# Organic and Inorganic Arsenic in Natural Health Products: Issue Analysis Summary (IAS)

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## SUMMARY


## 1. ISSUE

- Two forms of arsenic (As) exist in the environment: inorganic (known carcinogen) and organic (very low toxicity).
- NHPD limit is for total arsenic in finished NHPs (0.14 µg/kg bw/day); calculated by dividing NSF limit of 0.01 mg/day by 70 kg.
- An NHP may exceed total arsenic limit, but actually contains more of the less toxic organic arsenic (oAs) than inorganic arsenic (iAs).

## 2. PURPOSE/OBJECTIVE

- Is there enough scientific evidence to support separate limits for oAs and iAs?
- Do we have adequate analytical methods to distinguish between the two forms?

## 3. BACKGROUND

### 3.1. Arsenic and its Derivatives

- Arsenic occurs naturally in the environment as iAs (-3, +3, +5) and oAs forms
- Examples of iAs forms (As-trioxide, sodium arsenite, As-trichloride, As-pentoxide)
- Examples of oAs forms (arsanilic acid, methylarsonic acid, arsenobetaine)
- Arsenic is also present in environment from pesticide use and industrial activities
- Arsenic is present in soil (potential for plant uptake), water, marine animals and marine plants (*kelp/seaweed where oAs > iAs)

### 3.2. Analytical Methodology

- AAS – atomic absorption spectrophotometry is a common method for total As
- Chemical difference between iAS and oAS species makes the separation of the two possible prior to analysis (e.g. by complexation with chloride ions to form $AsCl_3$ followed by distillation)
- Extraction for various As species in algae possible by using different solvents

- In general, extraction → chromatographic separation → detection (e.g. ICP-MS, ICP-AES, HPLC-ICP MS, HPLC-ICP-AES)

### 3.3. Physiological Role of Arsenic

- Essentiality of As in humans is not clearly defined due to limited human data

- Essentiality of As has been demonstrated in various animals

### 3.4. Metabolism of Arsenic

- Complete detoxification pathway for iAs in mammals is not yet elucidated

- Available data in variety of species indicates detoxification generally occurs by: (1) reduction of arsenate ($As^{5+}$) → arsenite ($As^{3+}$), followed by (2) oxidative methylation of $As^{3+}$ in liver → less reactive organic metabolites (MMA, DMA – which are excreted in urine)

- Limited human data on tissue distribution of oAs derivatives from consumption of fish and other seafood

### 3.5. Toxicology

- As and iAs compounds are carcinogenic to humans (CEPA 1993)

- Toxicity is a function of numerous factors: chemical form, solubility, valence state, dose, and duration of exposure

- In general, excretion of $As^{5+} > As^{3+}$ and retention of $As^{5+} < As^{3+}$

- Data suggests the order of toxic potential for As compounds as follows: MMA(III) > DMA (III) > As(III) > As(V) > MMA(V) > DMA(V)

- Chronic exposure: various adverse health effects on organs (i.e. kidney, liver, blood, skin) and organ systems

- Acute exposure: data is available on toxic effects of oAs metabolite exposure in animals (e.g. depressed motility and respiration, irritability, ataxia[1] and convulsions in mice)

### 3.6. Exposure

- For the purpose of estimating population exposure, it is generally assumed that most of As in air, water, and soil is inorganic, and the majority of As in plant and animal matrices is organic

[1] Ataxia: an inability to coordinate voluntary muscular movements that is symptomatic of some nervous disorders (Medline Plus: http://www.nlm.nih.gov/medlineplus/mplusdictionary.html)

- **Environmental exposure** depends on history of land use and proximity to industrial sources:

- **Dietary exposure** from food and water:
  *Total As*: 1-1000 µg/day in U.S., 38.1 µg/day in Canada (overall, 20-40% of total As is iAs)
  *iAs*: 8.3 – 14 µg/day in U.S., 4.8 – 12.7 µg/day in Canada

  **Drinking water (DW):** average exposure to iAs from DW is 5µg/day, or higher from contaminated sites; health effects associated with oral exposure to iAs are more likely to result from contaminated DW than food

  **Food:** grains, meat, *seafood (critical commodity at ~90% of dietary As, but contributing mostly oAs)

  **Seafood** consumption has not been linked with As toxicity in humans or other mammals; seafood has low levels of toxic iAs compounds (1-3% of total As)

  Estimated dietary consumption of fish & seafood varies among countries:
  Total As: <10 to 200 µg/day
  *oAs*: > 1000 µg/day in populations dependent on fishing for food
  *iAs*: 10-20 µg/day

  Kelp/seaweed contains mostly oAs (arsenosugars), except hijiki seaweed. Arsenic content of various seaweed types (brown, red, and green) are provided in IAS (Table 2):
  *Total As*: brown > red > green
  *iAs*: brown > red > green

  Measuring human exposure to As using total urinary As as a biomarker is problematic (i.e. confounded by high [oAs] in seafood, food preparation method, and bioavailability of As species).

- **Exposure from therapeutic products**:
  Historically used as a therapeutic drug for various ailments (Fowler's solution, As-triiodide, iAs preparations, oAs antibiotics such as Salvarsan).

- **Exposure and speciation:**
  Arsenic speciation in plants is influenced by many factors. In turn, As speciation determines exposure, uptake/absorption, toxicodynamics and bioavailability. Bioavailability data is critical to estimating risk, however research is directed towards assessing exposure to total As.

### 3.7. Current Limits of Exposure

See Table 3 in IAS.

*Inorganic As tolerance limit*

ATSDR (2007) indicates the following MRLs for chronic oral exposure in humans:
Chronic exposure (≥365 days): 0.0003 mg iAs/kg/day (= 0.3 µg iAs/kg/day)

Dietary intake of iAs: 8.3 – 14 µg/day in U.S., 4.8 – 12.7 µg/day in Canada
Chronic MRLs calculated for DRI lifestage groups: 1.8 – 21 µg/day (Table 4 of IAS)
Since diet accounts for ~50% of exposure to iAs → conservative approach is warranted

Set tolerance limit by applying 10X factor to chronic MRL (→ **0.03 µg iAs/kg/day**)
Chronic TDIs calculated for DRI lifestage groups: 0.18 – 2.1 µg/day (Table 5 of IAS)

Is this new limit practicable? Yes it is, considering:
- TDIs of ~2 µg/day, and medicinal herbs found to contain mean [As] of 2 µg/g, and commercial preparation further reduces [As] by 100-1000X
- exposure calculations using iAs levels found in common marine algal supplements, and typical dosage levels, indicate affected NHPs would meet new limit (Appendix I of IAS)

*Organic As tolerance limit*
ATSDR (2007) indicates the following MRLs (minimal risk levels) for humans:
Chronic exposure: 0.01 mg MMA/kg/day (= 10 µg MMA/kg/day)
Chronic exposure: 0.02 mg DMA/kg/day (= 20 µg DMA/kg/day)
No MRLs for naturally-occurring oAs derivatives seafood or algal supplements (no suitable data available)

Chronic MRL for DMA of **20 µg DMA/kg/day** is a conservative, practicable limit considering:
- oAs derivatives are much less toxic than iAs, but not completely innocuous
- assuming ~100% of arsenosugars and arsenolipids may be metabolized to DMA (major metabolite)
- exposure calculations using oAs levels found in common marine algal supplements, and typical dosage levels, indicate affected NHPs would meet new limit (Appendix I of IAS)

*Total As tolerance limit*
Current NHPD tolerance limit for total As in finished NHPs is 0.14 µg/kg bw/day; calculated by dividing NSF limit (0.01 mg/day) by 70 kg.

This limit is very conservative (<50% of ATSDR chronic MRL for iAs, 7% of JECFA pTDI).

Tolerance limit for total As appears adequate to mitigate any risk to health, considering:
- most of daily As intake is from dietary sources (food and water) rather than dietary supplements
- most of health risk is associated with iAs exposure

**OPTIONS ANALYSIS**

Option#1: maintain current limit of 0.14 µg/kg bw/day for total As (considering dosage and subpopulations) with no distinction between iAs and oAs

Option #2: maintain current limit of 0.14 µg/kg bw/day for total As; if total As in the NHP exceeds limit (considering dosage and subpopulations), company may conduct additional testing to demonstrate level of iAS consumed in product would be <0.03 µg/kg bw/day and level of oAs consumed in product would be <20 µg/kg bw/day.

## 4. RECOMMENDATION

Option #2.

## 5. DECISION

Option #2 was supported by Health Canada's Marketed Health Products Directorate and Health Products and Food Branch Inspectorate, the NHPD Expert Advisory Committee, with input from The United States Pharmacopoeia (additional methodologies).

## 6. REFERENCES

See IAS.

## APPENDIX 1: DEMONSTRATION CALCULATIONS

See IAS.