INTERNATIONAL JOURNAL OF CIRCUMPOLAR HEALTH
2024, VOL. 83, 2428471
https://doi.org/10.1080/22423982.2024.2428471

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AMAP HUMAN HEALTH IN THE ARCTIC

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Methodologies and challenges in Arctic human health risk assessment: case studies and evaluation of current practices

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ABSTRACT

In Arctic populations, a primary route of exposure to contaminants is through the diet. The health risks associated with these exposures can be characterised by conducting human health risk assessments. However, while there is guidance from many international and national organisations, there are limited examples of human health risk assessment in the Arctic. The 2022 AMAP Human Health Assessment Report was the first AMAP report to describe, in one place, the utility of food-based, dietary intake-based and human tissue-based contaminant data in estimating risk. Here, we present available tools, case studies and challenges associated with conducting human health risk assessments in the Arctic. Future efforts in the Arctic should be able to use this information to best interpret human exposure to contaminants in a risk-based context.

ARTICLE HISTORY
Received 19 December 2023
Revised 5 August 2024
Accepted 7 November 2024

KEYWORDS
AMAP; Arctic; risk assessment; human health; guidance value; contaminants; biomonitoring

Introduction

Human health risk assessment is the process of estimating the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future [1]. Robust guidance from international and national programmes (e.g. WHO [2]) offers the necessary tools to conduct risk assessments, which continues to evolve to address confounding factors, methodological challenges, exposure to mixtures and other limitations [3–10]. However, the modern scientific paradigm, consisting of a certain set of concepts, approaches, methodologies and standards according to which "human health risk assessment" is carried out, is very diverse and may be contradictory [8–10].

Traditional Arctic diets are crucial for the social, cultural, spiritual, economic, and nutritional well-being of Indigenous communities in the circumpolar North. These diets, including locally harvested fish and marine mammals, provide essential nutrients such as omega-3 fatty acids, vitamin D, iodine, copper, cobalt, selenium, and zinc, and support health-promoting cultural practices. However, they also pose health risks due to contaminants like mercury, lead, cadmium, and arsenic. This creates "The Arctic Dilemma", highlighting the challenge of balancing these benefits with the risk of contaminant exposure. While reducing the consumption of these traditional foods may decrease contaminant exposure, it could also result in the loss of their nutritional and cultural benefits [11–15].

This unique dietary landscape results in diverse contaminant exposure levels among Arctic populations, which vary more dramatically than in regions with more uniform diets. Risk assessments in the Arctic must carefully consider these varied inputs and assumptions to avoid mischaracterising risks for specific populations [16,17]. Unlike other geographical locations where dietary exposures tend to be homogenous, the Arctic showcases significant variability due to regional dietary practices influenced by available species, such as marine mammals in coastal areas and terrestrial mammals and freshwater fish in inland regions [18,19]. This variability is further complicated by seasonal food

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availability, traditional food reliance, and unique cultural dietary preferences, such as gender-specific consumption roles [20]. These factors necessitate a tailored approach to risk assessments that can address both intermittent and cumulative exposures, accurately weighing the risks from contaminants against the benefits of nutrient intake. Consequently, adapting risk assessment methodologies to suit these Arctic-specific conditions is essential to ensure that assessments reflect the true risk and benefit profiles for these populations [11,21].

While many multi-year biomonitoring and cohort studies have been carried out in the circumpolar Arctic for over 30 years, few guidance values have been based on effects observed in Arctic research studies. Mercury (Hg) is one notable exception, as very strong Arctic databases have been used in Hg risk assessments worldwide [22,23]. Advancing the development of risk assessment guidance values based on Arctic-specific data may assist Arctic risk assessment and risk communication efforts.

In this article we present the utility and related challenges of estimating human health risks associated with exposure to environmental contaminants in the circumpolar Arctic, specifically via the consumption of local (traditional or country) foods. This article focuses primarily on persistent organic pollutants (POPs) and metals in blood because samples in this matrix have been collected by all countries participating in the Arctic Monitoring and Assessment Programme's (AMAP) Human Health Assessment Group circumpolar collaboration since the 1990s [23–25]. Human milk, urine and other matrices are not discussed here as they are collected infrequently, making international and interregional comparisons more difficult. We describe the types of food-based, dietary intake-based and human tissue-based contaminant data that can be compared against different types of reference values to estimate risk. Reference and guidance values are described that are applicable to AMAP work, especially dietary exposure to contaminants. The reader is referred to AMAP [23,25] for a compilation of specific values. This article also provides examples of how guidance values have been used in an Arctic context and details some of the challenges and limitations of using these values to interpret the type of information derived from human health research in the Arctic.

General principles, approaches and methodologies of human health risk assessment in the Arctic

The conventional risk assessment process, which incorporates hazard assessment, exposure assessment and risk characterisation, is used to quantify the probability of harmful and adverse effects on human health.

Hazard assessment involves identifying and characterising the hazards associated with a contaminant. Evidence is available from epidemiological studies, in vitro or in vivo toxicological studies in animals and modelling research. Many risk assessments are based on toxicological data and these may be supported by toxicokinetic modelling, a complimentary tool in quantifying human exposure to environmental pollutants based on their levels in human biological matrices. Use of epidemiological studies may address the issue of multiple contaminants, the interaction between chemical and nonchemical stressors, and may decrease the need to apply uncertainty factors [26].

Many methods are available for assessing exposure. For example, in terms of dietary information, food frequency questionnaires or recall surveys collect information on possible sources of exposure from foods. These data can then be combined with contaminant levels measured or modelled in food items to estimate dietary exposure. Total exposure from multiple sources may be estimated through human biomonitoring data, i.e. the measurement of a chemical in a biological matrix, such as blood.

Risk characterisation combines the results of the hazard and exposure assessments to describe the risk of adverse effects from a given exposure. Approaches to characterise risk from dietary exposure to environmental chemicals include comparing contaminant levels in foods to food safety limits (e.g. MRLs – maximum residue levels); comparing estimated daily intakes (EDIs) to contaminant intake guidance values (e.g. TDIs – tolerable daily intakes); and, comparing contaminant concentrations in blood (human exposure levels) to blood guidance values. Modelling can be used to support these approaches by describing human exposures.

Different jurisdictions set different guidance (or reference) values for POPs and metals which can differ based on estimated dietary intakes (for food safety limits), approaches to uncertainty, and other factors such as organisational mandate. Table 1 presents a summary of guidance values that can be used to assess and interpret human health risks associated with environmental contaminants in the Arctic. A comparison is available values is presented in AMAP [25].

Application of risk assessment methodologies

Human health risk assessments of contaminants in the Arctic are limited. Here we present three case studies from different Arctic regions.

Table 1. Overview of guidance values applicable for assessment and interpretation of human health risks associated with environmental contaminants in the Arctic.

Type of Value	Jurisdiction	Meaning	Comments
FOOD SAFETY LIMITS (permissible concentration of a contaminant in a food item); expressed as milligram (mg) of a contaminant per kilogram (kg) of a food (wet weight (ww))			
MRL (maximum residue level), mg/kg ww	Codex Alimentarius Commission (CAC)[1]; European Food Safety Authority (EFSA)[2]; Health Canada	The highest level of a pesticide residue that is legally permitted in or on foods and animal feed [27–29]	MRLs, MALs and MLs are derived from estimations based on comprehensive toxicological assessments that consider all classes of consumers, including vulnerable populations such as pregnant women, infants and children. MRLs, MALs and MLs for contaminants in foods are not direct human health risk assessment parameters, but do represent a level below which there is no concern for human health.
MAL (maximum allowable level), mg/kg ww	Russian Rospotrebnadzor (Federal Service for Supervision of Consumer Rights Protection and Human Welfare)[3]	The highest levels of pesticides, polychlorinated biphenyls (PCBs) and metals residues that are legally permitted in foods [30,31].	
ML (maximum level), mg/kg ww	CAC[1]	The highest levels of a contaminant that is legally permitted in foods and animal feed [32].	
RMI (recommended maximum intake), g tissue/week or month	Health Canada	These values represent an amount of food or tissue that can be safely consumed over a period of time and can be used by the responsible health authority to determine if risk management is needed.	RMI calculations assume that consumption of this tissue/food represents the only source of contaminant intake from the diet. This scenario is unlikely and the authority should consider this uncertainty when determining if consumption advice is warranted.
ORAL/DIETARY CONTAMINANT INTAKE GUIDANCE VALUES; expressed as amount (in mg) of daily/weekly/monthly contaminant consumption with food per kg bodyweight (bw)			
ADI oral (acceptable daily intake), mg/kg bw/day	Implemented by the CAC[1] and Russian Rospotrebnadzor[3]	Daily intake of a chemical which, during the entire lifetime, appears to be without appreciable risk to the health of the consumer [27].	ADIs and TDIs are used interchangeably. ADIs and TDIs are usually based on experimental toxicological animal studies and/or epidemiological studies. ADIs and TDIs are derived from a point of departure (POD) from a study divided by an uncertainty factor. The POD may be a no- or lowest- observed-adverse-effect-level (NOAEL or LOAEL) from the study or a dose – response modelling value such as benchmark dose (BMD) from a study. ADIs and TDIs are applied to non-carcinogens as well as non-genotoxic carcinogenic contaminants (which have a threshold).
TDI oral (tolerable daily intake), mg/kg bw/day TWI oral (tolerable weekly intake), mg/kg bw/week TMI oral (tolerable monthly intake), mg/kg bw/month	Joint FAO/WHO Expert Committee on Food Additives (JECFA)[4]; Health Canada; EFSA; World Health Organization (WHO)[5]/ International Programme for Chemical Safety (IPCS)[6]	Daily, weekly or monthly intake of a substance in food, which, during the entire lifetime, appears to be without appreciable risk to the health of the consumer [33].	
RfD oral (reference dose), mg/kg bw/day	United States Environmental Protection Agency (US EPA)[7]	A daily estimate of exposure that is likely to be without adverse effects [34].	The RfD is analogous to the ADI or TDI. The 100-fold Uncertainty Factor (UF) converts a NOAEL from animal studies to a safe level of human intake. This UF includes a 10-fold factor for interspecies differences, split into 4.0 for toxicokinetics and 2.5 for toxicodynamics, and a 10-fold factor for interindividual variation, divided into two subfactors of 3.16 each. The UF may be adjusted based on scientific judgement to be higher or lower. Defined in four time scales of exposure: Acute: less than 24 hours Short term: up to 30 days Subchronic: up to 10% of the average lifespan Chronic: up to a lifetime

(*Continued*)

Table 1. (Continued).

Type of Value	Jurisdiction	Meaning	Comments
ATSDR-MRLs oral (minimal risk levels), mg/kg bw/day	Agency for Toxic Substances and Disease Registry (ATSDR)[8]	Daily human oral intake of a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure [35].	ATSDR-MRLs are similar to ADIs, TDIs or RfDs, but they are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) exposure durations. Cautionary note: the ATSDR- minimal risk level (MRL) in mg/kg bw/day has the same abbreviation as the food safety maximum residue level (MRL) in mg/kg ww but the meaning is different.
Oral ADIs, TDIs, RfDs or ATSDR-MRLs can be compared to a population specific Estimated Daily Intake (EDI). EDI is the amount (in milligrams) of daily contaminant consumption with food per kilogram body weight (mg/kg bw/day). EDI = C x IR/BW, where C = concentration of a contaminant in a food item (mg/kg ww); IR = daily food ingestion rate (kg/person/day); BW = average body weight (usually 60 or 70 kg). EDIs for the individual food items can be summed to represent total EDI for a contaminant from all food sources.			
Risk estimates of individual LIFETIME NON-CARCINOGENIC RISK associated with chronic oral exposure to contaminants			
THQ oral (target hazard quotient) or HQ oral (hazard quotient)	US EPA	The ratio of a substance or exposure route to a reference where adverse effects are unlikely to occur [36].	THQ = EDI/RfD (or TDI or ADI or ATSDR-MRL) of a non-carcinogenic (or non-genotoxic carcinogenic) contaminant. The resulting THQ is a unitless risk estimate.
THI oral (total hazard index)	US EPA	The ratio of multiple substances or exposure routes to a reference where adverse effects are unlikely to occur [36].	THI is a summation of THQs for all non-carcinogenic (or non-genotoxic carcinogenic) contaminants to which an individual is orally exposed. The THI for contaminants with reference doses based on the same toxic endpoint, e.g. organ or organ system, should not exceed a value of 1.0 (calculated by summing the HQs for individual contaminants). A value greater than 1.0 indicates an increased risk of non-cancer health effects.
Risk estimates of individual LIFETIME CARCINOGENIC RISK associated with chronic oral exposure to contaminants			
SFO* oral (or CSF, CFS, OSF, SFO, CPSo) – cancer oral slope factor; (mg/kg bw/day)$^{-1}$	US EPA	The increased cancer risk over a lifetime of exposure to a chemical, assuming a 95% confidence interval. Frequently used in estimating risks less than 1 in 100 [37].	Quantitative assessment of a contaminant as a carcinogen – the second step in human cancer risk assessment which defines the relationship between dose and response. A cancer slope factor is a key carcinogenic risk assessment parameter.
TCR oral (target cancer risk)	US EPA	The individual lifetime carcinogenic risk associated with chronic oral exposure to a contaminant.	TCR = EDI * SFO, where EDI is an estimated daily oral intake of a contaminant. A TCR is a unitless value. The calculated TCR should be compared to the level of acceptable cancer risk.
TTCR oral (total target cancer risk)	US EPA	Total individual lifetime carcinogenic risk associated with chronic oral exposure to contaminants.	A summation of TCRs for all carcinogenic contaminants to which an individual is orally exposed. The calculated TTCR should be compared to the level of acceptable cancer risk. For example, the estimated lifetime carcinogenic risk TTCR, equal to or less than 10^{-6} (corresponds to one additional case of cancer per 1 million exposed persons), is considered as minimal; risk in the range of 10^{-6}–10^{-4} is acceptable; risk equal to or greater than 10^{-3} (one case per 1000 people) is considered as high, requiring measures to reduce it [38].
HUMAN BIOMONITORING GUIDANCE VALUES			
RV95 (reference value)	German Human Biomonitoring Commission, Health Canada	Indicate the upper bound of background exposure of the general population to a given substance at a given time [39].	Statistical, not health-based, values that can be compared to individual data, community and population level data.

(*Continued*)

Table 1. (Continued).

Type of Value	Jurisdiction	Meaning	Comments
Biomonitoring Equivalents		Concentration of a chemical or metabolite in a biological medium (e.g. blood/urine) consistent with a reference value, such as TDI [39].	Intended as screening values to interpret population data in a risk-based context, but cannot be used to assess individual health risks.
Tissue-based guidance values		Relate human biomonitoring data directly to a health outcome [39].	Based on extensive scientific databases, these can be compared to measurements for an individual, use to evaluate risk and guide public health action and advice.

[1]Codex Alimentarius Commission (CAC).
[2]European Food Safety Authority (EFSA).
[3]Russian Rospotrebnadzor (Federal Service for Supervision of Consumer Rights Protection and Human Welfare).
[4]Joint FAO/WHO Expert Committee on Food Additives (JECFA).
[5]World Health Organization (WHO).
[6]International Programme for Chemical Safety (IPCS).
[7]United States Environmental Protection Agency (US EPA).
[8]Agency for Toxic Substances and Disease Registry (ATSDR).
*The SFO is a plausible upper-bound estimate of the probability of a cancer response per unit intake of a chemical over a lifetime. The slope factor is used to estimate the upper-bound probability of an individual developing cancer as a result of exposure to a specific level of a potential carcinogen. The SFO is expressed in units of the reciprocal of $(mg/kg\text{-}day)^{-1}$.

Canadian case study

This case study focuses on data from two barren-ground caribou herds; one from the eastern (Porcupine) and one from the western (Qamanirjuaq) Canadian Arctic. The Canadian Arctic Caribou Contaminant Monitoring Program monitors levels of various environmental contaminants in caribou herds to determine whether contaminant levels are changing over time and whether caribou remain a safe and healthy food choice for Northerners [40]. Results show that caribou meat (muscle) does not accumulate high levels of trace elements. Most trace elements measured in caribou organs are also not of concern for human health although higher levels of Hg and cadmium (Cd) appear to accumulate in kidney compared to other caribou tissues [41]. In caribou kidney, Cd concentrations result in the most restrictive recommended maximum intakes (RMIs) and as a result, Cd in caribou kidney is typically the focus of requested health risk opinions from Health Canada's Food Directorate. Health risk opinions on concentrations of trace elements in caribou kidney are provided to the responsible Regional Health Authority, upon request.

Health-based guidance values can be used to calculate RMIs (Table 2). These values represent an amount of food or tissue that can be safely consumed over a period of time and can be used by the responsible health authority to determine if risk management is needed, such as consumption advice for the traditional food in question. Table 2 provides a summary of the average and range of Cd concentrations calculated in the kidney samples for the two caribou herds. In the absence of information on other dietary sources of Cd, the RMI calculation for caribou kidney assumes that consumption of this tissue represents the only source of Cd intake from the diet. In providing a health risk opinion to the responsible authority, the Food Directorate will point out that this scenario is unlikely and that the authority should consider this uncertainty when determining if consumption advice is warranted.

In making this determination, the responsible authority may wish to consider the following: for example, if the estimated RMI is greater than the quantity of the traditional food the local populations are actually consuming then consumption advice may not be needed. For the responsible authority, accurate information of typical consumption patterns of traditional foods is key when considering potential consumption advice or advisories. It is recommended that the authority identifies the traditional foods consumed, quantifies the amount of each food consumed per eating occasion or serving, and determines the frequency of consumption (i.e. is the food in question a staple in the diet of the local population or only consumed on an occasional or seasonal basis). For example, if caribou are normally hunted in autumn, and organ meats are typically not preserved, this could be the only period during which kidney is likely to be consumed.

The RMIs should also be expressed in a way that makes sense to the local populations consuming the food in question. For example, the RMI can be expressed on a "meals" per weekly, monthly or yearly basis, it is then important to communicate what is considered to be the typical size of a "meal" (e.g. where X grams (g) represents a meal per week, month or year). In the case of caribou kidney it can be useful to know the average weight of a kidney for the herd because depending on the consumption patterns of the local population a recommendation of the

Table 2. Summary of caribou kidney data for cadmium for two barren-ground caribou herds, one from the eastern (porcupine) and one from the western (qamanirjuaq) Canadian Arctic [1].

Herd	Sampling years	Sample Size	Total average Cd concentration (range), micrograms (μg) Cd/g wet weight[1]	Recommended maximum adult intake, g kidney/month[2]
Porcupine	1990–2013, 2015	749	8.15 (5.02–12.82)	215
Qamanirjuaq	1992, 2006–2015	181	5.61 (3.49–7.59)	312

[a]The provisional tolerable monthly intake for Cd derived by the Joint FAO/WHO Expert committee on Food Additives and Contaminants [42,43] is 25 μg/kg bw/month.

[b]In absence of population specific information, an assumed average body weight of 70 kg is used for adults (default mean body weight for adults ≥20 years of age from the Canadian Community Health Survey – Cycle 2.2 on Nutrition [41]).

maximum number of kidneys per year may be the most relatable context.

Based on available data, consumption advice or advisories have not been issued for caribou kidney by Regional Health Authorities.

Russian case study

In the Russian parts of the European Union (EU) Kolarctic project (2013–2016) in the Pechenga district of Murmansk Oblast [44–50] and the United States of America (USA)-Russian project "Food Security and Lactic Bacteria Use in Alaska and the Bering Strait Region" (2016–2018) in coastal Chukotka [51–53] a variety of local foods (fauna and flora) have been analysed for metals; and fauna species, for POPs. These studies have served as an opportunity to apply several risk assessment tools to characterise the risk associated with exposure to contaminants.

Food-based guidance values

Russian hygienic regulations of legacy POPs in wildlife species are the most comprehensive when compared to other national and international jurisdictions. Nevertheless, the Russian regulations do not cover all legacy POPs and all subsistence species, which hampers the evaluation of the "degree" of contamination of different foods by different organochlorines. Russian MALs for PCBs are established only for the tissues of marine mammals and fish; chlordanes are regulated only in meat of terrestrial mammals and birds; dichlorodiphenyl-trichloroethanes (DDTs) and hexachlorocyclohexanes (HCHs) are not regulated in fish; and hexachlorobenzene (HCB) is not regulated at all [30,31].

In the Pechenga district of Murmansk Oblast (sampling of 2013), the concentrations of POPs in samples of local fauna species, where only HCB, DDTs and PCBs were detected, were tens to hundreds of times lower than the corresponding Russian MALs [44]. However, exceedances of Russian MALs were observed for Cd in mushrooms (laminar and tubular: brown cap boletus (*Leccinum scabrum*), orange cap boletus (*Leccinum aurantiacum*), bearded milkcap (*Lactarius torminosus*), milk mushroom (*Lactarius resimus*), russula (Russulaceae)), which were 1.5- to 2-fold higher, and for Hg in orange-cap mushrooms (*Leccinum aurantiacum*) which were up to 3-fold higher [45]. Exceedances of the outdated Union of Soviet Socialist Republics (USSR) MALs (derived in the 1980s) were found for nickel (Ni) in wild berries (up to 4.5-fold higher), garden berries (up to 2.5-fold higher), potatoes (up to 2-fold higher) and mushrooms (2.5- to 30-fold higher) [45].

The outdated USSR MALs were very helpful in carrying out the EU Kolarctic KO467 project aimed at the study of local food contamination by the nickel-copper smelter in the Pechenga district of Murmansk Oblast (Sampling of 2013). Interpreting the project's results was made difficult by the absence of internationally established food contamination standards for Ni and Copper (Cu), which were the key pollutants in the study area. Given the lack of updated reference points for Ni and Cu, a decision was made to focus on the contaminants with internationally agreed upon reference points, namely lead (Pb), Hg, Cd and arsenic (As), even though their levels were low in local food. The sole joint international publication [50] covering data from all countries (Norway, Finland, Russia) only briefly considered the risk of consuming wild foods and concluded that the elevated Ni and Cu concentrations observed in some mushroom samples could pose a risk to people who frequently consume mushrooms. It was recommended that these people should avoid collecting mushrooms near the smelter and in other areas with high concentrations of toxic elements in mushroom species. Several Russian publications have discussed in detail Ni-Cu dietary exposure (including local water) and the related human health risks [44–49]. The "outdated" MALs were "temporarily" used in the USSR during the 1980s and have not been officially re-approved in Russia after the collapse of the USSR in 1991. Despite being outdated, the MALs for

Ni, Cu, Zn, and Al hold great practical importance, particularly for the metal deposits area in the Pechenga district of Murmansk oblast, as there are no equivalent MALs for these metals available elsewhere worldwide.

In coastal Chukotka in 2016, the highest concentrations of POPs [51] in all analysed samples of land and marine mammals (meat and blubber), as well as fowl and fish (freshwater, migratory and marine) did not exceed the Russian MALs. Only the ringed seal blubber had a reported value of 100 µg/kg ww of ∑DDTs, equal to the MAL. As MALs for HCB in food do not exist, high concentrations of HCB (180–200 µg/kg ww) in whale blubber and mantak (whale skin with the adjacent thin layer of blubber) could not be compared to any limits.

Regarding metals in coastal Chukotka in 2016 [52], no exceedances of Russian MALs were observed for Pb, Hg, Cu, Zinc (Zn) and Ni in all of the samples of mammals, fowl, fish, seafood, berries, mushrooms and wild plants. However, the exceedances for As and Cd were significant, exceeding the As MAL by up to 270%, 160% and 280% in marine mammal blubber, land mammal meat and seaweed, respectively; and the Cd MAL by up to 160% in hare meat, 230% in berries and 45% in mussels. Some exceedances of chromium (Cr) were also observed in berries.

For the first time, very high concentrations of several metals were reported in a number of wild plants and seafood of coastal Chukotka [52]. Rhodiola arctica leaves accumulate aluminium (Al) (up to 75 mg/kg ww), manganese (Mn) (up to 190 mg/kg ww), Ni, barium (Ba) and strontium (Sr). Seaweed (Laminaria saccharina) contains very high levels of As (14 mg/kg) and Sr (310 mg/kg). Ascidians (particularly Halocynthia aurantium) are contaminated by Cr, Sr, and Al (up to 560 mg/kg). Blue mussels accumulate significant levels of Cd (2.9 mg/kg) and Al (140 mg/kg ww). Unfortunately, due to the absence of the established MALs for Al, Mn, Ni, Ba and Sr in many local subsistence foods, there are presently no instruments for the risk evaluation of very high concentrations of these metals in the given species.

Estimated daily intakes

Calculation of the estimated daily intakes (EDIs) of different contaminants with different food items provides an opportunity to evaluate the “structure” of dietary exposure to contaminants for the study population, that is, to assess the input of each food item to the total EDI for each contaminant. This approach was used in the Pechenga district of Murmansk Oblast [46] and in coastal Chukotka [51–53]. Mushrooms and fish were the primary contributors to metal intake in the Pechenga district of Murmansk Oblast. In contrast, in coastal Chukotka, the metals intake was mainly driven by seafood consumption, while the POPs intake was from consumption of marine mammal blubber.

Individual lifetime non-carcinogenic and carcinogenic risks

In the Pechenga district of Murmansk Oblast, in addition to evaluating exceedances over the food safety limits and describing the contribution of different food items to the EDIs of metals, the calculation of non-carcinogenic and carcinogenic risks associated with metals in local foods and drinking water has been carried out [46]. A non-cancer THI of 3.11 was associated primarily with Ni in mushrooms, wild berries and drinking water; Cd in mushrooms; Hg in fish; and As in fish and mushrooms. A TTCR of $1.25 \times 10\text{-}2$ was associated mainly with Ni in mushrooms, wild berries and drinking water, and partly to As in fish and mushrooms. Both of these calculations indicated very high non-cancer and cancer risks. It was concluded that recommendations are required for reducing consumption of certain local food products in the affected population and that clean alternatives to the local Ni-contaminated drinking water sources should also be identified [46,49].

Food intake criteria

A risk management approach (elaboration of the recommended food daily intake limits (RFDILs) to locally harvested foods was applied in coastal Chukotka [53]. RFDILs were developed based on the results of an analysis of five groups of legacy POPs and 11 metals analysed in samples of 12 locally harvested food groups collected in 2016. The aim of the study was to expand the toolset for setting dietary recommendations when assessing multiple contaminants in a variety of foods to promote reducing consumption of the most contaminated local food products.

To calculate the RFDILs [53], the established Russian and international ADIs and TDIs, and the highest concentrations (C) of legacy POPs and metals in the analysed food samples (each specific contaminant in each specific food item) were used: $\text{RFDIL} = (\text{TDI} \times \text{bw})/\text{C}$. All calculations were made for an adult human with a body weight of 60 kg regardless of gender and age. No limits to consumption were recommended for reindeer, hare, goose or mushrooms. The heaviest restrictions were 20 g/day/person for multiple food items, such as seaweeds, ascidians, and mussels because of their extremely high contamination by As, Cd and Al, while the lightest restrictions were placed on marine mammal meat (230–400 g/day/person) due to somewhat elevated contamination by As, Hg and Al.

Toxicokinetic modeling of methylmercury: insights from the Norwegian fish and game study

Indigenous Arctic populations were identified as a population in need of improved contaminant exposure estimation tools [54,55]. Several mechanistic models have been published that focus on the exposure of Arctic Indigenous human populations to environmental contaminants. The human food-chain bioaccumulation model ACC-HUMAN was combined with either the environmental fate model CoZMoPOP2 [56] or the global fate and transport model GloboPOP [57–59] to simulate PCB exposure in Arctic populations. PBPK models have been developed as well to assess lifetime internal exposure in Arctic Indigenous women for different POPs, based on the physiology and reproductive history of the subjects [60], or on blood concentrations [61].

A modelling system consisting of three linear toxicokinetic models for describing the fate of methylmercury (MeHg), inorganic Hg and metallic Hg in the body, in order to estimate daily intake of Hg as measured through total Hg concentrations in the blood has been developed [62]. Results stemming from the modelling system were compared to those of the detailed semi-quantitative food frequency questionnaire (FFQ) of the Norwegian Fish and Game (NFG) Study, a project that focused on dietary mercury exposure.

One of the aims of the original NFG Study [63] was to measure total Hg in blood and urine and estimate the dietary exposure of Norwegians with a diversity of seafood and game consumption. Participants provided blood samples, and dietary information for the preceding 12 months was obtained using a detailed semi-quantitative FFQ. The FFQ had been designed and validated for the Norwegian Mother and Child Cohort Study and contained 340 questions covering 255 different food items [64,65]. The results indicated that toxicokinetic modelling based on blood levels gave higher daily intake values of Hg compared to those of the FFQ. The bias was minimal in terms of the estimates between the median daily intake of Hg, being 0.043 µg Hg/kg bw/day as estimated by the FFQ and 0.050 µg Hg/kg bw/day as estimated by the toxicokinetic model. That said, the values for the intake of MeHg by the FFQ and the toxicokinetic modelling had a correlation of only 0.38. There was also an intra-class correlation coefficient of 0.298 between the FFQ and the toxicokinetic model.

Limitations and strengths of the present model should be noted. The main strengths are utilising a modelling system comprising a validated two-compartmental model to simulate the fate of inorganic Hg, a validated multi-compartmental model to simulate the fate of organic Hg, and an independent blood compartment for linking the main models together. In addition, data employed in the modelling system were based on detailed information about dietary sources and demographic factors in addition to accurate Hg measurements in blood [63]. In modelling, there are certain limitations that may lead to under- or overestimation of the actual exposure, such as the estimated shares for MeHg and inorganic Hg, the concentration of Hg in foods other than fish, the lack of precise Hg intake information for the study participants, significant variations in the dietary exposure estimates between individuals and data on inorganic Hg, and dental amalgam fillings in the NFG Study. Unique genetic backgrounds, individual diet and health status, and socio-demographic variables may have a significant role in exposure rates (Figure 1). The proportions of different forms of Hg in blood need to be addressed in order to construct a complete model. However, it should be emphasised that the levels of total Hg measured from blood provide a firm basis for the future development of toxicokinetic modelling, enabling better estimates of health impacts associated with exposures.

Comparison of current exposures to biological-based guidance values

Blood-based guidance values exist for Hg and Pb, in part because their routes of exposure and health effects are well established, especially in epidemiology studies [25,54,66–69]. In this section we present a comparison of biomonitoring results to blood-based guidance values for Hg and Pb that have been described in AMAP [25].

Hg data are available for men, women including women of child-bearing age (WCBA), pregnant women and children from Canada, Greenland, Iceland, Sweden, Faroe Islands, Finland and Russia. These data were compared to Hg guidance values of 8 µg/Litre (L) for WCBA, pregnant women and youth and 20 µg/L for adults, derived by Legrand et al. [70]. As can be observed in Figure 2, exceedances of 8 µg/L are much higher in Arctic Canada and Greenland compared to other countries. Within these countries there are regional differences. Exceedances from the Eastern Canadian Arctic ranged from 36.0% to 57.3% vs the Western

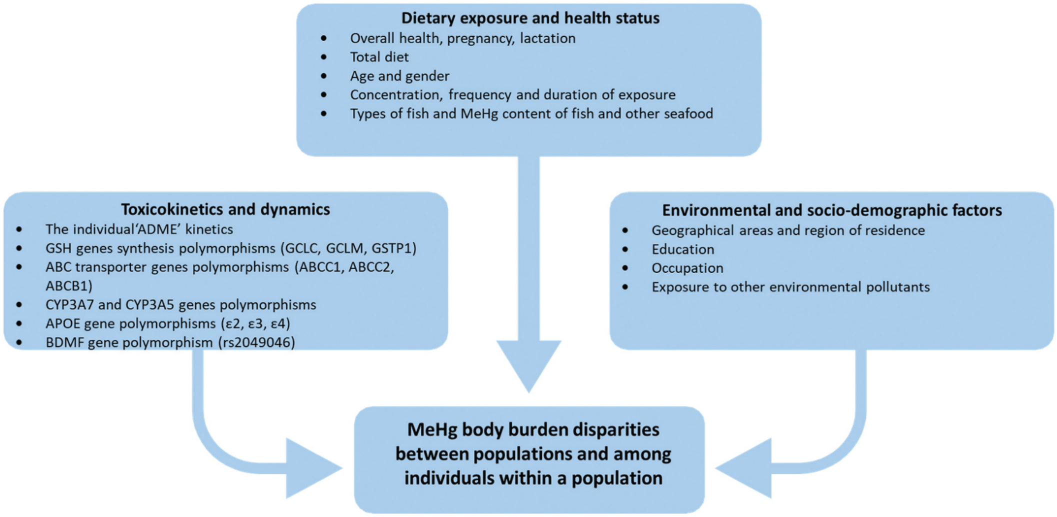

Figure 1. Overview of factors influencing MeHg body burden disparities. The figure illustrates the interplay of dietary exposure, genetic predispositions, and environmental/socio-demographic factors in influencing methylmercury body burden disparities among populations and individuals. It highlights the roles of health status, age, and seafood consumption patterns in dietary exposure, while genetic variations in detoxification and metabolism genes and external environmental conditions, such as geographical location and occupation, contribute to individual and population differences in MeHg accumulation.

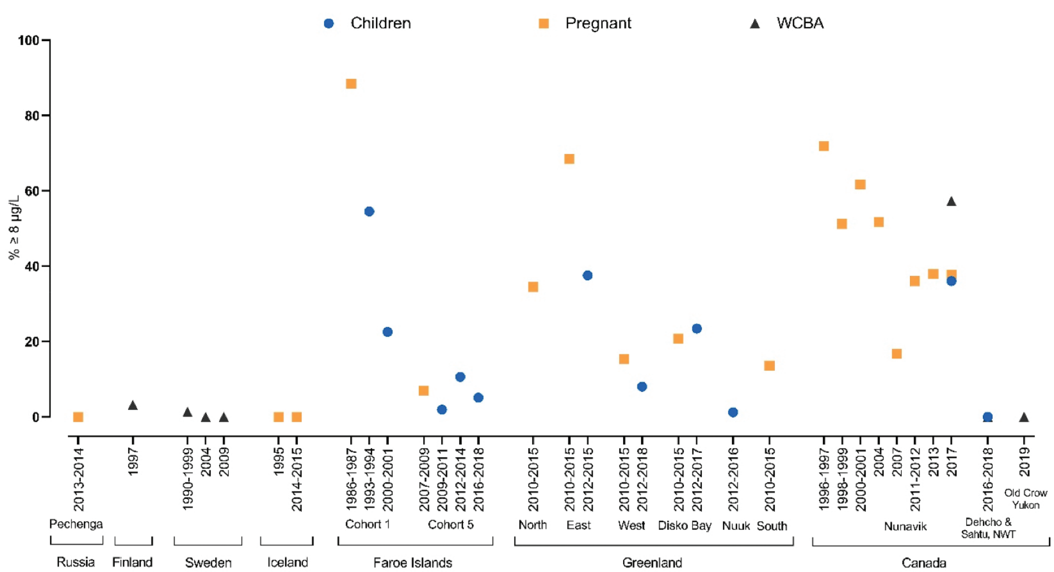

Figure 2. Exceedance of blood guidelines for total mercury in populations from several Arctic regions. Data presented as a percentage of the study population above 8 µg/L for each target population group.

Canadian Arctic, where there were no exceedances. Similarly, in Greenland, more exceedances are seen in the North and the East (range 34.4% to 68.4%) compared to the South and the West (range 13.6% to 15.3%) where consumption of country and traditional foods is typically lower. Exceedances are also observed in the Faroe Islands. In Faroe Islands Cohort 1, exceedances among children appeared to decline, but once in adulthood, exceedances increased slightly from 1.4% to 5.7% between 2008–2009 and 2013–2016. In Faroe Islands Cohort 5, exceedances among children were highest at age 5 years in 2012–2014 (10.6% above 8 µg/L), but decreased by 2016–2018 in children at age 9 years (5.1% above 8 µg/L). Less than 5% of reported concentrations from Finland and Russia exceeded their respective guidelines. No exceedances were observed in the data from Iceland or Sweden.

Unlike women of childbearing age and children, across the Arctic very few exceedances (0–6%) of the Hg guideline of 20 µg/L were observed in adults, with the exception being Nunavik (Eastern Canadian Arctic) where exceedances of >20% were observed [25].

For Pb, blood guidance values of 10 µg/decilitre (dL) and 3.5 µg/dL have been set by Health Canada and the US Centers for Disease Control and Prevention (CDC) respectively [71,72]. Exceedances are observed more infrequently than for Hg. In regions with multiple time points, such as Sweden and Canada, there appears to be a declining trend of exceedances (Canada 60.3% to 6.7% and Sweden 1.7% to 0%). In Canada, higher exceedance rates were observed in the population aged 50 years or more [25]. It should be noted that more detailed exceedances are reported in the AMAP 2021 assessment [25]. These are based on the guidance values that were available at the time, specifically the exceedances of the 5 and 10 µg/dL guidance values as described in the original AMAP 2021 assessment, prior to the establishment of the 3.5 µg/dL guidance value

Conclusion and future prospective

Tools are available to interpret biomonitoring data in a human context. Reference levels can vary in complexity, from a maximum level in a food item, to a recommended maximum dietary intake, to a level measured in human matrices below which effects are unlikely to be observed. These can be based on epidemiological, toxicological and/or modelling studies. Different jurisdictions set different reference values for POPs and metals. The values can differ based on estimated dietary intakes, approaches to uncertainty and organisational mandate, among others.

There are challenges to the use of these tools in an Arctic context (Table 3). The profile of exposure to contaminants in many Arctic populations may differ from those of reference populations used to derive guidance values based on human data. Even across the Arctic, differences in diet (including differences in type of species consumed), can have a dramatic effect on contaminant intake, resulting in regional differences across countries. Dietary and seasonality patterns, cultural practices, environmental and sociodemographic variables, among other factors, may play a significant role in the susceptibility of exposure of Arctic Indigenous populations to environmental contaminants. Several mechanistic models and physiologically-

Table 3. Challenges for human health risk assessment in an Arctic context.

Research area	Challenges	Areas for future focus
Dietary assessments	Conventional food frequency questionnaire (FFQ) are an imprecise method for estimating the intake of individual food items. Diet is regionally and culturally different and depends on season and many environmental (incl. warming climate) conditions in the Arctic, alter availability/intake of individual food items and hence contaminant intake. Real-life common practice of consumption of mixed food items (e.g. dishes consisting of blubber + offal + fish + berries + wild plants, etc.) results in uncertainty in quantifying individual food items in mixed dishes, and hence – uncertainty in concentrations of contaminants in mixed dishes. Culinary processing of raw foods (drying, salting, smoking, fermentation, etc.) may alter concentrations of contaminants in finished foods.	Quantitative dietary surveys demonstrate the FFQ and a Weighed Food Record (WFR) method (or duplicate-food collection) as the most precise approach for estimating food and/or nutrient intakes. FFQ and WFR should be carried out in more than one season (e.g. summer and winter). Attention should be paid to mixed foods and culinary processed foods.
Food safety limits on POPs	MRLs are established by CAC and EFSA for some legacy POPs only in land mammals, fowl and eggs. Russia has the most comprehensive list of MALs, and the only values for marine mammal and fish tissues (incl. PCBs). MRLs for foods in Canada are designed for retail products, and are not relevant to country foods. Available values may differ between jurisdictions based on many factors, including analytical measurements and different approaches to uncertainty. For some POPs this difference is 50- to 100-fold. MRLs and MALs have not been established for emerging "new" POPs, such as brominated and fluorinated compounds.	The lack food safety limits for some POPs and metals should be addressed. In particular, limits for contaminants measured in Arctic research studies would be beneficial. International and inter-jurisdictional cooperation to establish guidance values, as well as standardise analytical measurement protocols and approaches to uncertainty, would improve the ability to compare the conclusions of risk assessments across regions, and contribute to sharing of resources and expertise.
Food safety limits on metals	MLs are established by CAC for Pb and Hg and MRLs by EFSA (for Hg) in raw foods. Russian MALs for Pb, Hg, As and Cd in raw foods cover almost the entire suite of species (incl. marine mammal tissues). The USSR MALs for Cu, Zn, Ni, Cr and Al were established in the 1980s for several food groups. These MALs have not been revised, but are still in use in Russia owing to the lack of any other standards for these metals worldwide. Available values for Pb and Hg may differ between jurisdictions by as much as 5-10 times. Food safety limits are not established for many toxic metals like Mn, Ba, Sr, Cobalt (Co), Vanadium (V), etc.	

(*Continued*)

Table 3. (Continued).

Research area	Challenges	Areas for future focus
Oral/dietary contaminant intake guidance values	ATSDR-MRLs and US EPA RfDs cover almost the entire list of legacy POPs, some brominated compounds and a variety of metals. In general, reference levels exist when there is a strong health effects database and weight of evidence to support a derivation. For contaminants of emerging concern there may be few hazard or exposure data on which to base a guidance value.	Additional research of emerging contaminants of Arctic concern [73] is needed to support the development of guidance values for these compounds. When guidance values are lacking, other approaches may be taken. For example: • Exposures in one study may be compared to exposures in other populations. • A margin-of-exposure approach may be used to compare known or suspected health effects with observed exposures. • Provisional guidance values, specific to a given project may be developed based on studies in the literature.
Genetic variability	Allelic frequencies in environmentally responsive genes differ between Inuit and other ethnic groups, and the consideration of such genetic data may help explain variations in biomarker levels of toxicants and nutrients as well as exposure-biomarker associations.	While there are no immediate clinical or public health implications of these findings, consideration of such gene-environment results may help improve the ability to conduct exposure (and ultimately risk) assessments of country foods.
Exceedances over guidance values	Exceedances over guidance values (food-based, dietary intake-based, tissue-based, calculated non-carcinogenic and carcinogenic risks) for some POPs and metals are observed in some regions of circumpolar Arctic.	Continued international chemicals management is essential to reduction of environmental contamination and decreasing the human exposure to POPs and metals in the Arctic.
Mixture exposure to multiple contaminants	Causal links between contaminant exposures and biological/health effects are often discussed from a single cause-effect perspective, with a focus on single contaminants, but do not consider the occurrence of multiple chemicals as mixtures and their combined effects. When contaminants are mixed, their combination can increase or decrease the overall effect, or even lead to different effects.	Human health risk assessment must consider cumulative (combined) effects from exposure to a mixture of multiple contaminants (possible additive, synergistic or antagonistic effects. General methodology for cumulative risk assessments is imperfect and should be updated regularly as knowledge develops.
Epidemiological studies on dose-effect	Studies on effects of contaminant exposure are based on a variety of methods and study designs which has made it difficult to combine and compare original studies.	Cohort studies are the gold standard for studying the long-term health effects of contaminants. While very resource intensive, these types of studies should be supported. Study protocols should be harmonised to improve opportunities for comparing contaminant levels and effects data.
Toxicokinetic modelling	Increasingly employed to reconstruct past contaminant exposure and to relate exposure and body concentrations.	Employing a general toxicokinetic model for a particular contaminant may be insufficient. Unique genetic backgrounds, among other factors, may have a significant role in individual/population susceptibility to a contaminant body burden.
"Arctic Dilemma"	Arctic peoples are exposed to a wide range of contaminants through consumption of country foods which at the same time provide necessary nutrition (incl. essential elements, vitamins, etc.), maintain health, keep traditions and socio-cultural connections. The complicated risk-benefit balance associated with the consumption of country foods has been referred to as the "Arctic Dilemma".	The results of human health risk assessments must be considered along with nutritional, physiological, sociological, cultural considerations to provide balanced risk-benefit advice about contaminants in country foods.

based pharmacokinetic models have been developed to assess Arctic Indigenous human population exposure to environmental contaminants. Among Indigenous groups in several Arctic regions, consumption of country and traditional foods represents the primary route of exposure to POPs and Hg, while also representing a significant proportion of nutrient intake. Science-based risk assessments that balance risk from contaminants with benefits from nutrients are difficult to perform. In addition, risk-benefit analyses require information from other knowledge holders to address sociological, spiritual and community considerations.

Future studies are necessary in order to reduce uncertainties and better characterise health risks associated with environmental contaminants by better identifying sources of contamination; deriving and/or updating reference values for key contaminants; exploring risk assessment methods to address risks associated with mixtures; and improving the overall process of health risk assessment, including harmonisation of reference values where possible. In order to be of benefit to Arctic communities, future human health risk assessment must consider inputs that are specific to regions or communities (e.g. food intake, seasonal intake), address benefits of food consumption and be open to incorporating other local and Indigenous knowledge and perspectives.

Acknowledgments

This article is based on the AMAP 2021 human health assessment report chapter 5, which was completed prior to February 2022.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was supported by a grant from the Academy of Finland [grant number 356604]. The funding sources had no influence on the study design, collection, analysis, or interpretation of data, the writing of the report, or the decision to submit the article.

Author contributions

Conceptualisation, K.A., A.A.D. and C.K.; writing – original draft preparation, K.A., A.A.D., B.A., Z.G., A.R. and C.K.; writing – review and editing, L.N. All authors have read and agreed to the published version of the manuscript.

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