Public Health Ontario | Santé publique Ontario

Arsenic Poisoning: Overview and Case Study

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Occupational and Environmental Health Seminar

Learning Objectives

- Describe the chemical and toxicologic properties of arsenic
- List relevant sources and routes of exposure, with a focus on natural health products
- Identify associated acute and chronic health outcomes
- Summarize clinical workup, diagnosis, and management

Outline

1. Toxicologic profile of Arsenic:
   a) Occupational and Environmental Sources
   b) Routes of exposure
   c) Toxicokinetics and toxicodynamics
   d) Acute and Chronic health outcomes
2. Case
3. Workup/Diagnosis/Management
4. Review and Discussion

Conflict of Interest

- None to declare

Part 1: Background

Part 1: Background

- Arsenic is ubiquitous in the earth's crust, and naturally-occurring sources include volcanic eruptions and deposits leeching into soil and ground water
- Pure arsenic is a grey-colored metalloid that exists in a variety of compounds and valence states
- The major forms are classified as inorganic and organic:
  - **Inorganic** arsenic is typically found in its trivalent and pentavalent salts, oxides, or sulfides
  - **Organic** forms are commonly found as arsenosugars in seafood

Lewis, R and Kosnett, MJ. Chapter 30: Metals, in Current Occupational and Environmental Medicine Fifth Edition 2014. Toronto: McGraw Hill Education: 464.

Part 1: Background (cont'd)

- Anthropogenic sources include nonferrous metal mining and smelting, pesticide application, coal combustion, wood combustion, and waste incineration
- It does not biodegrade in soils, bioaccumulation in plants and grains occurs
- In seafood arsenic bioaccumulates as compounds such as arsenosugars and arsenobetaine

Rossman TG. Chapter 64: Arsenic, in Environmental and Occupational Medicine 4th Ed Rom WN ed. Lippincott Williams and Wilkins, New York, 2007: 1006.
United States Environmental Protection Agency. Arsenic in Rice and Rice Products. The US Food and Drug Administration. Last updated 10/25/2017. Available at: https://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm319870.htm.

Organic Arsenic (Organoarsenicals)

- Generally considered to be of low toxicity compared to inorganic forms
- Forms typically found in seafood are arsenobetaine and arsenocholine, which are considered “essentially non-toxic”
- Major forms in agriculture include herbicides monomethylarsonic acid (MMA) and its salts (MSMA is most widely recognized), dimethylarsinic acid (DMA, also known as cacodylic acid) and its sodium salt, and roxarsone
  - Some concern given that many of these convert to inorganic forms after application
  - All but MSMA have been banned for use in the US; in Canada MSMA is used for control of bark beetle in forests until 2004
- Arsine gas is usually described separately given its unique properties

Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp2.pdf

Inorganic forms

- The most common inorganic forms include:
  - In the air: Arsenic trioxide (As2O3)
  - In water, soil, or food: Arsenates (AsO4-3) or arsenites (AsO2-)
  - Trivalent forms (e.g. arsenite, arsenic trioxide) have been identified as more toxic than pentavalent forms (e.g. arsenate, arsenic pentoxide) by a factor of approximately 2-3 times

Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp2.pdf

History

- Used since antiquity for embalming (ancient Egypt), then as pesticide, in cosmetics and in medicines
- A significant component of 'Scheele's Green' (copper arsenite) – used as wallpaper dye in 18th and 19th centuries
- Chemical warfare gasses in early-mid 20th century
- Arsenic trioxide made up 1% of Fowler's solution, used in the 18th and 19th centuries for asthma, psoriasis, syphilis, and chronic myelogenous leukemia until 1958
- Used for treatment of trypanosomiasis until mid-1990s
- Approved by the FDA in 2000 for APML

Doyle, D. Notoriety to respectability: a short history of arsenic prior to its present day use in haematology. British Journal of Haematology, 2009. 145: 309–317. doi:10.1111/j.1365-2141.2009.07623.x

Part 2: Exposure Profile/Routes of Exposure

Part 2: Exposure Profile

A) Sources:

Occupational

Inhalation of arsenic-containing particulate is the most important route of entry in a variety of settings:

- Mining, smelting and other metallurgical industries
- Coal powered power plants
- Battery assembly, lead-acid battery recycling
- Preparation of or work with CCA pressure-treated wood
- Glass making, and electronics (semiconductors, light-emitting diode) manufacturing

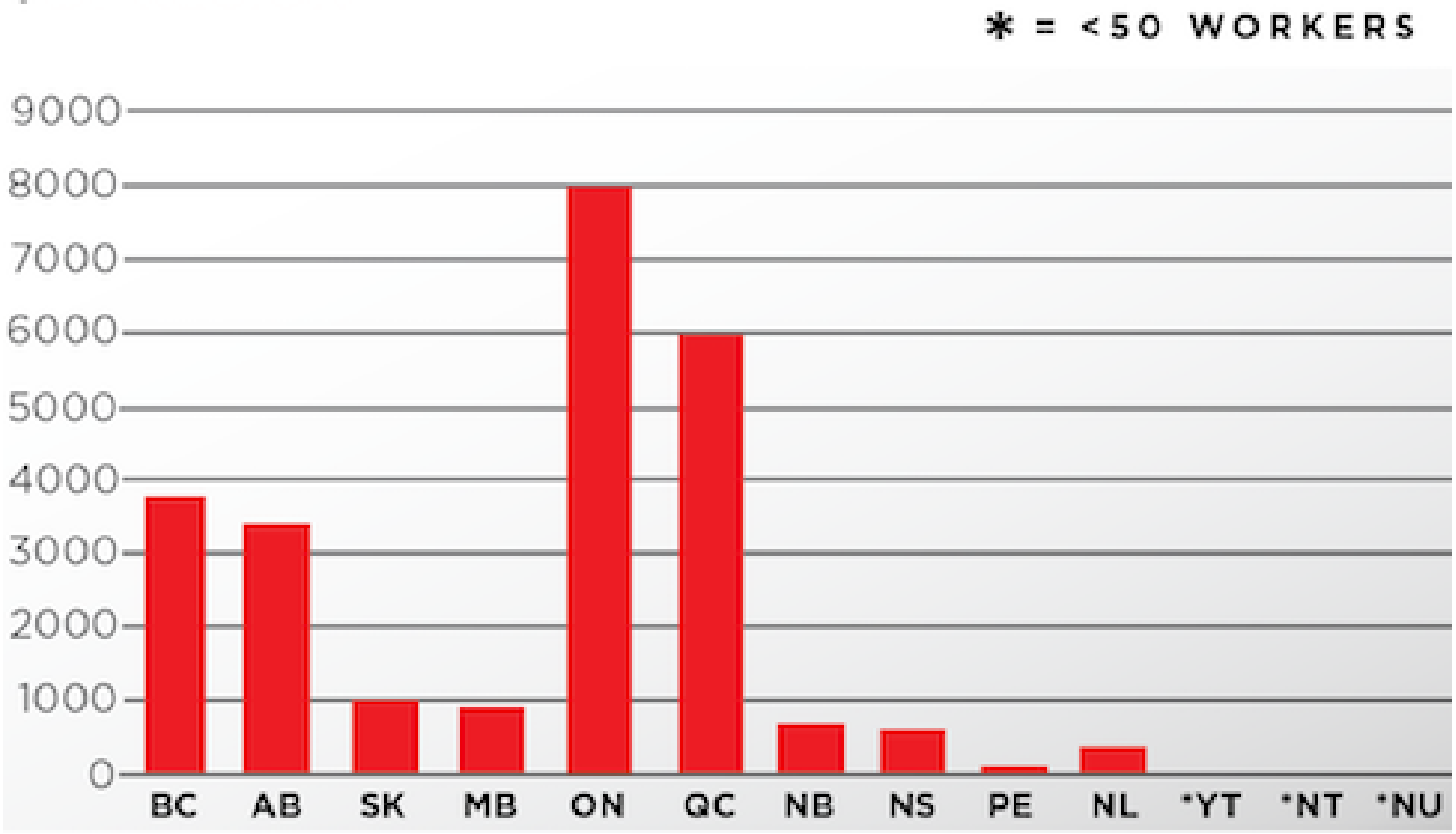
International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, volume 100C. Arsenic and Arsenic Compounds. Lyon, France: IARC; 2012. Available from: http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-6.pdf.

25,000 WORKERS (EST.) ARSENIC EXPOSURE IN CANADA

FIVE LARGEST EXPOSURE GROUPS BY INDUSTRY		PROPORTION OF INDUSTRY EXPOSED
Foundation, structure, and building exterior contractors	3,000	<5%
Sawmills and wood preservation	2,800	<5%
Non-residential building construction	2,700	<5%
Farms	2,100	<5%
Residential building construction	1,100	<5%

Carex Canada. “Arsenic.” Carex. Simon Fraser University. Vancouver, BC. 2017. Available from https://www.carexcanada.ca/en/arsenic/.

WORKERS EXPOSED TO ARSENIC BY REGION



Carex Canada. “Arsenic.” Carex. Simon Fraser University. Vancouver, BC. 2017. Available from https://www.carexcanada.ca/en/arsenic/. Accessed Dec 12, 2017.

Chromated Copper Arsenate (CCA)

- Fungicide and preservative containing 47.5% hexavalent chromium, 18.5% copper, and 34% inorganic arsenic
- Used in pressure treatment for structural wood from 1940's until it was banned by the EPA for residential use in 2003
- Widely found in decks, picnic tables, landscaping, fencing, boardwalks, and playground structures
- Since 2004 only used in Canada in some shakes and shingles, permanent wood foundations, and utility poles
- Exposure routes - ingestion (hand-mouth or pica) via direct contact or from adjacent dusts on surfaces and soils, inhalation of sawdusts, or of smoke from incineration

Chen AY-Y and Olsen T. Chromated copper arsenate–treated wood: a potential source of arsenic exposure and toxicity in dermatology. Int J Womens Dermatol. 2016 Mar; 2(1): 28–30.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental

- Most exposure occurs via certain foods (primarily organic) and drinking water (inorganic)
- Potential non-food exposures include:
  - Herbal/traditional medicines or supplements (inorganic)
  - Domestic/community CCA wood exposure (inorganic)
  - Livestock feed additive (organic -> inorganic)
  - Fungicides/pesticides (organic-> inorganic)

Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp2.pdf

Part 2: Exposure Profile cont'd

A) Sources:

Environmental

- Very small contribution from airborne arsenic particulate which is primarily anthropogenic in origin (but some naturally occurring as well)
- Average levels in Canada in 1990 from 10 cities and one rural area was 0.001ug/m^3 (Ontario AAQC is 0.3ug/m^3)

Carex Canada. "Arsenic." Carex. Simon Fraser University. Vancouver, BC. 2017. Available from https://www.carexcanada.ca/en/arsenic/. Accessed Dec 12, 2017.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental (water)

- GI exposure via drinking water is well-documented
- NOAEL derived from the work of Tseng et al. in a case-control study in Taiwan in the 1960s

Tseng, WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453-463.
Tseng, WP. 1977. Effects and dose-response relationships of cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental (water)

- More recently exposure from well water in Bangladesh has received widespread media attention
- Up to 77 million exposed since the 1970s from "tube wells"

- More than half sampled contain >5x the MAC of 10ug/L

Flanagan SV, Johnston RB and Zheng Y. Arsenic in tube well water in Bangladesh: health and economic impacts and implications for arsenic mitigation. Bulletin of the World Health Organization. The WHO 2012;90:839-846. Available from: https://www.who.int/bulletin/volumes/90/11/11-101253/en/.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental (water)

- Concentrations in Canada vary widely by region:
  - In BC, levels as high as 580µg/L in groundwater have been reported
  - In NS 9% of samples tested were >25ug/L, with some communities having >93% of tested wells >50ug/L in 1984
  - NL has also reported concentrations from 6 to 288 µg/L in public water supplies (54 tested wells) in 2002
  - In ON levels from 1997-2002 ranged from 2.5 to 68 µg/L with an average of 2.5 µg/L

Health Canada. Page 6: Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Arsenic. Health Canada. Ottawa. May 2006. Available from: https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-arsenic.html.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental - Food

- Arsenic is found in low concentrations in many foods
- The average dietary intake in Canadians is estimated at 0.51-0.97ug/Kg BW/day of which 20-40% is inorganic
- Seafood (fish, crustaceans and seaweed) contain higher concentrations than most other foods, but the predominant form is organic arsenic, which has much lower risk for toxicity than inorganic forms

Canadian Food Inspection Agency (CFIA). Food safety action plan report; 2011-2013 Targeted surveys – chemistry; Arsenic speciation in selected foods. CFIA. Ottawa, 2013.

Part 2: Exposure Profile cont'd

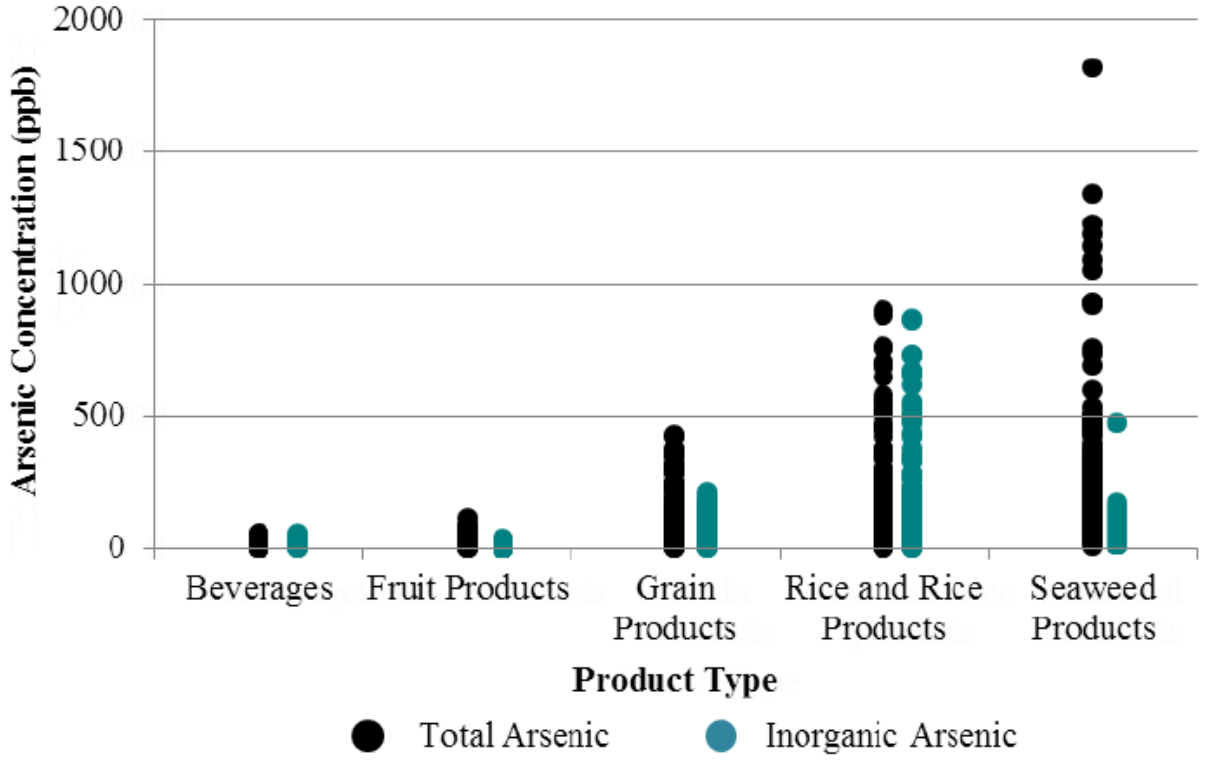


Figure 3 – Concentrations of total and inorganic arsenic in samples by product type

Canadian Food Inspection Agency (CFIA). Food safety action plan report; 2011-2013 Targeted surveys – chemistry; Arsenic speciation in selected foods. CFIA. Ottawa, 2013.

Part 2: Exposure Profile cont'd

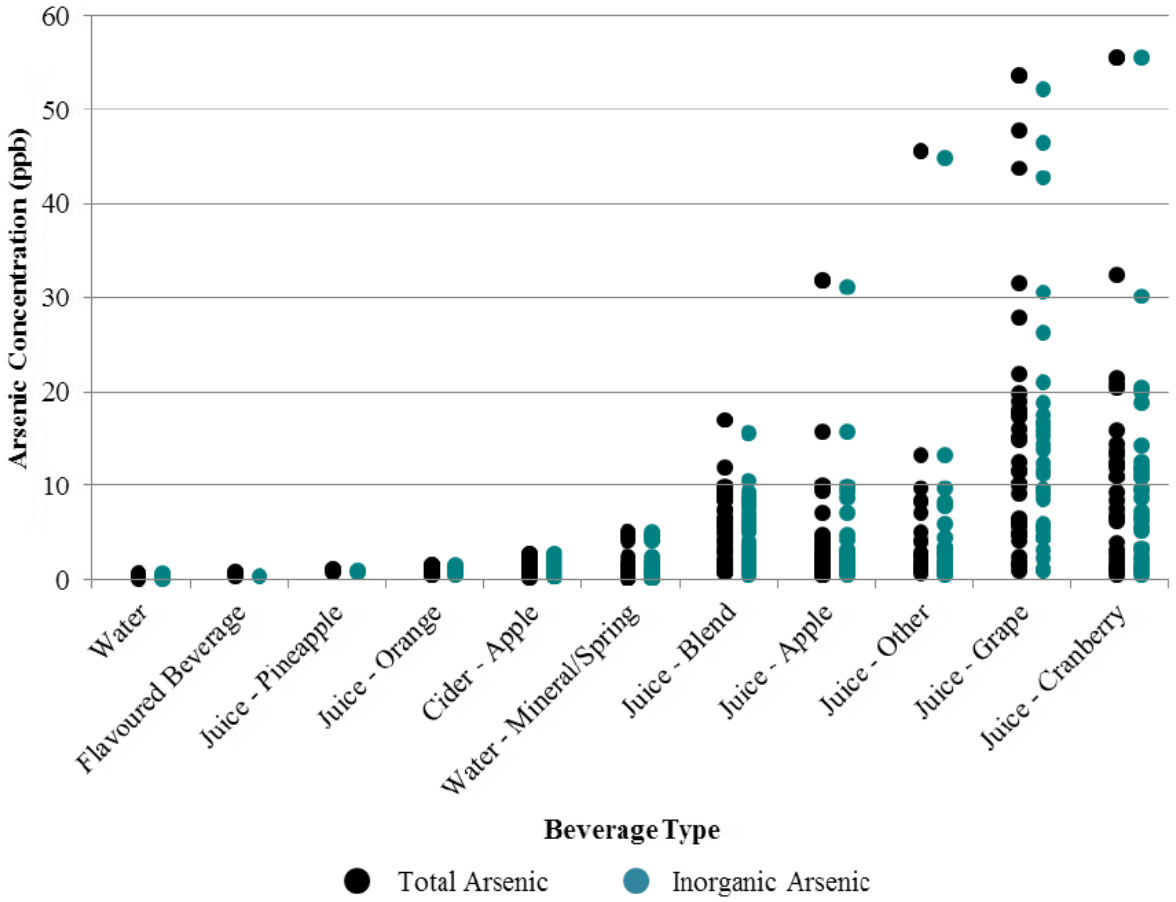


Figure 4 - Concentrations of total arsenic and inorganic arsenic in samples by beverage type

Canadian Food Inspection Agency (CFIA). Food safety action plan report; 2011-2013 Targeted surveys – chemistry; Arsenic speciation in selected foods. CFIA, Ottawa, 2013.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental cont'd

- Herbal/traditional medicines are ubiquitous, with estimates as high as 80% of the world population using them on a regular basis[1]
- A 2010 Ipsos-Reid survey found that 73% of Canadians regularly take Natural Health Products (NHPs) including vitamins and minerals, herbal products, and traditional/naturopathic/homeopathic medicines[2]
- The Fraser Institute's 2016 report found that in Canada, 14% surveyed reported using herbal medications at some point in their lifetime, with an Ontario prevalence of 19%[3]

1. Shaban, NS, Abdou KA, Hassan NEHY. Impact of toxic heavy metals and pesticide residues in herbal products. Beni-Suef University Journal of Basic and Applied Sciences 5 (2016) 102–106.
2. Health Canada, "Natural and Non-prescription Health Products," https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription.html.
3. Esmail, N. Complementary and Alternative Medicine: Use and Public Attitudes 1997, 2006, and 2016. The Fraser Institute. April 2017. Available at: https://www.fraserinstitute.org/sites/default/files/complementary-and-alternative-medicine-2017.pdf.

Part 2: Exposure Profile cont'd

This is relevant because:

- There are case reports of NHP adulterants and contaminants causing illness:
  - Strychnine poisoning from an Asian herbal remedy[1]
  - A case series of Arsenic poisoning from various homeopathic remedies[2]
  - Lead poisoning from contaminated Ayurvedic and herbal medications[3]
  - 2004 study found 20% of preparations tested contained heavy metals[4]

1. Terry Singhapricha and Adam C.Pomerleau "A Case of Strychnine Poisoning from a Southeast Asian Herbal Remedy," The Journal of Emergency Medicine Volume 52, Issue 4, April 2017, Pages 493-495.
2. Dipankar Chakraborti, Subhash Chandra Mukherjee, Khitish Chandra Saha, Uttam Kumar Chowdhury, Mohammad Mahmudur Rahman & Mrinal Kumar Sengupta "Arsenic Toxicity from Homeopathic Treatment" *Journal of Toxicology: Clinical Toxicology* Vol. 41 , Iss. 7, 2003, 963-967.
3. Krishna S Gunturu et al., "Ayurvedic herbal medicine and lead poisoning," *Journal of Hematology & Oncology* 2011, 4:51.
4. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. Heavy Metal Content of Ayurvedic Herbal Medicine Products. *JAMA.* 2004;292(23):2868-2873. doi:10.1001/jama.292.23.2868

Part 2: Exposure Profile cont'd

A) Sources:

Environmental cont'd

- A 2018 study from China found 94% of 84 traditional and patent medicines tested contained varying levels of arsenic[1]
- A study performed in California on traditional Chinese herbal medicines found 14% of all samples contained arsenic in quantities up to 114,000ppm[2]
- An earlier study performed heavy metal analysis on **traditional Chinese herbal balls**, (hand-rolled mixtures of herbs and honey)[3]
  - In that study they found 8 of the 9 tested commercially-produced imported products contained arsenic, with concentrations as high as 36.6mg per ball

1. Liu L et al. Speciation and bioaccessibility of arsenic in traditional Chinese medicines and assessment of its potential health risk. Science of the Total Environment 619–620 (2018) 1088–1097.
2. Ko RJ. Adulterants in Asian patent medicines [letter]. N Engl J Med. 1998;339:847
3. Espinoza EO, Mann M-J, Bleasdell B. Arsenic and mercury in traditional Chinese herbal balls. N Engl J Med 1995;333:803-4.

Part 2: Exposure Profile cont'd

Traditional Chinese Herbal Balls:

- Many types, depending on purpose
- Mixture of herbs and honey, to dissolve in tea and consume daily
- Daily chronic consumption linked to development of arsenic-induced skin disease and subsequent skin cancer in one case report[1]

1. Seok J et al. Squamous Cell Carcinoma and Multiple Bowen's Disease in a Patient with a History of Consumption of Traditional Chinese Herbal Balls. Case Rep Dermatol 2015;7:151–155.

Part 2: Exposure Profile cont'd

A) Sources:

Environmental cont'd

- Traditional Chinese Medicine (TCM):
  - A systematic review from 2001 identified 22 cases of heavy metal toxicity associated with TCM use, four of which were chronic arsenic poisonings
  - An additional 6 cases of arsenic poisoning from chronic TCM consumption were identified
  - 9/10 present with multisystemic symptoms but dermatologic changes almost universal

Ernst, E. and Coon JT. Heavy metals in traditional Chinese medicines: A systematic review. Clinical Pharmacology & Therapeutics Dec 2001: 70; 6: 497-504.

Part 2: Exposure Profile cont'd

B) Toxicokinetics/Toxicodynamics

Part 2: Exposure Profile cont'd

B) Toxicokinetics

- Routes of exposure:
  - Gastrointestinal exposure - up to 90% ingested absorbed.
  - Respiratory absorption estimated at 60-90% for arsenic trioxide
  - Dermal absorption is negligible
- Once in the bloodstream, reduced from Arsenate to Arsenite
- Once methylated, it is distributed to tissues and rapidly cleared with a half-life of 3-4 hours in the blood and whole-body half life of 10 hours, via urine

Rossman TG. Chapter 64: Arsenic, in Environmental and Occupational Medicine 4th Ed Rom WN ed. Lippincott Williams and Wilkins, New York, 2007: 1006.
Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9.
Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007: 260.
Tokar EJ, Boyd WA, Freedman JH, Waalkes MP. Chapter 23: Toxic Effects of Metals, in Casarett and Doull's Toxicology; The Basic Science of Poisons, 8th ed. Toronto: McGraw Hill Medical, 2013: 987.

Part 2: Exposure Profile cont'd

B) Toxicodynamics:

- Once metabolized, arsenic's toxic effects act at the cellular level in two ways:
  1. Binds sulfhydryl groups and disrupts sulfhydryl-dependent enzymes and processes.
  2. "Uncouples" mitochondrial respiration by displacing phosphorus in a variety of biochemical reactions.

Impairment in tissue respiration → **Cellular and tissue dysfunction** →

Reactive Oxidative Species → **Tissue damage** → **Dysfunction/Disease**

- The carcinogenic processes that have been associated with arsenic are as numerous as the identified forms of arsenic, and so there is no single mechanistic process thought to give rise to cancer

Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9.

Part 2: Exposure Profile cont'd

Acute Health Effects:

Inorganic Arsenic (exposures >0.1mg/kg/day) [1,2]

- GI upset
- Cardiovascular, hematologic, neurologic effects
- In significantly high exposures, death (>1-3mg/kg)[2]

Arsine Gas

- Generalized symptoms (malaise, fatigue, GI upset) as well as a massive hemolysis and subsequent hemoglobinuria which causes kidney dysfunction or failure

Organic Arsenic

- GI upset (high doses)

1. Lewis, R and Kosnett, MJ. Chapter 30: Metals, in Current Occupational and Environmental Medicine Fifth Edition 2014. Toronto: McGraw Hill Education: 464.
2. Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9: 61.

Part 2: Exposure Profile cont'd

Chronic Health Effects (Inorganic only):

- Non-cancer[1]:
  - Multisystemic effects, with the most prominent being dermatologic, neurologic, and vascular
  - Respiratory, gastrointestinal, hepatic, cardiac, hematologic, all recognized outcomes
  - Reproductive, developmental effects as well
- Cancer:
  - IARC Group 1 for inhalational exposure and lung cancer (SCLC/NSCLC), and GI exposure for skin, lung and bladder cancers; kidney, liver, prostate also associated
  - Latencies estimated at 10 years for Bowen's, 20 for invasive skin, and 30 for lung[2]

1. Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007: 260.
2. Miki Y, Kawatsu T, Matsuda K, Machino H, Kubo K. 1982. Cutaneous and pulmonary cancers associated with Bowen's disease. J Am Acad Dermatol 6:26–31.

Part 2: Exposure Profile cont'd

Health Effects – Chronic (inorganic cont'd)

1. Dermatologic (1-2 years latency):
   - Palmoplantar hyperkeratosis
   - Corn-like keratoses

Fig. 1. Patient 3. Multiple plantar keratoses.

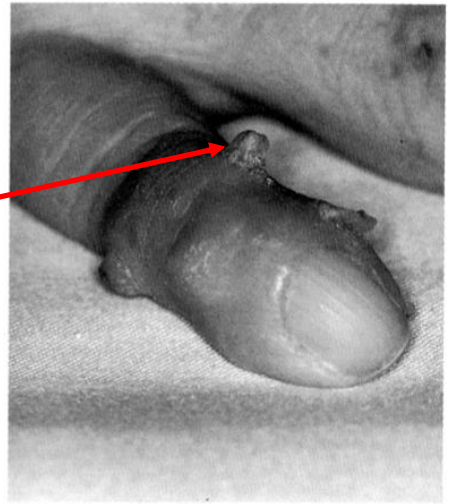


Fig 1 – Right hand: Firm keratotic papules on little finger (patient 1)

Fawcett, R.S., Linford, S., and Stulberg, D.L. (2004) Nail abnormalities: clues to systemic disease. Am. Fam. Physician 69(6), 1417–1424.
Wong SS, Tan KC, Goh CL. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. J Am Acad Dermatol 1998. 38:179–185.
Wong ST, Chan HL, Teo SK. The Spectrum of Cutaneous and Internal Malignancies in Chronic Arsenic Toxicity. Singapore Med J 1998: Vol 39;4 171-173.

Part 2: Exposure Profile cont'd

Health Effects – Chronic (inorganic cont'd)

1. Dermatologic (1-2 years latency):
   - Mees' Lines
   - "Raindrop" hyperpigmentation

Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9.

Sharma S, Gupta A, and Deshmukh V. Arsenic poisoning and Mees' lines, *QJM: An International Journal of Medicine*, Volume 109, Issue 8, 1 August 2016, Pages 565–566, https://doi-org.myaccess.library.utoronto.ca/10.1093/qjmed/hcw068

Part 2: Exposure Profile cont'd

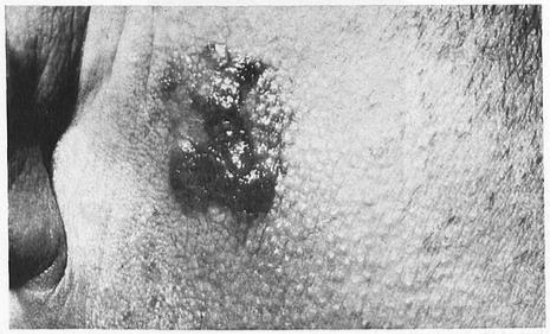
Health Effects – Chronic (inorganic cont'd)

Skin Cancer (10-30 yrs latency):

- Bowen's disease (Intraepidermal/in-situ squamous cell carcinoma)
- Squamous cell carcinoma
- Basal cell carcinoma

Figure 2. Bowen's disease on the left thigh.

Fig. 2. Patient 12. SCC of left thumb arising from keratoses.



Cöl M, Cöl C, Soran A, et al. 1999. Arsenic-related Bowen's disease, Palmer keratosis, and skin cancer. Environ Health Perspect 107(8):687-689.
Wong SS, Tan KC, Goh CL. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. J Am Acad Dermatol 1998. 38:179–185.
Tay CH. Cutaneous Manifestations of Arsenic Poisoning Due to Certain Chinese Herbal Medicine. Aust. J . Derm. 1974;15:121.

Part 2: Exposure Profile cont'd

Health Effects – Chronic (inorganic cont'd)

2. Neurologic:

- Peripheral sensorimotor polyneuropathy

3. Vascular:

- "Blackfoot disease"

4. Hematologic:

- Anemia, leukopenia

Part 3: Clinical Case

Part 3: Case

History:

- A 73-year-old monolingual Cantonese male presents to the emergency department with approximately 2 months of progressive fatigue, malaise, low appetite, and numbness in hands and feet
- Further history suggests use of traditional herbal medications and blood work for heavy metals is performed:
  - **Urinary speciated arsenic level = 1,235ug/L (ref <10)**

Part 3: Case (cont'd)

History (cont'd)

- He is evaluated in consultation for the elevated metal levels
- Further history reveals:
  - His symptoms also included the development of "freckling" on the torso and thickened skin on his palms and soles

Part 3: Case (cont'd)

- Occupational history:
  - Retired years ago from work as food factory worker and bus driver in China
- Environmental exposures:
  - Consumes a wide variety of seafood on a daily basis
  - Drinks herbal teas several times daily
  - Has been taking home-made herbal preparations for decades:
    - Multiple (up to 80) distinct herbs are collected, dried, ground, mixed with honey and rolled into pea-sized spheres
    - Consumed daily
    - Was instructed to stop taking these in late November, two months prior to evaluation

Part 3: Case (cont'd)

- Physical examination:
  - Neurologic exam demonstrates decreased sensation to hands and feet
  - Skin exam reveals:

Part 4: A) Workup

Part 4: A) Workup

- History:
  - Onset and characterization of symptoms, looking for toxidrome
  - Exposure history:
    - Environmental - Home, diet (drinking water, supplements), hobbies, pets
    - Occupational – Job titles, durations, processes
- Physical Examination
  - Arsenical toxidrome – skin, nerves, circulation
- Investigations:
  - Biomarkers of exposure:
    - **Urine speciated arsenic level**
      - 24-hour or spot corrected for creatinine

Part 4: Workup (cont'd)

- Investigations:
  - Environmental testing (as determined by history):
    - Drinking water
    - Foods
    - Supplements
    - Air sampling (IH)

Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9.

Part 4: B) Diagnosis

Appropriate exposure history +

Expected constellation of clinical findings +/-

Elevated inorganic urinary arsenic levels =

Consistent with chronic toxic exposure

Cessation of exposure with improvement of symptoms and biomarkers supportive

Agency for Toxic Substances and Disease Registry. Arsenic Toxicity; What is the Biologic Fate of Arsenic in the Body? US Center for Disease Control. Available at https://www.atsdr.cdc.gov/csem/csem.asp?csem=1&po=9.

Part 4: C) Management

- In chronic exposures, cessation of exposure is mainstay, with serial monitoring of levels to ensure source control/ improvement
- Chelation in chronic arsenic toxicity:
  - A study in West Bengal demonstrated a modest improvement in subjective clinical symptoms but no histological skin improvement was found, suggesting that the neoplastic outcomes are not likely modifiable[1]
  - There is no current consensus on chelation for chronic arsenic poisoning and therapeutic benefit in this context remains unestablished[2]

1. Mazumder, DNG. Revised Draft – June, 2000; Chapter 4: Diagnosis and treatment of chronic arsenic poisoning. Institute of Post Graduate Medical Education and Research, Calcutta. Available at: http://www.who.int/water_sanitation_health/dwq/arsenicun4.pdf: 26.
2. Kosnett MJ. The Role of Chelation in the Treatment of Arsenic and Mercury Poisoning. J. Med. Toxicol. (2013) 9:347–354.

Part 4: C) Management

- Public health challenges:
  - Regulation and monitoring of herbal and traditional preparations is not done uniformly, and in many cases not possible to do proactively
  - A 2009 report from the WHO outlines some of the challenges:
    - Source material variability
    - Distillation or preparation method variability
    - Concentration/dilutional variability
    - Media/dilutent/contaminant variability

The World Health Organization (WHO). Safety issues in the preparations of homeopathic medications. WHO. Geneva. 2009. Available from: http://www.who.int/medicines/areas/traditional/Homeopathy.pdf.

Part 5: Case Revisited

Part 5: Case Revisited

- Recall the patient's urinary inorganic arsenic level was 1,235ug/L (ref <10ug/L)
- Recall that herbal medicine balls have been demonstrated to contain as much as 36.6mg of As
- Dose-response estimates:
  - Hyperpigmentation and palmoplantar hyperkeratosis:
    - The IRIS LOAEL is 0.014mg/Kg/day, or in an average 70Kg person, 0.98mg/day[1]
    - This is used to establish the RfD of 0.0003mg/kg/day, or in an average 70Kg person, 0.021mg/day
  - Peripheral sensorimotor neuropathy:
    - GI exposure of >0.1mg/kg/day, or in a 70Kg person, 7mg/day has been associated[2]

1. Integrated Risk Information System. Arsenic, inorganic; CASRN 7440-38-2. U.S. Environmental Protection Agency. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary.pdf.
2. Agency for Toxic Substances and Disease Registry. Arsenic. U.S. Department Of Health And Human Services, August 2007: 180.

Case Revisited (cont'd)

- Based on the history and clinical findings, supported by elevated urinary levels, the patient was diagnosed with chronic arsenic toxicity causing dermatologic changes and glove-and-stocking sensory polyneuropathy
- The patient was referred to dermatology for ongoing cancer surveillance
- He was referred to neurology for nerve conduction testing
- Arsenic levels were decreasing with cessation of exposure

Part 6: Take-Home Points

- Though arsenic is ubiquitous in the environment, toxicity is rare
- Exposure history is integral to the assessment
- Traditional and herbal medicines are important potential source of exposure
- Chronic arsenic toxicity, like all toxins, has a specific toxidrome of which skin changes are sentinel
- Laboratory testing can be helpful but not mandatory for diagnosis
- Management is based on cessation of exposure

Discussion/Questions

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