Sim et al. 2024. DoE-optimised HPLC-ICP-MS validation study. *Laminaria digitata* iAs exceeds 50% of total arsenic; recovery from hijiki CRM 99±9%. Seaweed is not a low-iAs matrix despite classification as a plant/algae ingredient.
- Hull et al. 2023. Foodweb arsenic study, Puget Sound legacy lakes. Sediment arsenic predicts fish iAs; inorganic arsenic fraction increases at lower trophic levels while organic arsenic enriches at higher trophic levels. Mechanistic trophic-transfer evidence showing iAs is the bioaccumulating fraction.
- Sadee et al. 2023. Review of arsenic speciation methods in vegetables. Contextualises the iAs vs organoarsenical distinction across non-marine food matrices and HPLC-ICP-MS analytical approaches.

10 | How this page was promoted

This synthesis page was promoted on 2026-05-13 following P4 batch ingest sessions 10 and 11. The thread was first surfaced in the batch 10 close synthesis-proposals entry, where davydiuk2023, liu2023, and kagawa2023 were identified as a three-paper cluster challenging the organoarsenical inertness assumption from distinct methodological directions. Batch 11 added raab2024, walenta2024, and sim2024, extending the thread from marine fish into microalgae, mushrooms, and seaweed and resolving the borderline status of criterion 2 (spanning multiple matrices and products). The synthesis-proposals entry was upgraded to all-4-criteria-met after batch 11 closed, and Karen approved direct promotion. Eight A-tier anchor sources, three independent research traditions (biomonitoring, analytical chemistry, epidemiology), and three food matrix types (seafood,

fungi, microalgae/seaweed) support the thesis at promotion. The synthesis is provisional; it does not assert arsenobetaine toxicity, only that the evidence base for the inertness assumption has weakened in specific and documented ways. Re-synthesis is expected when an in vivo human feeding study establishes or fails to establish iAs absorption from seafood, or when a non-Japanese cohort replicates or fails to replicate the Kagawa hypertension signal.

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REVIEW

STATUS AND LICENCE

Editorially reviewed in-house; no external peer review has been completed on this finding. Published as a preprint with its review state tracked on the article page. Released under CC BY 4.0.

COMPETING INTERESTS

The Heavy Metal Index reports what the peer-reviewed and regulatory literature supports. It is operated separately from any certification program, does not evaluate or endorse brands, and does not use certification thresholds as evidence for the statements made here.

DATA AVAILABILITY

Every source behind this finding is listed with its own extraction record at <https://heavymetalindex.com/synthesis/-organoarsenical-inertness-assumption#sources>, each linking to the ingest receipt, the extracted values, and the file hash of the document it was built from.

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