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Emerging evidence on selenoneine and its public health relevance in coastal populations: a review and case study of dietary Se among Inuit populations in the Canadian Arctic

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Abstract

Selenium is an essential mineral yet both deficiency and excess are associated with adverse health effects. Dietary intake of Se in humans varies greatly between populations due to food availability, dietary preferences, and local geological and ecosystem processes impacting Se accumulation into agricultural products and animal populations. We argue there is a need to evaluate and reconsider the relevance of public health recommendations on Se given recent evidence, including the metabolic pathways and health implications of Se. This argument is particularly pertinent for Inuit populations in Northern Canada, who often exceed dietary tolerable upper intake levels and exhibit very high whole blood Se concentrations due to their dependence on local country foods high in the newly discovered Se compound, selenoneine. Since selenoneine appears to have lower toxicity compared to other Se species and does not contribute to the circulating pools of Se for selenoprotein synthesis, we argue that total dietary Se or total Se in plasma or whole blood are poor indicators of Se adequacy for human health in these populations. Overall, this review provides an overview of the current evidence of Se speciation, deficiency, adequacy, and excess and implications for human health and dietary recommendations, with particular reference to Inuit populations in the Canadian Arctic and other coastal populations consuming marine foods.

Key words: **dietary recommendations: Inuit populations: micronutrients: selenium: selenoneine**

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Introduction

Selenium (Se) is a chalcogen trace element that is essential for human health[1]. Over the last three decades, there has been considerable advancement in our understanding of the sources and biological functions of Se. An important outcome of this research is the understanding that the health effects of Se depend upon the species of Se ingested and their metabolism[2–4]. This insight corresponds with the current trend in toxicological and public health research of determining the diverse health effects of various forms or species of several other elements found in the natural environment (for example, mercury and arsenic)[5,6]. In Inuit Nunangat (the Inuit homelands of the Canadian Arctic comprised of Inuvialuit Settlement Region, Nunavut, Nunavik, and Nunatsiavut), the traditional diet of Inuit populations (comprised of 'country foods', as they are called locally) is exceptionally high in Se, largely due to the presence of selenoneine (SeN) – an organoselenium compound and Se isologue of ergothioneine – in marine foods, and particularly beluga skin, that serve important roles in food security, nutrition, and cultural integrity[7,8]. As a result, Inuit populations across Inuit Nunangat exhibit considerably higher blood Se concentrations than other reference populations in North America and Europe[9,10]. There is a need for both individuals, who may wish to take responsibility for their own health, and government agencies, which often establish public nutrition programming and nutrition guidelines, to be attentive to SeN as it relates to Se dietary sufficiency, metabolism, and health implications. The objective of this article is to review the current evidence on Se as it pertains to Inuit populations in the Canadian Arctic and make recommendations for cohesive, evidence-based research priorities, risk assessment, and public health decision-making that considers the presence of SeN as a major selenium species in several key marine foods.

Human selenoproteins

The biological actions and proposed nutritional essentiality of Se occur largely through selenoproteins. Selenium metabolism of major forms of dietary Se and selenoprotein synthesis are

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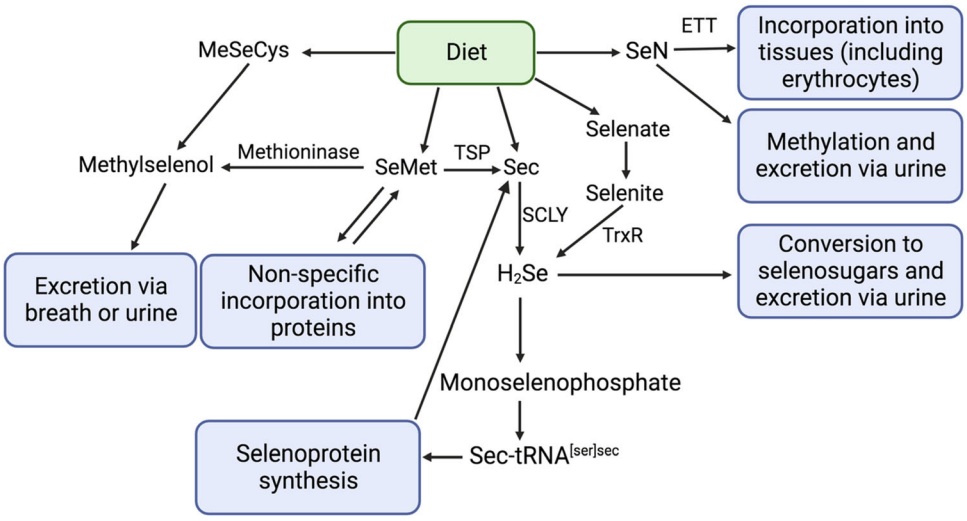

Fig. 1. Metabolism of Se food species, adapted from Combs (2001)[11], Kayrouz *et al.*, (2022)[71], Rayman *et al.* (2008)[3], Rayman (2012)[15], and Yamashita *et al.* (2010)[65]. ETT, ergothioneine transporter; SCLY, selenocysteine β-lyase; SeMet, selenomethionine; Sec, selenocysteine; H_2Se, hydrogen selenide; CH3SeCys, Se-methyl-selenocysteine; SeN, selenoneine; CH3SeH, methyl selenol; TSP, transsulfuration pathway.

well-documented[3,11–14]. Organic forms of selenium, including selenomethionine (SeMet) and selenocysteine (Sec), are the most abundant forms of dietary Se, while inorganic compounds (selenite and selenate) represent a minor proportion of dietary intake[15]. Following absorption, Se compounds are mostly transported to the liver, which is the principal site of Se metabolism[14]. Dietary SeMet can be trans-selenated to Sec but is primarily non-specifically incorporated into body proteins (such as blood albumin) or converted to methylselenol (CH_3SeH) (Fig. 1), although the importance of the latter process in humans is not known[16]. Surplus Se may accumulate as SeMet in blood albumin or may be converted to methylated metabolites for excretion in the breath or (more commonly) urine[3]. In the liver, most Se compounds are metabolised to hydrogen selenide (H_2Se). Subsequently, Sec is phosphorylated, leading to the formation of monoselenophosphate, which is used for the production of unique transfer RNA, Sec $tRNA^{[Ser]Sec}$, that provides Sec for selenoprotein synthesis. In the presence of a Sec insertion sequence (SECIS), the UGA codon (which is normally a stop codon) is recoded to specify the insertion of Sec[17]. A SECIS-binding protein recruits Sec $tRNA^{[Ser]Sec}$ for ribosomal translation and incorporation of Sec into nascent polypeptides[17].

Approximately 25 selenoproteins have been identified thus far that play a functional role in a variety of physiological processes, including cell maintenance, oxidative homeostasis, thyroid hormone metabolism, brain activity, and immune response[17]. For a summary of selenoproteins and their nomenclature and functions, please refer to Pitts and Hoffman (2018)[18]. Optimum blood plasma Se levels are between 60 and 150 μg/L to maximize selenoprotein synthesis and activity[19,20]. It is commonly accepted that when Se intake is sufficient, plasma selenoprotein concentrations and activities plateau. Several researchers have therefore argued that plateau concentrations of plasma selenoproteins reflect functional Se sufficiency[21–23]. Consequently, total plasma Se concentrations and plasma selenoprotein (e.g., glutathione peroxidase 3 (GPX3) and selenoprotein P (SELENOP)) concentrations and activity levels are the most commonly used biomarkers for determining Se adequacy[24].

Dietary reference values and safe upper limits

Although Se deficiency is rare, it is linked with reduced tissue concentrations and activity levels of selenoproteins and can contribute to Keshan disease (congestive cardiomyopathy caused by depletion of selenoprotein glutathione peroxidase, GPX), Kashin-Beck disease (atrophy and necrosis in cartilage tissue, possibly due to oxidative stress), hypothyroidism (due depletion of iodothyronine deodinases)[25], as well as increased risk of miscarriage and other reproductive and obstetric complications[26–29]. Conversely, Se toxicity (selenosis) can occur with acute or chronic ingestion of excess Se. The most common adverse health impacts of selenosis are alopecia and nail brittleness and loss[30], as well as gastrointestinal disturbances, skin rash, garlic breath odor, fatigue, irritability, and eventually nervous system abnormalities and paresthesia[31,32]. Mechanisms of Se toxicity remain unconfirmed but selenosis likely occurs as a result of oxidative stress generation and consequent disruptions of cellular and mitochondrial function[33,34]. Biomonitoring equivalents associated with protection against selenium toxicity range from 400–480 μg/L in whole blood and 180–230 μg/L in plasma[35].

Over the past three decades, authoritative bodies have established dietary reference intakes (DRIs) for Se. In their 2001 assessment, the Institute of Medicine established the recommended dietary allowance (RDA) and tolerable upper intake limit (UL) at 55 μg Se/day and 400 μg Se/day respectively for individuals above 14 years of age[25]. These values were subsequently adopted by several national regulatory authorities, including Health Canada[36] and the United States Department of Health and Human Services[37]. This UL was reaffirmed in separate risk assessments conducted by the National Health and Medical Research Council of Australia and New Zealand[38] and the World Health Organization in coordination the Food and

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Table 1. Whole blood Se concentrations in Inuit compared to other global populations

Country or region (year)	Population whole blood Se concentration (95% CI or SD, if reported) (μg/L)	Range, if reported (μg/L)
Canada		
Nunavik, Inuit adults (2017)[110]	300 (283–307)*	NR
Nunavik, Inuit adults (2004)[9]	261†	118–3555
Nunavik, Inuit pregnant mothers (2001)[111]	316†	182–980
Nunavut, Nunatsiavut, and Inuvialuit Settlement Region, Inuit adults (2007-08)[95]	280†	150–1500
First Nations, general (2011)[47]	189 (182–196)*	NR
Canadian, general (2007-09)[48]	203 (199–208)*	NR
Greenland Inuit, across three communities (1999-2001)[46]	169 – 354*	(NR)–1767
Greenland, Inuit adults (2005-09)[112]	285*	68–5600
United States		
United States, general (2011-12)[49]	190 (187–193)*	NR
Europe		
Czech Republic, general (1996-2001)[113]	80 (79–81)*	NR
Austria, adults (2002-2004)[114]	86 (±24)‡	42–183
Italy, adults[115]	140 (137–143)*	82–178
Germany, general[116]	132*	85–182
Brazil, Amazonian adults (2006)[117]	284†	142 – 2029
French Polynesia, adolescents (2007)[118]	250†	NR

NR=not reported.
* Geometric mean.
† Median.
‡ Arithmetic mean.

Agriculture Organization of the United Nations[39]. Meanwhile, the Scientific Committee on Food (which provided the European Commission on scientific advice on food safety prior to the establishment of the European Food Safety Authority (EFSA)) established a UL of 300 μg Se/day[40] and the UK Expert Group on Vitamins and Minerals established a UL of 450 μg Se/day[41]. While the methodology for these risk assessments varied slightly, all were based on a limited number of observational and experimental studies conducted in China[32,42,43], the US[44], and New Zealand[21]. Recently, following a request from the European Commission, the EFSA Panel of Nutrition, Novel Foods, and Food Allergens (NDA) undertook a systematic review to establish a scientific opinion on the UL for Se. Grounded primarily in data from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), this panel recommended a UL of 255 μg Se/day based on a lowest-observed-adverse-effect-level of 330 μg Se/day and an uncertainty factor of 1·3[13].

Case study: Selenoneine and Se status among Nunavimmiut

Inuit living in the Arctic have blood concentrations of Se that are among the highest in the world due to consumption of traditional country foods that are exceptionally replete in Se. (Table 1). Indeed, Inuit from Nunavik[9], Nunavut[45], and Greenland[46] have considerably higher whole blood Se concentrations than First Nations populations in southern Canada[47] and general populations in Canada[48], USA[49], and Europe.

Research involving Nunavimmiut (Inuit living in Nunavik, Québec) suggests a large portion of dietary Se is consumed as SeN, which is a major Se compound in RBCs in this population. Analyses on 881 blood samples collected during the *Qanuippitaa?* 2004 Nunavik Inuit Health Survey showed that SeN accounted for up to 92% of Se in red blood cells (geometric mean: 26%)[8]. Findings from this study also suggest Se intake is approximately 214 μg/day (range: 10–1973 μg/day) in a representative sample of Nunavimmiut based on food frequency questionnaire data[50] and using food Se concentrations derived from Navarro-Alarcon 2008[51] and Lemire *et al.* 2015[7]. Of all consumed foods, *mattaaq* (skin and underlying fat) derived from beluga whales, which is considered a delicacy by Inuit, is the richest source of total Se for Nunavimmiut[10]. Specifically, SeN accumulates in the skin layer and comprises the majority (median 54% in five samples) of Se found in beluga *mattaaq*[8]. Consumption of beluga *mattaaq* is strongly correlated with RBC SeN concentrations among Nunavimmiut[10]. Lesser amounts of Se (including SeN) are also found in other traditional marine foods, including walrus[52]. This dietary Se profile differs from reference populations in southern Canada[53,54], United States[55–57], Europe[58,59], New Zealand[60], and Australia[61], who obtain Se almost exclusively through purchased meats, eggs, and cereals and other crops grown in Se-containing soil. Due to the accumulation of SeN in RBCs, Inuit exhibit a non-linear relationship between plasma and whole blood Se, in which plasma Se levels plateau around approximately 200 μg/L[9,46]. This contrasts with inland populations in Amazonian Brazil[62], Malawi[63], and the United Kingdom[64], which exhibit a linear association between whole blood Se and plasma Se. Further, despite high whole blood Se, plasma Se and selenoproteins concentration among Inuit are in the normal ranges as reported elsewhere[9]. Such findings therefore underscore that Se speciation in food plays a role in the Se species present, as well as their distribution in blood fractions, in consumers.

A closer look at selenoneine: A unique Se species from the marine environment. Selenoneine (2-selenyl-*N*α,*N*α,*N*α-trimethyl-L-histidine or 3-(2-hydroseleno-1*H*-imidazol-5-yl)-2-(trimethylammonio) propanoate) is a selenoamino acid and

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Se-isologue to the sulfur-containing compound ergothioneine[65]. SeN was identified in 2010 in the blood of bluefin tuna at concentrations in the range of 5–40 μg Se/g. Despite this, following more than a decade of subsequent research, SeN has also been reported in different biological matrices of marine animal origin, including beluga whale *mattaaq*[8], dolphins[66], sea turtles[67], various fishes (e.g., swordfish, Pacific mackerel, sardines, and tilapia)[68], and seabirds[69], indicating trophic transfer through marine food webs. When found in animals, SeN is likely derived from the diet as only some fungi and bacteria synthesize ergothioneine and SeN[65,70,71]. Once consumed, SeN is transported across cell membranes by the ergothioneine transporter (ETT; formerly known as OCTN1), which is present in various tissues and organs[68]. In the bone marrow, uptake of SeN by maturing erythroid cells leads to SeN concentrating in red blood cells[72].

Selenoneine and human health. Researchers have raised questions about potential health implications of SeN in animals, including humans[10,73]. Such questions are particularly relevant to coastal populations that consume high amounts of marine foods, including Inuit living in northern Canada. As yet, however, relatively little is known about the chemistry and physiological functions of SeN.

SeN is one of several dietary Se species. The nutritional chemistry of Se is complex, and dietary Se compounds and their metabolites exhibit their own reactivity and biological activity. The metabolic pathways of the different forms of dietary Se and the relative abundance of Se metabolites are important to determine the overall health impacts of Se consumption (Fig. 1). Notably, as described above, hydrogen selenide (H_2Se) plays a central role in Se metabolism; most dietary Se is transformed to H_2Se before conversion to selenophosphate and incorporation into selenoproteins as Sec[74]. However, SeN does not follow the H_2Se metabolic pathway. Instead, SeN is distributed to organs and tissues via the ETT. In bone marrow, where the ETT is highly expressed, SeN is taken up by red blood cell precursors and incorporated into mature erythrocytes[68,72]. The physiological functions of SeN remain poorly elucidated. SeN has strong radical scavenging and antioxidant activity, and most researchers agree that this may be its primary function[12,68,75,76]. Indeed, it was shown to be more resistant to irreversible oxidative degradation compared to ergothioneine and engages in reversible oxidation and reduction reaction under conditions that irreversibly degrade ergothioneine[77]. SeN has furthermore been shown to bind to myoglobin and hemoglobin to prevent auto-oxidation of iron[68]. SeN crosses the blood-brain barrier[78] and a recent study showed that the SeN can accumulate in the brains of giant petrels[69]. Authors suggest that SeN may play a role in the protection and function of the central nervous system. Additional implications on mammalian health have been noted; for example, animal model and in vitro studies have shown that SeN inhibits tyrosinase in melanoma cells and melanocytes (potentially by chelating copper at the active site of the enzyme)[79], is protective against colorectal cancer in mice[80], may attenuate hepatocellular injury and hepatic steatosis[81], and has ACE-inhibiting activity[79].

Several metals, including lead, arsenic, cadmium, and Hg, form insoluble metal-selenide complexes in yeast, a reaction that may protect cells from both metal toxicity[82,83] and sodium selenide toxicity[84]. It is well recognized that Se can selectively bind with Hg and protect against MeHg toxicity, which is found in high concentrations at upper trophic levels of marine ecosystems[83]. Recent experimental and epidemiological research provides evidence for the potential of Se to mitigate the cardiovascular and neurotoxic effects of MeHg exposure in humans[85–91]. Following the discovery of SeN, several researchers have suggested that it may play a role in the detoxification of MeHg, possibly through demethylation of MeHg leading to the formation of stable inorganic mercury selenide (Hg-Se) complexes[8,73,92]. Palmer and colleagues (2015) speculate that SeN promotes MeHg-induced proteolytic cleavage of Hg-C bonds, thereby demethylating MeHg prior to Hg-Se precipitation[92]. Stable inorganic mercury selenide (Hg-Se) complexes are found to accumulate over time in the livers of marine birds and marine mammals, as well as in the brains of humans exposed to high levels of MeHg[83,93,94], indicating that demethylation mediated by SeN or other forms of Se occurs *in vivo* and may simultaneously reduce metal toxicity and functional availability of Se. Indeed, studies on zebrafish embryos showed reduced MeHg accumulation and toxicity in the presence of SeN[73]. It is likely that such mechanisms have bearing on human health. Among Nunavummiut (Inuit living in Nunavut) and Nunavimmiut, high whole blood Se status (a large portion of which was likely SeN) exhibited a protective effect against the adverse cardiovascular health effects of high MeHg exposure[85,95], suggesting that Se-mediated detoxification of MeHg may occur in humans. This is particularly relevant due to the elevated exposure of Inuit populations to MeHg through their traditional dietary staples, including marine mammals and predatory fish species[7].

Overall, current research paints an incomplete picture of the physiological functions and health implications of SeN. Despite growing interest in recent years, further biological assessment of SeN has been hampered by the absence of a commercial source[12]. However, as mentioned, an important observation of the research to date is that SeN does not appear to contribute to the pool of H_2Se for selenoprotein synthesis. Incubating cells with SeN causes no effect on GPX or SELENOP despite cells rapidly taking up the compound[96]. By contrast, incubation with reference selenium compounds selenite and selenomethionine induce increased activity of selenoproteins[97]. We can therefore conclude that SeN metabolism, biological function, nutritional essentiality, and toxicity differ from those of SeMet, Sec, and other better-understood Se species that are metabolized through the H_2Se cycle. Furthermore, current evidence suggests that SeN is less toxic than other forms of Se[70]. Drobyshev and colleagues (2023) demonstrated that SeN causes no toxic effects up to 100 μM concentration in hepatocytes and capillary endothelial cells[96]. Such findings add evidence to the suspicions of previous authors, including Yamashita *et al.*, (2010), who posited that SeN has limited toxicity in their paper describing the discovery of SeN[10,65]. Thus, individuals consuming a high percentage of Se as SeN may not experience the same detrimental health effects as populations consuming high

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amounts of SeMet, Sec, selenite, and selenate, despite high total Se intake and high whole blood total Se. Conversely, populations consuming the majority of their dietary Se as SeN may need to ensure they have other dietary sources of Se to ensure adequate selenoprotein synthesis and activity.

The flaws of current Se recommendations for Inuit populations living in Canada

Dietary Se guidelines and information sheets often refer to dietary reference intakes established by the Institute of Medicine, with the goal of preventing overt signs of deficiency and excess[36]. Under Health Canada's Chemicals Management Plan, which aims to assess and manage chemicals to "protect the health of Canadians and the environment", the Government of Canada has published an assessment of Se and its compounds[98]. As a part of this assessment, Health Canada prepared and distributed an overview of information on Se focused on North and Northern communities, which notes that "Se can be harmful to human health at levels above what the body needs to function" and "blood levels of selenium above the international guidance level (i.e. 480 microgram/L) have been measured in up to 28% of Inuit" (Health Canada, Information on Selenium in the North, 2018, personal communication). Notably, however, these assessments and communication contain no reference to SeN, which comprises one of the primary species of dietary Se among Nunavimmiut and likely all Inuit living in northern Canada.

The continued failure to disaggregate Se species in research, dietary guidelines, and communications about Se is problematic and may lead to unnecessary concern about selenosis among Inuit populations. This trend is reflected in the fact that RDAs and ULs apply to *total* Se intake, thereby overlooking dietary Se speciation and disregarding the varied functions of dietary Se compounds and metabolites[3]. The RDAs developed by the IOM are based on only two experimental studies – one conducted by Yang and colleagues (1987) in China[23], and one conducted by Duffield and colleagues (1999) in New Zealand[21]. These foundational studies have limited external validity due to their small sample sizes, interventions that comprised only one Se species (SeMet) or unquantified Se species, and a limited number of female, youth, and elderly participants. Such limitations minimize the generalizability of findings to other global populations, including Inuit in northern Canada, for whom SeMet is not the primary form of dietary Se. Further, studies that informed the development of RDAs used GPX activity as an indicator of Se sufficiency[21,23]. A major limitation of this approach is that, despite their contributions to total dietary Se intake, SeN accumulates in RBCs and has little bearing on plasma Se or selenoprotein synthesis or activity, as stated earlier. Indeed, evidence suggests that Inuit populations exhibit normal levels of selenoproteins despite very high total Se intake and RBC Se status[9].

Similarly, ULs promoted by the IOM are based on two observational studies – one conducted by Yang and colleagues (1994) in Enshi, China[42], and another conducted in western United States[44]. These studies were once again limited in their external validity due to small sample sizes and unspecified Se species and exposure routes, thereby limiting their relevance in determining ULs for Inuit populations. The recent systematic review and scientific opinion published by the EFSA NDA recommended lowering the UL from 300 to 255 µg Se/day. While this review recognized the existence of SeN in marine foods, their risk assessment failed to consider dietary Se speciation in establishing ULs.

Despite very high dietary intake of Se (often exceeding ULs promoted by the IOM and EFSA NDA) and whole blood Se concentration, Inuit populations in Nunavut[95], Nunavik[9], and Greenland[46] exhibit little evidence of selenosis. Since marine food consumption has declined rapidly following colonial policies enforced by the Government of Canada (e.g., forced settlement and introduction of retail foods)[99], it is reasonable to assume that SeN intake was considerably higher prior to colonial contact. Although data do not exist prior to 1992, there is no historical record of selenosis (or symptoms thereof) among Inuit. It is likely that dietary Se speciation accounts for variations in perceived tolerances of total Se intake between populations. For example, it has been shown that selenite ingestion leads to excess at much lower doses compared to SeMet[25], while SeN appears to be a non-toxic form of Se, as previously mentioned[68]. Overall, this research suggests that current DRIs and recommendations on Se are not relevant for Inuit populations, and future risk assessments and communications regarding Se exposure in northern Canada need to be cognizant of dietary intake of SeN in combination with other Se species.

Future directions for research and risk assessment incorporating evidence on SeN

There remain several gaps in our understanding of SeN. First, little is known regarding the natural synthesis and origins of SeN in the marine food chain. Ergothioneine, the sulfur analogue of SeN, is synthesized by bacteria and fungi but not plants or animals[100], and researchers have speculated that the same is true of SeN[71]. Recently, Kayrouz *et al.* (2022) used a genome-mining strategy to identify a three-gene cluster that encodes a dedicated enzymatic pathway for producing selenoneine in bacteria, disproving prior theories that selenoneine is synthesized due to non-specific incorporation of Se during ergothioneine production[71]. Since animals do not synthesize SeN, marine species exhibiting high concentrations of SeN (e.g., beluga whales and tuna) likely obtain SeN through dietary sources or through their microbiome[8], however additional research is necessary to identify and confirm natural sources of SeN. Furthermore, given the emerging nature of evidence on SeN, there is a need for research on SeN kinetics, metabolic pathways, biological functions, and health implications to appropriately assess the benefits and potential risks of SeN consumption. Such research must consider Se and SeN bioavailability and metabolism vis-à-vis consumption of metallic elements, including MeHg. It is also imperative that researchers, health practitioners, and public health agencies work together to identify and appropriately deploy relevant and appropriate biomarkers of Se status. In particular, whole blood Se concentration may be a poor measure of Se adequacy for selenoprotein function, considering SeN accumulates in red blood cells but does not serve as a Se reservoir for selenoprotein

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synthesis. Researchers should instead measure plasma Se and selenoproteins (e.g., SELENOP concentration and GPX activity) as biomarkers of Se functional sufficiency. Meanwhile, there is a need for more widespread measurement of SeN levels among humans to determine the concentrations and distribution of this compound across global populations. Recent advances in SeN analytical methods published by Achouba and colleagues (2023) should make this process more accessible, sensitive, specific, precise, and cost effective[101].

It is important to recognize the value of traditional country foods of marine origin, which are often high in Se, to the cultural integrity and food basket of Inuit populations. This recognition must permeate all research and public health messaging that occur with Inuit populations in northern Canada. Above all, country foods play an integral role in Inuit life by providing a spiritual connection to the land[102] and improving nutritional status[103,104], food security[105], and mental health[102,106]. Thus, it is important to recognize the dangers of endorsing and disseminating existing ULs for Se, as such actions may exacerbate current fears surrounding the consumption of country foods that have arisen due to zoonotic diseases (e.g., *Giardia* spp., *Trichinella* spp., *Toxoplasma gondii,* etc.) and environmental contaminants (e.g., MeHg and persistent organic pollutants, among others)[107,108]. Given the significance of country foods to Inuit populations, we must be careful to not discourage country food consumption due to its importance for food security and nutrition[7]. It is therefore crucial to provide the best evidence on Se and SeN to local public health practitioners and clinicians (including physicians and midwives) to help them promote country foods while minimizing the risk of exposure to harmful contaminants when designing and implementing public health education and clinical recommendations on environmental contaminants, Se, and other country food nutrients among Inuit populations.

While this case study has focused primarily on the Inuit populations, our arguments likely have broader relevance. SeN is found in high concentrations in many marine animals that serve as staple food sources for populations globally. Marine foods are especially crucial to the food security, nutrition, and cultural traditions of coastal populations, including coastal Indigenous populations[109]. For example, SeN has been also identified as a major Se compound found in the blood of human populations consuming large amounts of marine foods in northern Japan[10,70]. Although population-level analyses of blood SeN concentrations are extremely limited, we posit that SeN may comprise a large fraction of whole blood Se in coastal populations around the globe. As such, the evidence reviewed in this manuscript, and the arguments emerging therefrom, may be broadly applicable to coastal populations globally. There is a need for additional research on Se status, Se adequacy, and SeN sources and whole blood concentrations in understudied coastal populations. Following this, there is a need to incorporate such evidence into our existing body of research, DRIs, and public health guidance regarding Se to reflect the presence of SeN in foods and human populations. As a further complication, SeN and MeHg often occur in high concentrations in the same marine foods (e.g., Lemire *et al.* 2015[7]) and are highly correlated in human populations (e.g., Achouba *et al.* 2019[8]). Such evidence must comprise an important component of any risk assessment and public health strategy on Se.

Conclusion

In recent years, there have been substantial advancements in the study of different chemical forms of Se in food sources and tissues. The recent discovery of SeN, a selenoamino acid and Se-isologue to the sulfur-containing compound ergothioneine that accumulates in red blood cells, underscores the importance of Se speciation in research, risk assessment, and dietary reference intakes. In this article, we have argued a case to evaluate and reconsider the relevance of public health recommendations on Se with a special focus on Inuit in northern Canada, who consume a large portion of their dietary Se as SeN. Our arguments may have relevance for other populations who consume marine diets high in SeN. Since SeN does not appear to be as toxic as other dietary Se species and does not contribute to synthesis of selenoproteins, it is important to consider nuanced dietary and public health guidelines for Se that are responsive to emerging evidence. While selenoneine has limited relevance to Se metabolism involving synthesis of selenoproteins, there is a need for further research on the health implications of this compound, including its potential to serve as a strong dietary antioxidant and detoxifying agent for methylmercury.

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Competing interests

The authors declare none.

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Authorship

Matthew Little: Conceptualization, Data curation, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing Adel Achouba: Conceptualization, Writing – review & editing Mélanie Lemire: Conceptualization, Data curation, Formal analysis, Writing – review & editing Pierre Ayotte: Conceptualization, Data curation, Formal analysis, Writing – review & editing. All authors read and approved the final manuscript.

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