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Review

Recent progress on our understanding of the biological effects of mercury in fish and wildlife in the Canadian Arctic

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HIGHLIGHTS

- Hg levels in some fish and wildlife exceed thresholds for biological effects.
- Direct evidence of potential Hg effects in Arctic wildlife is inconclusive.
- Strong Hg-Se associations have been found in tissues of Arctic mammals and birds.
- More studies are needed to clarify the effects of Hg on Arctic fish and wildlife.
- Further research is needed on the protective role of selenium against Hg toxicity.

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ABSTRACT

This review summarizes our current state of knowledge regarding the potential biological effects of mercury (Hg) exposure on fish and wildlife in the Canadian Arctic. Although Hg in most freshwater fish from northern Canada was not sufficiently elevated to be of concern, a few lakes in the Northwest Territories and Nunavut contained fish of certain species (e.g. northern pike, Arctic char) whose muscle Hg concentrations exceeded an estimated threshold range (0.5–1.0 μg g^{-1} wet weight) within which adverse biological effects begin to occur. Marine fish species generally had substantially lower Hg concentrations than freshwater fish; but the Greenland shark, a long-lived predatory species, had mean muscle Hg concentrations exceeding the threshold range for possible effects on health or reproduction. An examination of recent egg Hg concentrations for marine birds from the Canadian Arctic indicated that mean Hg concentration in ivory gulls from Seymour Island fell within the threshold range associated with adverse effects on reproduction in birds. Mercury concentrations in brain tissue of beluga whales and polar bears were generally lower than levels associated with neurotoxicity in mammals, but were sometimes high enough to cause subtle neurochemical changes that can precede overt neurotoxicity. Harbour seals from western Hudson Bay had elevated mean liver Hg concentrations along with comparatively high muscle Hg concentrations indicating potential health effects from methylmercury (MeHg) exposure on this subpopulation. Because current information is generally insufficient to determine with confidence whether Hg exposure is impacting the health of specific fish or wildlife populations in the Canadian Arctic, biological effects studies should comprise a major focus of future Hg research in the Canadian Arctic. Additionally, studies on cellular interactions between Hg and selenium (Se) are required to better account for potential protective effects of Se on Hg toxicity, especially in large predatory Arctic fish, birds, and mammals.

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Contents

1. Introduction

From an environmental toxicology perspective, methylmercury (MeHg) is the most important of the different chemical forms of Hg. Methylmercury biomagnifies through food chains, is very efficiently absorbed from the diet, distributes into many organs of the body including the brain, and is highly toxic. The toxic effects of MeHg in wildlife have been reported and scientifically studied for over 50 years, during which time much has been learned about its food chain transfer, metabolism, and toxicity (Wiener et al., 2003). In recent years, increasingly subtle but important biological effects have been documented, including behavioural, neurochemical, hormonal, and reproductive changes in predatory fish and wildlife exposed to environmentally relevant levels of MeHg (Scheuhammer et al., 2007, 2012). Potential population-level impacts are now being assessed for some species, such as the common loon (*Gavia immer*) (Burgess and Meyer, 2008). However, there is a general paucity of information regarding the effects of MeHg exposure in Arctic wildlife species.

Because MeHg biomagnifies through food webs, it is generally agreed that top predatory animals, particularly those linked to aquatic food chains, are at greatest risk for increased dietary MeHg exposure and potential Hg-related health effects (Wiener et al., 2003). In the Arctic, species at greatest risk include polar bears (*Ursus maritimus*), seals, toothed whales, various predatory seabirds, and large piscivorous fish such as lake trout (*Salvelinus namaycush*), northern pike (*Esox lucius*), and sharks. Conversely, Hg levels are generally far below those required to cause toxic effects in lower trophic level animals; and in most Arctic terrestrial animals not associated with aquatic food webs. Although there is evidence to suggest that non-aquatic birds, such as some forest passerine species, can experience elevated dietary MeHg exposure in sites near Hg-contaminated waterways (Brasso and Cristol, 2008; Cristol et al., 2008), similar scenarios are less likely to occur in the Canadian Arctic where large-scale industrial activity is less prevalent. Data on Hg in insectivorous passerines in the Arctic are currently lacking, but concentrations in other terrestrial avian species are low compared to aquatic predatory species.

For the last decade, the Canadian Government's Northern Contaminants Program (NCP) has funded research to investigate biological effects of mercury in the Canadian Arctic. Using information collected from NCP-funded research as well as other literature sources, we review and assess recent Hg exposure in freshwater and marine species, and summarize findings from recent studies that have begun to investigate potential toxic effects of Hg in Arctic wildlife. An emphasis is placed on geographically-linked information specific to Canada, which

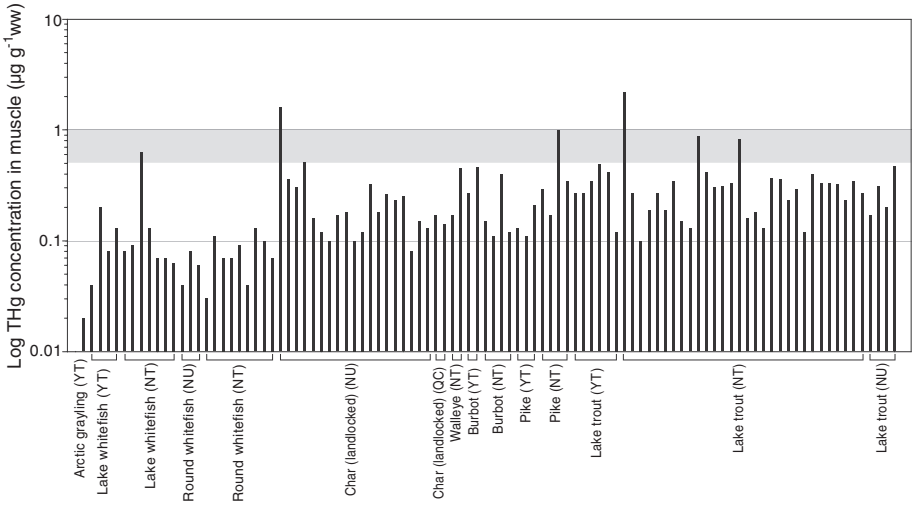

Fig. 1. Mean concentrations of total Hg (THg) in muscle of selected freshwater fish species from various Canadian Arctic lakes (NT = Northwest Territories; NU = Nunavut; YT = Yukon Territory; The shaded area represents an estimated threshold range for fish toxicity based on assessments by Sandheinrich and Wiener (2011) and Dillon et al. (2010). Data plotted are from Depew et al. (2013).

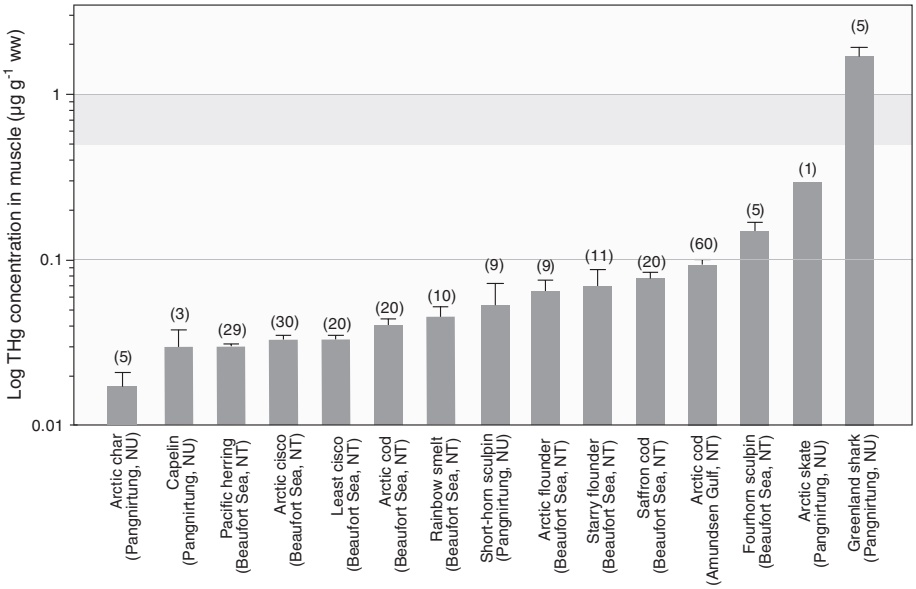

Fig. 2. Mean concentrations (±SE) of total Hg (THg) in muscle of selected marine fish species from various Canadian Arctic locations. (NT = Northwest Territories; NU = Nunavut; YT = Yukon Territory. Bracketed values are sample sizes. The shaded area represents an estimated threshold range for freshwater fish toxicity based on assessments by Sandheinrich and Wiener (2011) and Dillon et al. (2010). Data are from Loseto et al. (2008) for fourhorn sculpin (*Myoxocephalus quadricornis*), least cisco (*Coregonus sardinella*), Pacific herring (*Clupea palasii*), rainbow smelt (*Osmerus mordax*), saffron cod (*Eliginus gracillis*), and starry flounder (*Platichthys stellatus*); and from McMeans et al. (in this issue) for capelin (*Mallotus villosus*), shorthorn sculpin (*Myoxocephalus scorpius*), and Greenland shark (*Somniosus microcephalus*). For graphical purposes, dry weight data from Loseto et al. (2008) were converted to wet weight based on an estimate of 75% water content for fish muscle.

complements a recent more generalized review of biological effects for the circumpolar Arctic (Dietz et al., 2013).

2. Mercury effects studies

2.1. Freshwater and marine fish

Studies published within the last decade have documented a range of toxic effects in fish at environmentally relevant levels of MeHg exposure. In a critical review of the recent literature, Sandheinrich and Wiener (2011) concluded that changes in biochemical processes, damage to cells and tissues, and reduced reproduction in fish begin to occur at concentrations of about 0.5–1.0 µg Hg g^{-1} wet weight (ww) in axial muscle (>90% of Hg in muscle is MeHg). Similarly, Dillon et al. (2010) conducted an assessment of numerous fish toxicology studies and estimated with a mathematical model a lowest observable adverse effects level (LOAEL) of about 0.3 µg Hg g^{-1} ww in the whole body of fish—or about 0.5 µg Hg g^{-1} ww in axial muscle. Using 0.5–1.0 µg Hg g^{-1} ww in axial muscle as an estimated LOAEL range for fish, it is apparent that lake-averaged total Hg concentrations in northern Canadian freshwater fish species sampled since 2002 seldom enter or exceed this range (Fig. 1). However, average Hg concentrations in landlocked char from Amituk Lake on Cornwallis Island and lake trout from Cli Lake in the Northwest Territories clearly exceeded the suggested threshold range. Preliminary research has revealed increasing cell damage (necrosis) with increasing Hg concentrations in livers of char from Amituk Lake (Drevnick, 2013).

Concentrations were within the suggested threshold range for landlocked char from Char Lake (Nunavut), as well as for other fish species in several lakes in the Northwest Territories, specifically northern pike and whitefish from Narrow Lake, and lake trout from Kelly Lake and Lac Ste. Therese. A larger, older database of Arctic fish Hg levels from 1971 to 2001 (Lockhart et al., 2005a) showed that length-adjusted mean Hg concentrations in highly predatory species – lake trout, walleye (*Sander vitreus*), northern pike and burbot (*Lota lota*) – exceeded 0.5 µg g^{-1} in < 25% of the survey lakes (n = 29–94 lakes per species). Research is warranted to study possible reproductive or other toxic effects of Hg in fish in Arctic lakes where LOAEL thresholds are exceeded.

Consistent with fish data reported in Dietz et al. (2013) for the circumpolar Arctic, muscle Hg concentrations in many common marine fish in Canadian waters tend to be substantially lower than in freshwater fish. As shown in Fig. 2, mean muscle Hg levels in most marine fish species from the Canadian Arctic were many-fold lower than the suggested LOAEL range. The single exception was the Greenland shark (*Somniosus microcephalus*), a large long-lived predatory species for which greater bioaccumulation and thus higher Hg concentrations are expected. Based on elevated muscle Hg concentrations, studies are warranted to investigate possible toxic effects of Hg in sharks and other large carnivorous marine fish species in the Canadian Arctic.

2.2. Marine birds

2.2.1. Reproduction

Tartu et al. (2013) reported that increasing blood Hg concentrations in black-legged kittiwakes (*Rissa tridactyla*) from Svalbard were related to a higher likelihood of skipped breeding, and abnormal reproductive hormone responses; but in general, few Hg effects studies have been undertaken on Arctic bird species. However, recent research on common loons serves to illustrate the kinds of population-level effects that environmentally relevant exposures to MeHg can have on wild fish-eating birds. A strong positive relationship between female blood Hg and egg Hg concentrations was used to demonstrate a link between blood Hg and various adverse reproductive effects in common loons (Evers et al., 2003). By integrating this and other relationships into a population matrix model, Evers et al. (2008) were able to effectively predict and identify North American loon populations that are experiencing reduced fledging success associated with elevated MeHg exposure. In Maine and New Hampshire, MeHg toxicity was the main factor associated with a 41% decline in average reproductive success over an 11-year period, with a Hg LOAEL identified as 3.0 µg g^{-1} (ww) in blood (Evers et al., 2008; Scheuhammer et al., 2012). Based on comparable findings from two parallel studies using similar field protocols in New England (Evers et al., 2008), and in Wisconsin and the Canadian

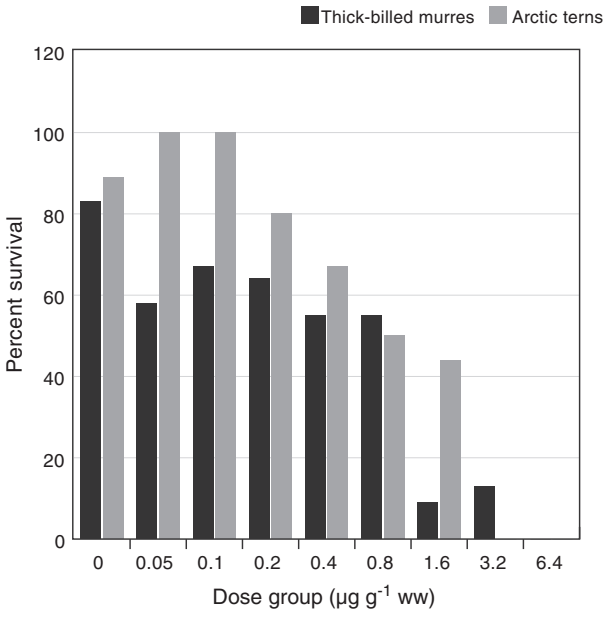

Fig. 3. Percent survival to 90% of embryo development of thick-billed murre and Arctic tern eggs dosed with methylmercury (CH_3HgCl) at 0.05–6.4 µg g^{-1} ww (Braune et al., 2012). Dose group concentrations are not corrected for maternally deposited Hg. For each species, 12 eggs were tested per dose group. The control eggs were injected with Hg-free safflower oil.

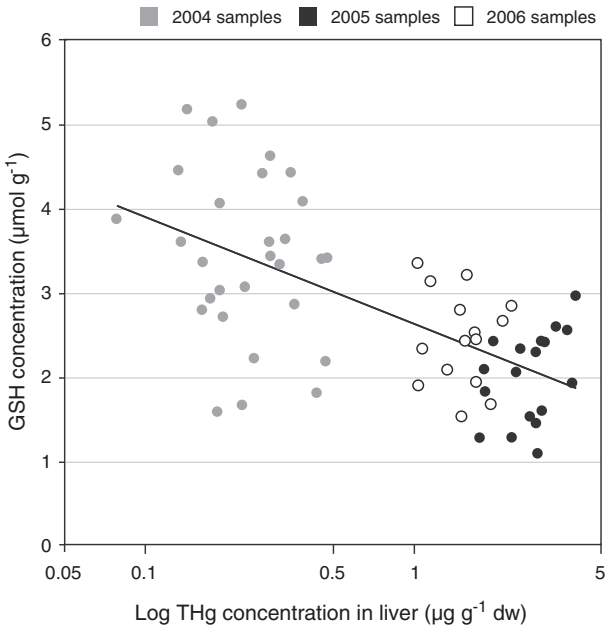

Fig. 4. Relationship between log-transformed hepatic total Hg (THg) and reduced glutathione (GSH) concentrations in glaucous gull chicks from two sites (Karak Lake, Nunavut; and Devil Island) in the Canadian Arctic ($r^2 = 0.32$, $p < 0.001$). Hepatic GSH concentrations were adjusted to a common measurement of body size and the relationship is shown across all years (source: Wayland et al., 2010).

Maritimes (Burgess and Meyer, 2008), maximum productivity for breeding loon pairs declined by at least 50% when whole-body concentrations of Hg in prey fish exceeded about 0.2 µg g^{-1} ww.

Dietary MeHg is efficiently transferred to avian eggs in a dose-dependent manner, and reproduction is one of the most sensitive endpoints of Hg toxicity in birds (Wolfe et al., 1998). Nearly 100% of the Hg transferred to eggs is in the form of MeHg with the majority (about 85–95%) deposited into the albumen (Wiener et al., 2003). Mercury concentrations found in the egg are a good indicator of Hg risk to avian reproduction (Wolfe et al., 1998). Some of the documented effects of MeHg on avian reproduction leading to substantial overall reductions in productivity include aberrant reproductive behaviour, reduced clutch sizes, increased rates of embryonic deformity and mortality, and reduced hatchability (Thompson, 1996; Wolfe et al., 1998). Dietary MeHg exposure, insufficient to cause obvious signs of Hg toxicity in adults, can decrease reproductive success by 35–50% in birds (Wolfe et al., 1998).

Embryotoxic thresholds for Hg have been determined for a limited number of species—primarily from captive breeding studies – and are often applied generically to all avian species. However, Heinz et al. (2009) showed that there are significant interspecies differences in sensitivity to the embryotoxic effects of MeHg injected into fertile eggs. Using estimated median lethal concentrations (LC_{50}) for 26 tested species, Heinz et al. (2009) grouped the sensitivity of avian embryos to MeHg into three categories with LC_{50} values ranging from ≥ 1 µg g^{-1} ww in eggs of the low sensitivity group (e.g., Canada goose, hooded merganser, laughing gull, double-crested cormorant) to < 0.25 µg g^{-1} ww in eggs of those species exhibiting the highest sensitivity (e.g., American kestrel, osprey, snowy egret, tri-coloured heron). Species, such as common, royal, and Caspian terns, as well as herring gulls, were categorized as having medium sensitivity to MeHg based on a calculated LC_{50} ranging between 0.25 and 1 µg g^{-1} ww of Hg.

Using the egg-dosing protocol developed by Heinz et al. (2006), eggs of thick-billed murres and Arctic terns collected from the High Arctic were brought into the laboratory and injected with a range of environmentally relevant concentrations (0–6.4 µg g^{-1} ww) of MeHg chloride (MeHgCl) to determine the relative sensitivity of the developing embryos to MeHg (Braune et al., 2012). Roughly half of the murre eggs (48%) and tern eggs (62%) reached the chosen endpoint of at least 90% development. To compare the murre and tern data with the results for 26 species reported by Heinz et al. (2009), the median lethal concentration (LC_{50}) and 95% confidence intervals (CI) for each species were determined, with the survival data corrected for control mortality (Braune et al., 2012). The LC_{50} for the murre embryos was 0.48 µg g^{-1} ww (95% CI: 0.26–0.99) based on MeHg injected into eggs uncorrected for maternally deposited MeHg; whereas for the tern embryos, the LC_{50} was 0.95 µg g^{-1} ww (95% CI: 0.59–1.58) (Fig. 3). The wide 95% confidence intervals for the LC_{50} estimates suggest a lack of power in these tests. Nonetheless, based on these LC_{50} estimates, both the Arctic tern and thick-billed murre embryos would be categorized as having medium sensitivity to MeHg according to the sensitivity categories suggested by Heinz et al. (2009). This estimate places the Arctic tern in the same sensitivity category as three other tern species—common, royal, Caspian—included in the study by Heinz et al. (2009).

2.2.2. Neurochemical receptors

Concentrations of receptors in the brain for neurotransmitters such as acetylcholine (muscarinic [mACh] receptor) and glutamate (N-methyl-D-aspartic acid [NMDA] receptor), can be significantly altered by low-level dietary exposure to MeHg in adult birds and mammals. Thus, specific neurochemical changes may potentially be used as biomarkers of MeHg exposure and effects in wildlife (Basu et al., 2006, 2007a; Scheuhammer et al., 2008). However, Braune et al. (2012) found no significant correlation between Hg concentration and density of either NMDA or mACh neuroreceptors in brain tissue from thick-billed murre and Arctic tern embryos (Hg concentrations: 0–3.2 µg g^{-1} ww for the murre embryos and 0–1.6 µg g^{-1} ww for the tern embryos). Reasons for this apparent lack of response of embryonic neuroreceptors to Hg exposure *in ovo* are currently unknown.

2.2.3. Oxidative stress

Exposure to contaminants, including MeHg, can lead to oxidative stress in wildlife, where the presence of excessive reactive oxygen species results in cellular damage (Hoffman et al., 2011; Kenow et al., 2008). Glutathione (GSH) is an important low molecular weight

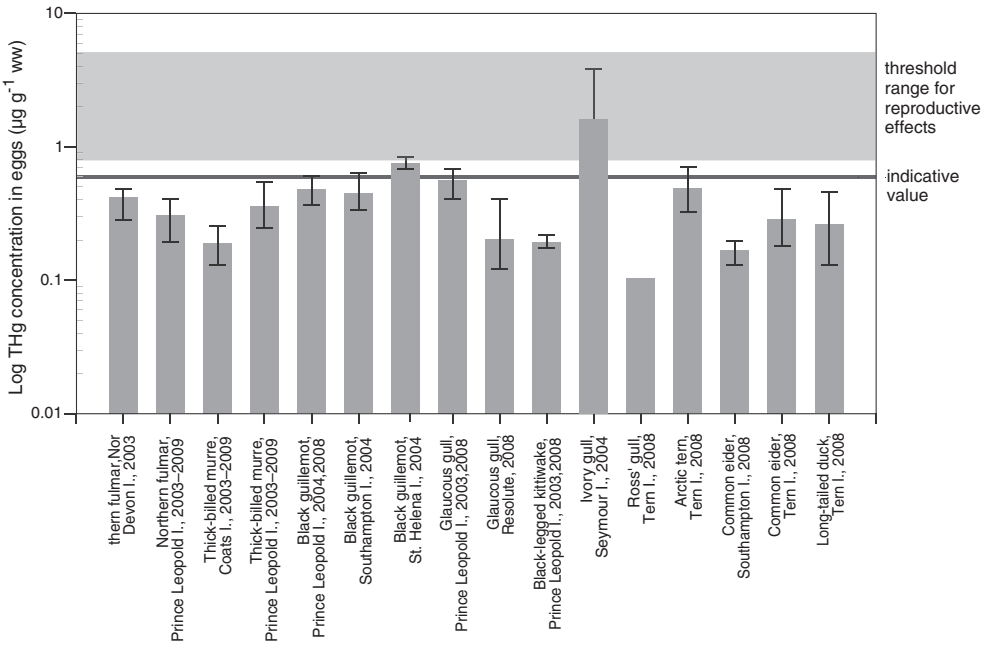

Fig. 5. Mean concentrations and range bars of total Hg (THg) in marine bird eggs from the Canadian Arctic (data from Scheuhammer et al., 2013). The threshold range of THg concentrations associated with adverse effects on reproduction (indicated by the grey bar) is based on an evaluation of published studies for a variety of non-marine bird species (Shore et al., 2011). The *indicative value* (dark horizontal line) is defined as the egg THg concentration below which 95% of species are protected against Hg-induced reproductive toxicity (Shore et al., 2011).

tripeptide involved in protecting cells from oxidative stress. A reduction in levels of the reduced form (GSH) and an increase in oxidized glutathione (GSSG) have been interpreted as indicators of greater risk for biological damage from oxidative stress (Hoffman et al., 2002). Wild diving ducks with higher liver Hg concentrations also had higher GSSG:GSH ratios (Hoffman et al., 1998). Although no critical ratio of GSSG:GSH has been proposed as an unequivocal indicator of oxidative damage, Hoffman (2002) suggested that significant elevations of this ratio in contaminant-exposed animals, compared with unexposed or reference animals, are indicative of oxidative stress, including an increased risk of cellular lipid peroxidation. Wayland et al. (2010) examined relationships between total Hg levels and indicators of oxidative stress in livers of nestling glaucous gulls at Karrak Lake (Nunavut) in the Queen Maud Gulf Bird Sanctuary, and on Devil Island. Results indicated that hepatic Hg levels were relatively low (0.1–4 µg g^{-1} dry weight [dw]) compared with lower-latitude field studies reporting on Hg exposure and oxidative stress in birds. In Arctic glaucous gull chicks, liver concentrations of both reduced GSH and oxidized GSSG were negatively

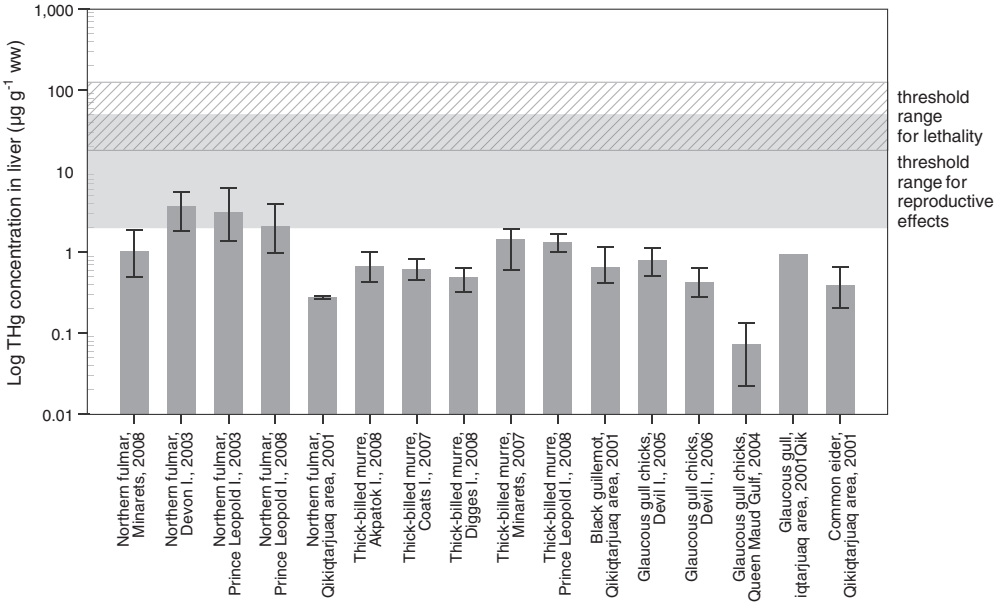

Fig. 6. Mean concentrations and range bars of total Hg (THg) in marine bird livers from the Canadian Arctic (data from Scheuhammer et al., 2013). The range of threshold THg concentrations associated with adverse effects on reproduction (indicated by the grey bar) and range of thresholds associated with lethality (indicated by diagonal lines) are based on evaluations of published studies for non-marine birds (Shore et al., 2011). It should be noted that implicit in the concept of a toxic threshold concentration in liver is the notion that most of the liver Hg is present as methylmercury (MeHg). However, this assumption may be incorrect, especially for older individuals for which a larger proportion of total Hg may be present as inorganic Hg bound to Se.

correlated with Hg concentrations (Fig. 4). This pattern was unexpected because decreased GSH is typically accompanied by increased GSSG, which is diagnostic of oxidative stress. Wayland et al. (2010) suggested that the observed decrease in both GSH and GSSG may have resulted from a low availability of dietary precursor compounds such as cysteine or glutamate, a situation that could potentially occur if the animals were food-stressed. This explanation is consistent with measured levels of thiols (protein-bound and total sulfhydryls) in the gull livers, which were negatively correlated with Hg concentrations. In addition, as suggested by a positive correlation between hepatic concentrations of Hg and thiobarbituric acid-reactive substances, Hg-related oxidative stress in birds from Devil Island may have been high enough to cause increased lipid peroxidation. However, overall evidence for a shift in cellular status to a more oxidized state – decreased GSH, increased GSSG, or elevated GSSG:GSH ratio—was weak, leading to the conclusion that the glaucous gull nestlings at the two colonies were exposed to lower levels of oxidative stress than birds in more highly contaminated environments.

2.2.4. Comparisons with Hg toxicity thresholds

Recent egg Hg concentrations for marine birds from the Canadian Arctic were compared with suggested avian egg toxicity values of 0.6 μg g^{-1} ww (proposed as an *indicative value* that is protective for most avian species; toxic effects for any species are improbable below this level), and 0.8–5.1 μg g^{-1} ww (a range within which adverse effects on reproduction begin to occur in various studied avian species) (Shore et al., 2011). These estimated thresholds are based on a recent evaluation of published field and laboratory studies for non-marine birds (Shore et al., 2011) and are applied here because no evaluation of Hg threshold concentrations in eggs is available specifically for Arctic marine birds. Only the mean egg Hg concentration for ivory gulls from Seymour Island exceeded the proposed indicative value (0.6 μg g^{-1} ww), and entered the threshold range of concentrations that are associated with adverse effects on reproduction (Fig. 5). Additional research to assess possible Hg-associated reproductive effects in this species is thus warranted. Some individual egg Hg values reported for black guillemots, glaucous gulls, and Arctic terns also exceeded the proposed indicative value (Fig. 5).

Liver Hg concentrations of Arctic marine birds were also compared to toxicity thresholds derived by Shore et al. (2011) for adverse effects on reproduction (2–52 μg g^{-1} ww) and lethality (18.4–127 μg g^{-1} ww) in non-marine birds. Levels of Hg in some of the northern fulmars exceeded the minimum liver threshold for potential adverse effects on reproduction. However, all measured liver levels were well below the threshold range for lethality (Fig. 6).

It should be noted that adverse-effects thresholds based on total Hg concentrations in liver implicitly assume that the relative concentrations of different major chemical forms of Hg present in the tissue is largely unimportant—an assumption that is probably not valid especially for long-lived species for which substantial proportions of liver Hg may be present as a non-toxic complex of inorganic Hg associated with Se (see section on Mercury-Selenium Interactions).

In their reviews of the published literature, Thompson (1996) and Burger et al. (2009) suggested that seabirds may be able to tolerate higher Hg exposure than birds that feed in other environments, and that pelagic seabirds have yet to be exposed to sufficiently high burdens of Hg to induce measurable effects on reproduction or survival, even though they often exhibit much higher tissue Hg concentrations than more terrestrial birds. However, there is little empirical evidence that seabirds differ fundamentally from other birds with respect to the metabolism of MeHg, or in their sensitivity to MeHg. If seabirds are indeed less sensitive to MeHg exposure, this may be related to more efficient demethylation of MeHg in these species. However, this is largely a speculative statement rather than one based on direct evidence. Although the capacity for demethylation does appear to vary among bird species (Eagles-Smith et al., 2009; Kim et al., 1996), there is no published evidence that seabirds demethylate MeHg more efficiently than other species. Indeed, common loons, which could be considered to be seabirds during the wintering season when they primarily occupy marine habitats, showed less apparent demethylation of MeHg in their brains than bald eagles (Scheuhammer et al., 2008). Further, breeding bald eagles feeding in freshwater lakes and rivers experienced greater Hg exposure than those feeding in marine or estuarine areas (Evers et al., 2005), and common marine fish species often have lower Hg concentrations than freshwater species (see Figs. 1 and 2). This indicates that marine environments may not pose as great a risk for dietary MeHg exposure in fish-eating birds as some freshwater environments, especially Hg sensitive environments where hydrologic and chemical conditions favour microbial Hg methylation and biomagnification.

Numerous bird species that breed in Canada are experiencing population declines. The ivory gull has been listed as *endangered* and the Ross's gull has been listed as *threatened* in Canada (COSEWIC, 2010). Both species are associated with polar environments, and the Ross's gull is the rarest breeding gull in North America (Mallory et al., 2006). There are reports that Arctic tern populations may also be experiencing declines (Hatch, 2002). The Hg concentration recorded for a single salvaged Ross's gull egg was relatively low; however, egg Hg levels for ivory gulls and Arctic terns were high relative to other species (Fig. 5). Although there is no conclusive evidence to date that Hg exposure is resulting in adverse biological effects in marine birds in the Canadian Arctic, it is generally acknowledged that it is often difficult to attribute population-level impacts to single specific factors and that a multiple-stressor approach may be more appropriate (Burger and Gochfeld, 2002; Letcher et al., 2010). Additional research is needed to determine if, and to what extent, MeHg exposure, possibly combined with other stressors such as climate change, is affecting ivory gull populations, or other Arctic marine bird populations.

2.3. Marine mammals

2.3.1. Neurotoxicity

The central and peripheral nervous systems are generally considered primary targets for MeHg toxicity because MeHg is efficiently absorbed from the diet and can readily pass the blood–brain barrier (Aschner and Aschner, 1990). Characteristic lesions of MeHg poisoning in mammals include structural degeneration of the occipital cortex and the cerebellum, as well as degeneration of spinal cord and peripheral nerve fibers leading to ataxia (loss of coordination and balance), weakness, tremors, convulsions, sensory impairment, and ultimately death (Heinz, 1996; Wiener et al., 2003).

Mercury toxicity thresholds in brain tissue have not been specifically determined for most species of environmentally exposed wildlife and certainly not for Arctic species. However, a review of several published studies provides a range of total Hg and/or MeHg concentrations in brain tissue that can be associated with various degrees of neurotoxicity in different mammalian species exposed to controlled doses of MeHg via their diets. Concentrations of Hg in brain tissue can be estimated from ww to dw values by multiplying the ww concentration by a factor of 4. Various older reports of MeHg poisoning in free-living wild mammal species indicate that brain Hg concentrations > 10 μg g^{-1} ww (or > 40 μg g^{-1} dw) are typically associated with severe poisoning and outright mortality (Wiener et al., 2003). Suzuki (1979) considered brain Hg concentrations less than 1.5 μg g^{-1} ww (or approximately 6 μg g^{-1} dw) as generally insufficient to cause clinical Hg neurotoxicity in mammals. The risk of Hg-associated neurotoxicity to polar bears, ringed seals and beluga whales was recently assessed by comparing Hg concentrations in two brain regions with the threshold concentrations for several toxic endpoints (Krey et al., 2015-in this issue). Several thresholds ranging from >0.1 μg total Hg g^{-1} ww for neurobehavioral changes to >6.75 μg total Hg g^{-1} ww for clinical signs of Hg intoxication were identified.

As a widely distributed predatory species which feeds mainly on fish and small mammals, mink are considered to be sensitive indicators of

environmental Hg bioavailability (Kucera, 1983; Wren et al., 1986). Captive mink fed diets dosed with different concentrations of MeHg (1.1, 1.8, 4.8, 8.3, or 15.0 μg g^{-1} Hg by analysis) for longer than three months developed histopathological lesions in brain tissue, accompanied by manifestations of clinical toxicity including anorexia and loss of coordination (Wobeser et al., 1976). Wobeser et al. (1976) concluded that brain Hg concentrations > 5 μg g^{-1} ww (or > 20 μg g^{-1} dw) in mink were consistent with overt MeHg neurotoxicity in this species. The majority of Hg in brains of captive mink fed MeHg-containing diets was assumed to be mostly MeHg, as this is the dominant chemical form reported in brains of wild mink (Haines et al., 2010). In adult rats chronically exposed to dietary MeHg (0.25 mg kg^{-1} day^{-1} dosage), Hg concentrations in the cerebellum averaged 12 and 7.3 μg g^{-1} ww in males and females, respectively, and were accompanied by loss of balance, paralysis, and peripheral nerve damage (Munro et al., 1980). Similarly, brain Hg concentrations associated with neurotoxicity (movement disorders including a loss of balance and lack of coordination) in cats dosed with MeHgCl or MeHg-contaminated fish were 16.3 μg g^{-1} ww (total Hg) and 10.9 μg g^{-1} ww (MeHg) in the cerebellum and 10.9 μg g^{-1} ww (total Hg) and 7.9 μg g^{-1} ww (MeHg) in the posterior cerebral cortex (Charbonneau et al., 1976). Taken together, dietary MeHg dosing studies on a variety of mammalian species indicate that brain Hg concentrations 5 – 10 μg g^{-1} ww and higher are commonly associated with severe toxicity and lethality (Shore et al., 2011), and that concentrations < 5 μg g^{-1} ww, as suggested by earlier researchers (Suzuki, 1979; Wobeser et al., 1976), are likely below thresholds for overt MeHg intoxication in most mammals (but may nevertheless be related to more subtle behavioural and neurochemical changes).

A number of biochemical changes in the brain are associated with concentrations of Hg that are substantially lower than those required to produce overt signs of neurotoxicity or death. The following receptors and enzymes have been found to vary significantly with Hg concentrations in the brains of wild bird and/or mammal species:

- NMDA (N-methyl-D-aspartic acid) receptor levels decreased with increasing Hg levels (total Hg and MeHg) in polar bears from East Greenland collected between 1999 to 2001 (Basu et al., 2009), wild mink (Basu et al., 2007a), and loons and eagles (Scheuhammer et al., 2008);
- levels of mACh (muscarinic cholinergic) receptor increased with Hg levels in wild mink (Basu et al., 2005a), loons, and eagles (Scheuhammer et al., 2008) but the opposite relationship was found in river otters (Basu et al., 2005b);
- GABA (gamma-aminobutyric acid) receptor levels decreased with increasing Hg levels (total Hg and MeHg) in river otters (Basu et al., 2005a);
- dopamine D2-receptor levels were negatively correlated with total Hg levels in wild river otters and wild mink (Basu et al., 2005a, 2005b); and
- MAO (monoaminoxidase) and ChE (cholinesterase) activities were negatively correlated to Hg levels in wild river otters (Basu et al., 2005b, 2007b).

Of these neurochemical markers, changes in NMDA and mACh receptor levels have proven to be among the most sensitive and robust correlates of brain Hg accumulation, and have thus been proposed as potential preclinical indicators of neurotoxic changes associated with MeHg exposure (Basu et al., 2005b; Manzo et al., 1996). Captive mink exposed to a range of dietary MeHg (0.1–2 μg g^{-1}) experienced subtle but significant changes in these neurochemical parameters at brain Hg concentrations between about 1–8 μg g^{-1} dw, levels that were not associated with overt signs of MeHg intoxication (Basu et al., 2006, 2007b, 2010). An average brain Hg concentration as low as 1.5 ± 0.34 μg g^{-1} dw was associated with a significant decrease in NMDA receptor density in the cerebellum and occipital cortex of captive mink (Basu et al., 2007b). Although there are differences in sensitivity between rat, mink, mouse, and human with respect to Hg-induced neurochemical changes (Basu et al., 2005c), 1.5 μg g^{-1} dw may be considered a conservative mammalian LOAEL for Hg-induced neurochemical response. The average Hg concentration reported by Gamberg et al. (2005) for brain tissue in wild mink from the Yukon (0.96 μg g^{-1} dw, or 0.22 μg g^{-1} ww) is below this proposed threshold for MeHg-induced neurochemical change. However, Basu et al. (2009) reported a significant negative association between brain Hg and NMDA receptor concentrations in the lower brain stem of Greenlandic polar bears at an even lower range of Hg concentrations (approximately 0.1–1.0 μg g^{-1} dw). Given the very low Hg concentrations that were associated with significant neurochemical effects in polar bears (Basu et al., 2009), it is suggested that additional studies be undertaken to further examine relationships between Hg accumulation and neurochemical endpoints in the polar bear brain.

Concentrations of MeHg in polar bear cerebellum from the Canadian Arctic (range: 0.13–0.45 μg g^{-1} dw; $n = 22$) were lower than concentrations observed to be toxic in animal feeding trials. However,

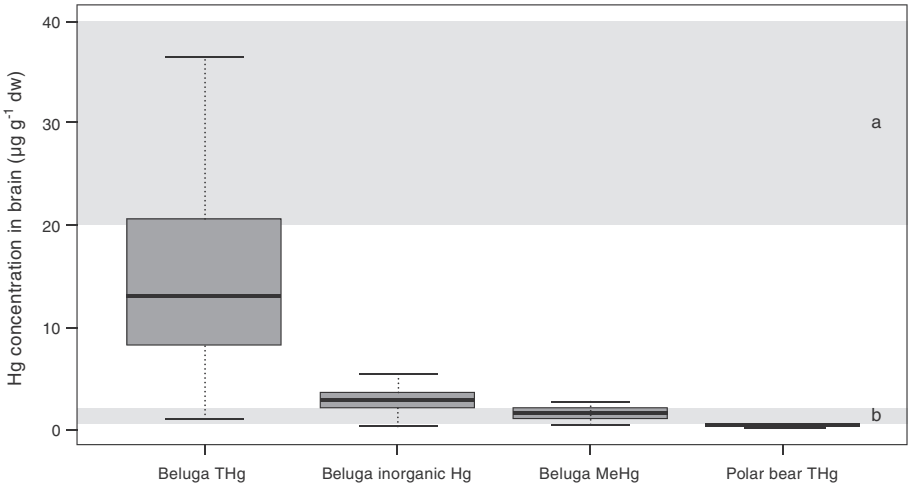

Fig. 7. Concentrations of total Hg (THg), soluble inorganic Hg (not including inorganic Hg that may be bound with Se in insoluble compounds), and methylmercury (MeHg) in polar bear from Nunavik (northern Quebec) harvested from 2000 to 2003 ($n = 24$) and in adult beluga whale cerebellum from the western Canadian Arctic harvested in 2008 ($n = 21$) (data from Krey et al., 2012; Ostertag et al., 2013). The concentrations are compared with effects levels identified in laboratory studies: a) approximate MeHg threshold range for overt MeHg poisoning and death; and, b) approximate MeHg threshold range for neurochemical change. The boxplots identify the 10th and 90th percentiles (error bars), the 25th and 75th percentiles (box) and the median concentration (bold line).

concentrations of MeHg in beluga whale cerebellum were sufficiently high to potentially cause significant neurochemical changes, but probably not high enough to cause overt MeHg neurotoxicity (Fig. 7). The formation of relatively inert Hg selenide compounds in the brains of beluga may provide a mechanism to reduce the risk of MeHg toxicity in these animals (see section on Mercury-Selenium Interactions). It should also be noted that different brain regions may react differently with respect to neurochemical changes in response to MeHg exposure (Basu et al., 2007a, 2010).

As liver is the most common tissue for monitoring environmental contaminant exposure in wildlife, researchers have attempted to establish toxicity thresholds for contaminants based on a consideration of the lowest liver concentrations that are associated with significant toxic effects in individual animals. For Hg in non-marine mammals, the most commonly cited threshold is probably that of Thompson (1996), recently updated by Shore et al. (2011), of 25–30 μg g^{-1} ww Hg in liver above which animals are likely to experience MeHg intoxication and death. Unfortunately, without additional information on the proportions of MeHg and inorganic Hg in the liver, a toxicity threshold expressed solely on a total Hg basis is insufficient for making confident toxicological assessments. The studies reviewed by Thompson (1996) and Shore et al. (2011) to estimate a Hg toxicity threshold based on total Hg in liver are all studies in which animals were exposed to relatively high doses of MeHg through their diets until they died or showed clinical signs of MeHg neurointoxication. Under such conditions, it is expected that most of the Hg in the dosed animals' tissues was present as MeHg. But for liver tissue from free-living mammals or birds, many species of which demonstrate variable proportions of inorganic Hg and MeHg, this assumption is not valid. There are many examples of apparently healthy free-living mammals and birds with very high (>100 μg g^{-1} ww) hepatic total Hg concentrations (Dietz et al., 1990; Norstrom et al., 1986; Smith and Armstrong, 1975; Thompson and Furness, 1989). As total Hg concentrations in liver increase in long-lived aquatic predatory wildlife, a progressively lower proportion is typically present as MeHg (Wagemann et al., 2000). Inorganic Hg resulting from demethylation in liver is often found in close association with selenium (Se), especially at higher Hg concentrations, and the Hg-Se complex is generally considered to be relatively non-toxic (e.g., Ikemoto et al., 2004). Without knowledge of the proportions of Hg in the liver that are present as MeHg versus inorganic Hg, plus an estimate of corresponding Se concentrations, confident toxicological assessments cannot be made (see section on Mercury-Selenium Interactions for additional discussion). Indeed, in their recent review, O'Hara et al. (2011) refrained from suggesting Hg toxicity thresholds for marine mammals, based largely on a recognition that much of the Hg in livers of these species may be non-toxic inorganic Hg bound with Se, and on a lack of clear empirical evidence of toxicity in marine mammals with elevated liver Hg concentrations.

In the absence of information on the proportion of Hg in liver that is present as MeHg, it is useful to have data on total Hg concentrations in certain other tissues, such as skeletal muscle. There is little or no evidence of demethylation in muscle tissue, and total Hg and MeHg concentrations are approximately equal in this tissue (e.g. George et al., 2011). In some of the dosing studies examined by Thompson (1996) and Shore et al. (2011) to estimate a Hg concentration in liver above which MeHg poisoning occurred in mammals, total Hg in both liver and muscle were reported. In these MeHg dosing studies, Hg in both liver and muscle were highly elevated in animals suffering from MeHg poisoning, with muscle Hg concentrations reaching about 1/3 to 1/2 of liver concentrations (e.g., Aulerich et al., 1974; O'Connor and Nielsen, 1980; Wobeser et al., 1976). Thus, for a concentration of Hg in liver of 25–30 μg g^{-1} ww (Shore et al., 2011) to be accepted as a valid threshold for MeHg intoxication, Hg in skeletal muscle tissue should be in the range of about 8–15 μg g^{-1} ww or greater. Conversely, if muscle Hg concentrations are found to be low (≤1 μg g^{-1} ww) in animals with elevated liver Hg, it is less likely that such individuals will be suffering from MeHg toxicity. An examination of available data on total Hg in both liver and muscle of Canadian Arctic beluga and seals confirmed that, although some animals had Hg concentrations in liver exceeding the putative 30 μg g^{-1} ww toxicity threshold, muscle Hg concentrations

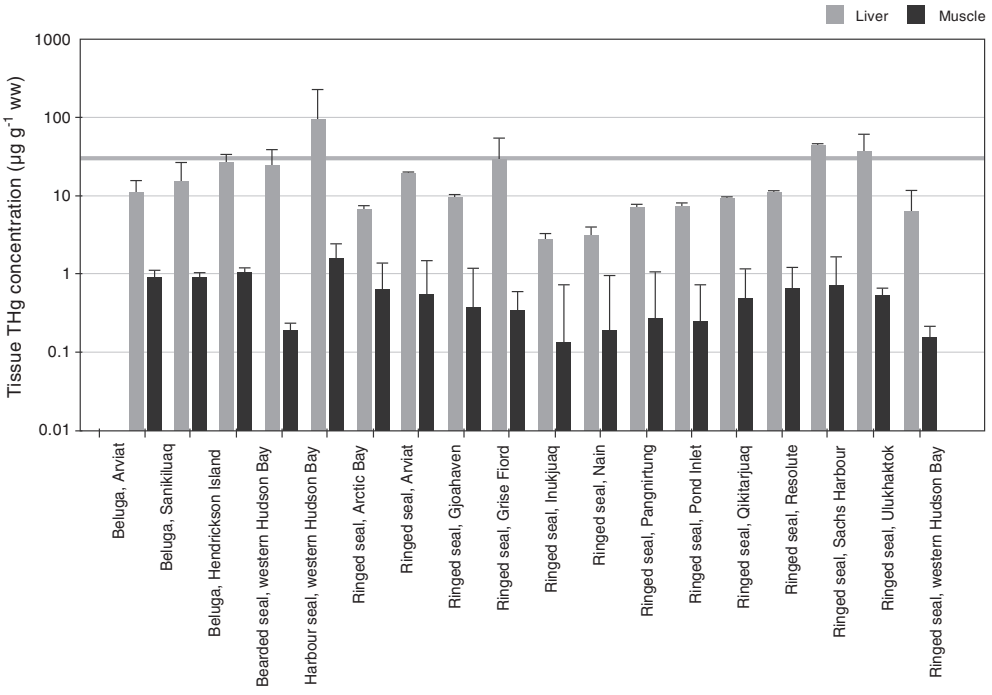

Fig. 8. Concentrations of total Hg (THg) in liver and muscle (log mean ± standard deviation) of Arctic beluga and seal compared to a toxic threshold of 30 μg g^{-1} ww suggested for terrestrial mammals (Thompson, 1996). Beluga data are from Gaden and Stern (2010) while seal data are from Braune et al. (in this issue) and Young et al. (2010). Comparisons between toxicity thresholds and liver total Hg concentrations should be interpreted with caution because a large portion of elevated liver Hg in these marine mammals is likely present in a less toxic inorganic form, as corroborated by relatively low (≤1 μg g^{-1}) total Hg concentrations in muscle for most samples.

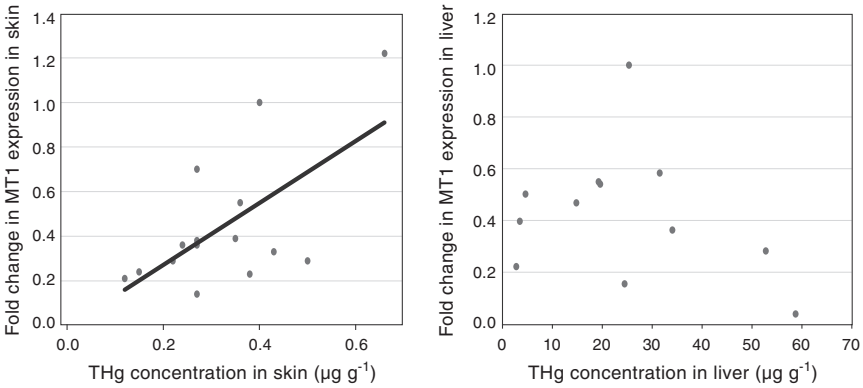

Fig. 9. Relationships between total Hg (THg) concentrations and metallothionein (MT1) gene expression in the skin ($r^2 = 0.51$, $p = 0.017$) and liver ($p =$ not significant) of male beluga whales sampled in 2008 ((Ross et al., Fisheries and Oceans Canada, University of Victoria, Unpublished data). The MT1 expression was first normalized to the expression of the gene encoding the ribosomal protein L8 and further normalized to the individual showing average contaminant concentrations.

were generally low, indicating that these species are unlikely to be experiencing significant MeHg neurotoxicity or reproductive impairment (Fig. 8). Only harbour seals from western Hudson Bay had highly elevated mean liver Hg along with muscle Hg substantially higher than 1 μg g^{-1} ww. Therefore, further study on possible health effects from MeHg exposure on this subpopulation of seals is warranted.

2.3.2. Methylmercury toxicity in other organs

Although it is generally accepted that the central and peripheral nervous system is the primary target for MeHg toxicity in mammals, other tissues can also show varying degrees of cellular effects in response to Hg accumulation. In a review by Sonne (2010), and further emphasized in Dietz et al. (2013), a liver Hg concentration of 11 μg g^{-1} ww was suggested as a threshold for hepatic effects in polar bears based on studies relating Hg concentrations with liver lesions in East Greenland polar bears. Sonne (2010) suggested a Hg concentration of 14 μg g^{-1} ww as a threshold for kidney lesions in adult male East Greenland polar bears. It is not known how debilitating the reported relatively minor hepatic or renal lesions may be for individual bears. However, it should be noted that much higher liver Hg concentrations were reported about 25 years ago in apparently healthy polar bears (e.g., Norstrom et al., 1986). Compared to liver Hg data from 2002 (Rush et al., 2008) and early 1980s (Norstrom et al., 1986), Routti et al. (2011) recently reported that in bears sampled in 2005–2008 from Alaskan, Canadian and East Greenland subpopulations, Hg in liver appeared to have increased only in East Greenland bears. Nevertheless, additional research is warranted to better characterize sublethal toxic effects of Hg accumulation in organs other than the brain in polar bears and other Arctic marine mammals.

2.3.3. Toxicogenomics and immunotoxicity in beluga

With a minimum estimate of 40,000 individuals (COSEWIC, 2004), the Beaufort beluga whale population is one of Canada's largest, and there is no indication of a population decline. Mercury monitoring from 1981 to 2002 revealed high levels in Beaufort Sea beluga whales relative to other Canadian populations and an increasing temporal trend (Lockhart et al., 2005b). This finding led to several studies aimed at identifying the main sources of Hg to the region; and as part of the beluga sampling program at Hendrickson Island, a health assessment of contaminant effects on known toxicological endpoints was conducted.

The impacts of Hg on gene expression in beluga are being investigated (Ross et al., Fisheries and Oceans Canada, University of Victoria, Unpublished data). The long-term goal of this research is to develop a highly sensitive technique that will provide a useful early warning indicator of the effects of Hg and other contaminant exposure on the health of the western Arctic beluga population. Metallothioneins (MTs) are low molecular weight sulfhydryl-rich proteins that are able to bind to group II metals, especially the essential trace metals copper and zinc, and the toxic non-essential metals cadmium and inorganic Hg. It is generally accepted that MT synthesis and binding of toxic metals provide protection against the cytotoxic action of these metals. In beluga liver,

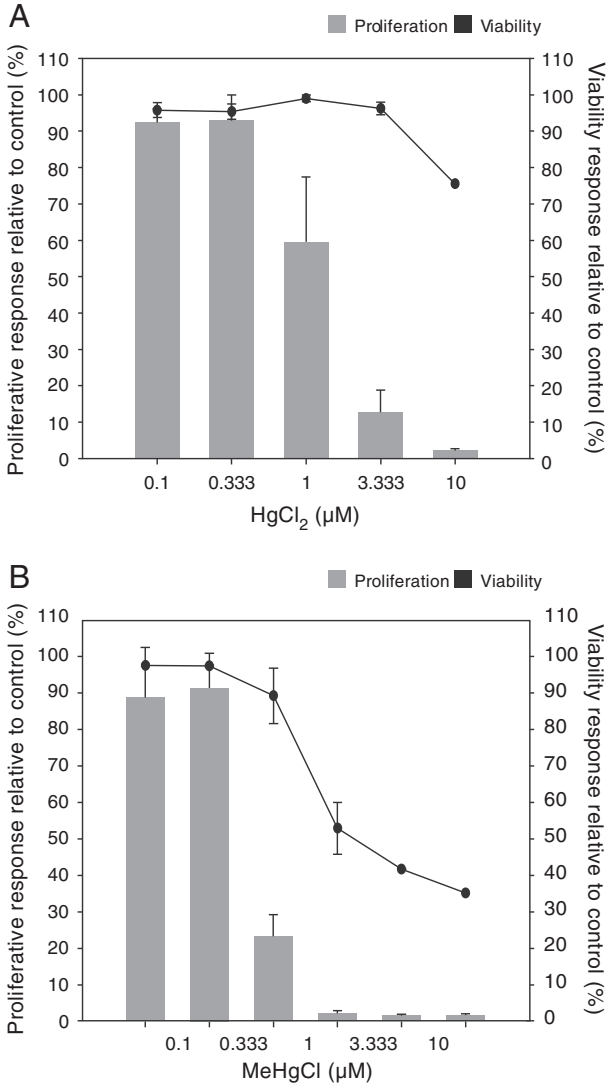

Fig. 10. The proliferation of T lymphocytes (bars) and their viability (lines) following different exposures to $HgCl_2$ (A) or MeHgCl (B). Results are expressed as a percentage (%) of the control response (unexposed cells) ($n = 4$ per dose group; mean ± standard error) (source: Frouin et al., 2012).

no significant correlation was found between MT1 gene expression and total Hg levels (Fig. 9), which suggests that MTs may not be the primary means of Hg detoxification in liver. This result is consistent with previous work showing that only 5% of Hg is bound to MTs in liver (Wagemann and Muir, 1984). In skin, a positive relationship between MT1 expression and total Hg levels was observed ($r^2 = 0.51$; $p = 0.017$), which suggests that MTs might play a significant role in the binding of inorganic Hg in the skin of beluga. However, Hg in the skin of cetaceans and pinnipeds is predominately in the form of MeHg (90%) rather than inorganic Hg (Dehn et al., 2006; Wagemann et al., 1998).

To investigate the effects of inorganic Hg and MeHg on the immune system of beluga whales, laboratory experiments were conducted on peripheral blood collected from four captive beluga held at the Vancouver Aquarium (Frouin et al., 2012). Lymphocyte suspensions were exposed *in vitro* for 66 hours to 0.1–10 μM of Hg chloride ($HgCl_2$) and 0.033–10 μM of MeHgCl. Relationships between Hg concentration and the proliferation of concanavalin A (Con-A)-stimulated lymphocytes were then evaluated. Cell viability was also measured. A significant reduction in T-lymphocyte proliferation was observed at ≥1 μM $HgCl_2$ and ≥0.33 μM MeHgCl (Fig. 10). Cell viability decreased only at the highest concentrations of $HgCl_2$ (10 μM), and at ≥1 μM of MeHgCl. Calculated doses for 50% inhibition of the proliferation response (ID_{50}) indicate that MeHgCl ($ID_{50} = 0.24$ μM) suppressed proliferation of beluga lymphocytes at concentrations ten times lower than $HgCl_2$ ($ID_{50} = 2.62$ μM). These results agreed with previous observations that MeHg is a more potent suppressor of splenocyte proliferation than inorganic Hg (De Guise et al., 1996), and they suggest that Hg, particularly MeHg, may be toxic to beluga whale immune cells at the range of concentrations (1–100 μg g^{-1}) that has been observed in the liver of some free-ranging populations of Arctic beluga whales (Lockhart et al., 2005b). However, *in vivo*, most MeHg in blood is bound to proteins such as haemoglobin within red blood cells and may not be as available to interact with lymphocytes compared to *in vitro* studies using isolated lymphocyte suspensions. Additional research to investigate the possible *in vivo* immunotoxic effects of MeHg exposure in Arctic marine mammals is warranted.

3. Mercury–selenium interactions

In some tissues of fish-eating and other predatory aquatic mammals and birds, MeHg from the diet is demethylated and the resulting inorganic Hg combines with Se. This Hg-Se sequestration occurs especially in liver and to some extent in kidney and brain. At higher concentrations of liver Hg, it is common to find an increasingly large proportion of total Hg present as inorganic Hg associated with Se, and less total Hg present as MeHg (e.g., Henny et al., 2002; Scheuhammer et al., 1998). A liver MeHg concentration of about 8–10 μg g^{-1} dw has been suggested as a threshold above which demethylation is activated in a number of wildlife species (Dietz et al., 1990; Eagles-Smith et al., 2009; Scheuhammer et al., 2008). At high total Hg concentrations (>50 μg g^{-1} dw), the molar ratio of Hg:Se in the liver often approaches 1:1 (Dietz et al., 2000; Koeman et al., 1975). Demethylation of MeHg and subsequent sequestration of inorganic Hg with Se has frequently been suggested as a probable detoxification mechanism for animals exposed to relatively high levels of dietary MeHg (Bjorkman et al., 1995; Caurant et al., 1996; Palmisano et al., 1995). Further, Ralston et al. (2008) reported that the molar ratio of Hg:Se was critical to the expression of MeHg toxicity. Together, these studies indicate that sufficient molar excesses of Se over Hg are important for protecting cells from the toxicity of Hg.

Mercury has an even greater binding affinity for Se than it does for sulphur (Sugiura et al., 1978). Therefore, tissue accumulation of Hg may potentially reduce the levels of bioavailable Se needed for seleno-enzyme synthesis essential for protecting the brain and other tissues from oxidative stress (Ralston et al., 2008). Certain seleno-enzymes (e.g., thioredoxin reductase) are highly sensitive to inhibition by low nanomolar concentrations of Hg and may be primary targets of MeHg toxicity at the molecular level (Carvalho et al., 2008). From a toxicological perspective, demethylation of MeHg in liver and the interaction between Hg and Se have important implications. Chief among these is a realization that confident toxicological assessments cannot be made based solely on total Hg concentrations commonly reported in tissues such as liver or brain. Rather than estimating LOAEL or similar threshold toxicity values based solely on total Hg concentrations in tissues that are prone to exhibit variable proportions of MeHg and inorganic Hg, it is preferable that concentrations of total Hg and MeHg as well as Hg:Se molar ratios be considered together to more confidently judge whether tissue Hg concentrations are sufficiently high to impair health or reproduction. It is also helpful to consider Hg concentrations in muscle tissue where little if any demethylation takes place, in addition to Hg in liver when making toxicological assessments.

For Arctic beluga whales, a strong association between inorganic Hg and Se in both liver and brain has been reported (Lemes et al., 2011). The relationship between Hg and Se co-accumulation has been investigated in a specific brain area (the cerebellum) of Arctic beluga whales and polar bears (Krey et al., 2015-in this issue): concentrations of Se and total Hg were positively correlated for both beluga whales and polar bears.

The molar ratio of Hg:Se was higher in beluga whale cerebellum than in polar bear cerebellum (Fig. 11) (Krey et al., 2012; Krey et al., 2015-in this issue; Ostertag et al., 2013). This finding may be of concern, given that belugas have much greater brain Hg concentrations than polar bears. As discussed by Krey et al. (2015-in this issue), a molar excess of Se over Hg was nevertheless observed in both polar bear and beluga brains, which indicates that beluga may, in general, be protected from MeHg toxicity in spite of relatively high brain Hg concentrations compared with polar bears. Because of the protective effect of Se on Hg toxicity, a high tissue Hg concentration accompanied by a high (>1) Hg:Se molar ratio is of greater concern than a high tissue Hg concentration accompanied by a low (<1) Hg:Se molar ratio. However, more research is necessary to better understand the role of Se in protecting the brains of Arctic predatory mammals and birds from Hg toxicity. Further discussion of Hg-Se interactions in marine mammals can be found in a review by O'Hara et al. (2011).

Data from the 1980s indicated that Hg concentrations in livers of Canadian polar bears were highest in western Arctic areas bordering the Beaufort Sea (mean approximately 100–200 μg g^{-1} dw). However, the Hg:Se molar ratio for these animals was approximately 1:1

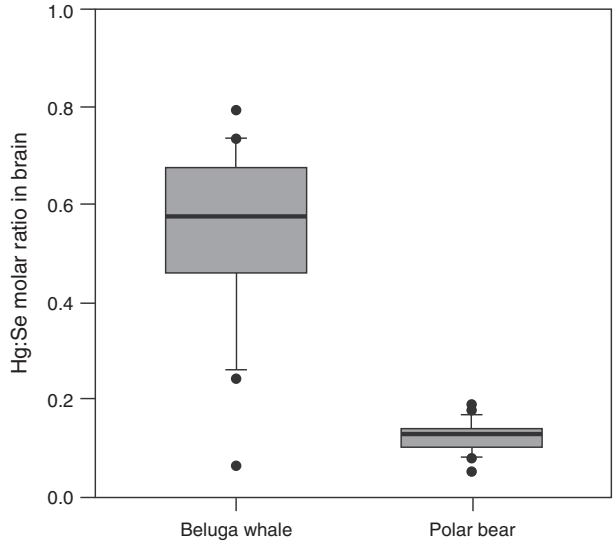

Fig. 11. Molar ratio of Hg:Se in beluga whale ($n = 21$) and polar bear ($n = 24$) cerebellum (Krey et al., 2012; Ostertag et al., 2013). The boxplots identify the 10th and 90th percentiles (error bars), the 25th and 75th percentiles (box) and the median concentration (middle line).

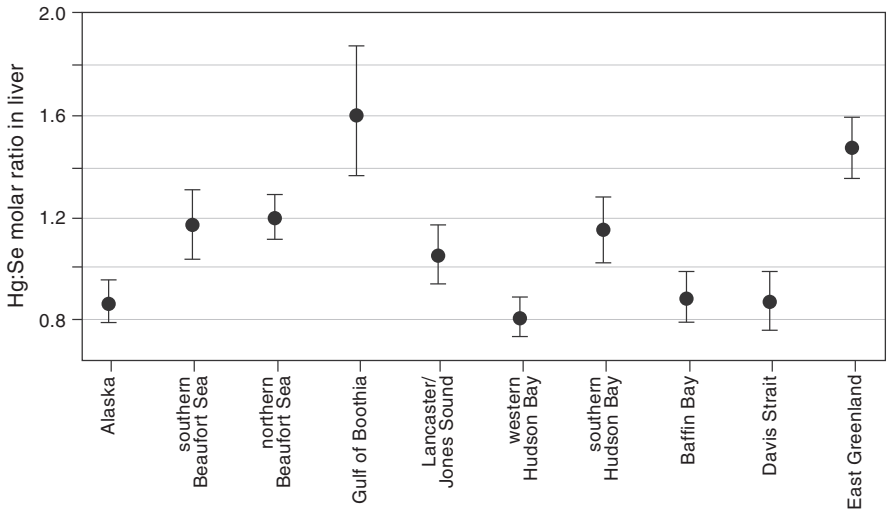

Fig. 12. Molar ratio of Hg:Se concentrations (±95% confidence intervals) in polar bear livers collected from Alaska, Canada, and Greenland in 2005 to 2008. Reprinted with permission from Routti et al. (2011). © The Royal Society of Chemistry.

indicating sufficient Se to sequester all Hg (Braune et al., 1991). More recently, Routti et al. (2011) reported that Hg concentrations were higher in the livers of polar bears sampled from 2006–2008 from the Beaufort Sea compared to animals sampled in the 1980s. However, Se concentrations increased concurrently with Hg resulting in stable Hg:Se molar ratios over time for this population. Geographic, and perhaps temporal, differences in Hg concentrations in polar bears are largely explained by differences in trophic position. There was a negative relationship between total Hg and $\delta^{13}C$ values, which suggested that polar bears feeding in areas with higher riverine inputs of terrestrial carbon (e.g. Beaufort Sea) accumulate more Hg than bears feeding in areas with lower freshwater input (Routti et al., 2012); $\delta^{13}C$ -unadjusted Hg and Se concentrations showed greater geographical variation among polar bear subpopulations compared with concentrations adjusted for carbon and lipid sources. The Hg concentrations adjusted for carbon and lipid sources in Bering–Chukchi Sea polar bear liver tissue remained the lowest among subpopulations. Routti et al. (2011) reported that the highest mean molar ratio of Hg:Se (1.6) in polar bear liver—indicating a molar excess of Hg over Se—was observed in bears from the Gulf of Boothia compared with several other northern Canadian locations sampled from 2006 to 2008 (Fig. 12). Total Hg concentrations in Gulf of Boothia bears, although lower than in Beaufort Sea bears, were not trivial (>20 μg g^{-1}), thus, there is currently a basis for concern that some bears from Gulf of Boothia may be at risk for Hg-mediated toxicity. In addition, polar bears from other locations where the Hg:Se molar ratio exceeds unity, especially where concentrations of Hg in liver are high (>80 μg g^{-1} dw), should be further assessed for possible Hg toxicity.

4. Summary

Although recent advances have been made, current information is insufficient to judge with confidence whether Hg exposure is having significant impacts on the health of any fish or wildlife species in the Canadian Arctic. Studies on MeHg accumulation and toxicity in temperate species, including information gleaned from controlled feeding studies, offer useful information that can be applied, with caution, to an assessment of Hg concentrations in tissues of Arctic species. Nevertheless, there is an explicit need for Hg effects information for Arctic species themselves. Therefore, bioeffects studies should comprise a major focus of future Hg research in the Canadian Arctic. These studies should include a variety of approaches (laboratory and field) to investigate potential toxicological effects (e.g., neurotoxicity, immunotoxicity) on individuals and link this information to potential consequences at the population level. Current Hg concentrations examined in this review for biota from the Canadian Arctic suggest that further toxicological investigations are warranted for some species of predatory freshwater fish, Greenland shark, several species of seabirds, harbour seal, beluga and polar bear. More research is also needed to better understand the role of Se in protecting Arctic predatory mammals and birds against the toxicological effects of Hg.

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