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# Organ-specific differences in mercury speciation and accumulation across ringed seal (*Phoca hispida*) life stages

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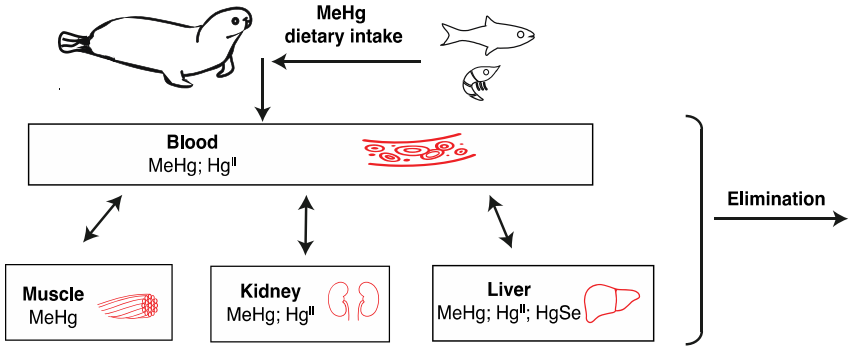
## HIGHLIGHTS

- A toxicokinetic model for Hg that includes HgSe was developed for ringed seals.
- Speciated Hg measured in tissues of ringed seals of various life stages.
- Model simulations show diet as the main driver of liver HgSe variability in adults.
- Observed data and model suggest different $Hg^{II}$ partitioning across life stages.
- Demethylation of MeHg to HgSe does not greatly decrease brain MeHg exposure.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Methylmercury (MeHg) is a central nervous system toxicant and exposures can adversely affect the health of marine mammals. Mercuric selenide (HgSe) in marine mammal tissues is hypothesized to result from a protective detoxification mechanism, but toxicokinetic processes contributing to its formation are poorly understood. Here, new data is reported on speciated Hg concentrations in multiple organs of $n = 56$ ringed seals (*Phoca hispida*) from Labrador, Canada, and compare concentrations to previously published data from Greenland seals. A higher proportion of Hg is found to accumulate in the kidney of young-of-the-year (YOY) ringed seals compared to adults. A toxicokinetic model for Hg species is developed and evaluated to better understand factors affecting variability in Hg concentrations among organs and across life stages. Prior work postulated that HgSe formation only occurs in the liver of mature seals, but model results suggest HgSe formation occurs across all life stages. Higher proportions of HgSe in mature seal livers compared to YOY seals likely results from the slow accumulation and elimination of HgSe (total body half-life = 500 days) compared to other Hg species. HgSe formation in the liver reduces modeled blood concentrations of MeHg by only 6%. Thus, HgSe formation may not substantially reduce MeHg transport across the blood-brain barrier of ringed seals, leaving them susceptible to the neurotoxic effects of MeHg exposure.



## 1. Introduction

Mercury (Hg) is a naturally occurring element and human activities such as mining, and fuel combustion have released large quantities of

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Hg sequestered in the lithosphere to the biosphere (Streets et al., 2017). Hg is transported globally in the atmosphere and oceans to remote regions like the Arctic and Subarctic (Soerensen et al., 2016). In aquatic ecosystems, some inorganic Hg is converted by microbes into methylmercury (MeHg), the only form of Hg that biomagnifies in food webs (Gilmour et al., 2013). As apex predators, marine mammals are exposed to MeHg through the fish they consume that have concentrations that are at least a million times higher than seawater (Lavoie et al., 2013). They are thus susceptible to apical outcomes associated with MeHg exposure such as nephrotoxicity and neurobiochemical changes (Dietz et al., 2013; Ostertag et al., 2013). Several detoxification mechanisms, including the formation of an insoluble mercury selenide species (HgSe), have been identified in marine mammals and may confer protection against high levels of MeHg exposure (Ikemoto et al., 2004; Koeman et al., 1973). Variability in these mechanisms across life stages and their toxicological significance for MeHg exposures in different target organs are still poorly understood. Here, new data is presented on speciated mercury concentrations in multiple organs from subarctic ringed seals (*Phoca hispida*) and develop a toxicokinetic model to better understand factors affecting differences in concentrations among target organs, across life stages, and among individuals.

Prior studies have suggested that marine mammals at different ontogenetic stages metabolize MeHg differently (Lyytikäinen et al., 2015; Palmisano et al., 1995). In young marine mammals, a greater fraction of the total Hg in their liver is typically present as MeHg compared to older individuals (Lyytikäinen et al., 2015; Wagemann et al., 1988). It is unclear whether this difference reflects lower demethylation of MeHg or a lack of significant HgSe accumulation at young ages. MeHg is the most toxicologically relevant Hg form (Clarkson and Magos, 2006; Dietz et al., 2013). Thus, understanding how MeHg demethylation varies among ringed seals of different life stages is important for characterizing exposure risks.

Biotransformation of MeHg to mercuric selenide (HgSe) is a poorly understood mechanism of demethylation in marine mammals (Arai et al., 2004; Wagemann et al., 2000). HgSe nanoparticles aggregate into inert crystallized granules, which have been frequently detected in marine mammals (Gajdosechova et al., 2016; Lyytikäinen et al., 2015; Wagemann et al., 2000). By contrast, prior work shows divalent inorganic Hg species ($Hg^{II}$) and MeHg preferentially bind to protein and have high mobility within the bodies of mammals (Kunito et al., 2004; Zayas et al., 2014). The presence of HgSe has mainly been reported using crystalline imaging methods such as extended X-ray absorption fine structure (EXAFS) and X-ray absorption near edge structure (XANES) spectroscopy (Arai et al., 2004; Gajdosechova et al., 2016; Nakazawa et al., 2011). Crystalline imaging-based HgSe detection methods are expensive, time consuming, and not well suited for quantifying concentrations (Gajdosechova et al., 2016). Analytical methods for estimating the concentration of insoluble Hg exist, but are only available at specialized facilities and are thus much less frequently reported than other Hg species (Lyytikäinen et al., 2015; Wagemann et al., 2000).

Toxicokinetic models for Hg species in marine mammals rely on generalizable kinetic data for transport and elimination of different Hg species from the literature. These models are useful for interpreting available Hg concentration data and for better understanding how HgSe formation affects MeHg exposure in target organs. Previous applications of such models have successfully represented MeHg demethylation to $Hg^{II}$ by microbes in the gut and improved understanding of the detoxification capacity of various terrestrial mammal species (Carrier et al., 2001b; Farris et al., 1993; Sundberg et al., 1998). However, prior models did not include a parameterization for HgSe formation, and thus have limited applicability to marine mammals.

The main objective of this work was to better understand pathways of MeHg accumulation and elimination in Subarctic ringed seals. New data on speciated Hg concentrations in the tissues of ringed seals from the Labrador, Canada was measured and compared to previously published tissue data from Greenland (Dietz et al., 1998). A toxicokinetic model was developed and evaluated for Hg species in ringed seals that includes demethylation of MeHg to HgSe in the liver. The model was used to test the hypothesis that production of HgSe in the liver is the prevailing detoxification mechanism (Caurant et al., 1996; Lailson-Brito et al., 2012; Palmisano et al., 1995), and to identify factors driving differences in Hg concentrations among organs, across life stages, and among individuals.

## 2. Materials and methods

### 2.1. Seal sample collection and age determination

Sampling from the Lower Lake Melville region of Labrador, Canada, focused on young-of-the-year (YOY) ringed seals, the predominant age class consumed by indigenous Inuit (Calder et al., 2016). In collaboration with the Nunatsiavut Government, skeletal muscle, liver, and kidney tissue samples were opportunistically collected by Inuit hunters from 56 ringed seals between April 2013 and July 2015. Sampling followed field protocols established by the Canadian Northern Contaminants Program (Brown et al., 2016). Samples were frozen and shipped to the Canada Center for Inland Waters in Burlington, Ontario, where they were stored at −20 °C until analysis.

Jaws were collected from 26 seals and used for age determination by counting the growth layers on the lower and upper canines at Matson's Laboratory in Manhattan, Montana using standard cementum aging techniques (Stewart et al., 1996). Results confirmed qualitative information from the hunters that most seals were harvested between 2 and 5 months of age (Smith et al., 1991). For the remainder of the seals ($n = 30$), length measurements were used to distinguish between YOY and older seals. All seals with a standard length (straight line from the nose to end of the tail) <100 cm were classified as YOY, following previously established age-length relationships (McLaren, 1958). In total, 42 seals were classified as YOY and 14 as either adult (>5 years) or juvenile (>1 year and <5 years).

### 2.2. Total Hg and MeHg analysis

Prior to analysis for Hg species, whole kidneys, whole livers, and muscle tissue samples were homogenized with a blender, freeze dried, and ground into an even powder. The mass of each sample was measured before and after freeze drying to determine moisture content. Total Hg concentrations were measured using thermal decomposition, gold amalgamation, and atomic absorption spectroscopy on a Milestone DMA-80 (Direct Mercury Analyzer) following EPA method 7473a (EPA, 1998). Blank concentrations, biological replicates, and certified standard reference materials (SRM: DOLT 5, TORT 3, and DORM 4) were measured at least once for every ten samples analyzed. SRM recoveries averaged 98 ± 8% (Table A5), and the method detection limit (MDL) for total Hg was 0.008 ± 0.02 ng $g^{-1}$ (calculated as blanks ±3× the standard deviation of blanks). The coefficient of variation was <6% for all biological replicates ($n = 26$) (calculated as standard error / sample mean × 100%).

Homogenized, dried tissue samples for MeHg analysis were digested in 5 N nitric acid at 55 °C for 10 h (Hintelmann and Nguyen, 2005). Acetate buffer was added to the samples before ethylation with sodium tetraethylborate (NaTEB). Ethylated samples were purged onto a Tenax packed column. MeHg concentrations were measured through separation by gas chromatography and cold vapor atomic fluorescence spectroscopy. The separation and detection processes were automated using a Brooks Rand MERX-M Automated Methylmercury system. Blanks, biological replicates, and certified reference materials (SRM: DOLT 5, TORT 3, and DORM 4) were analyzed at least once for every ten samples analyzed. Recoveries averaged 98 ± 6% (Table A6), and the MDL for MeHg was 0.4 ± 0.5 ng $g^{-1}$ (calculated as blanks ±3 times the standard deviation of blanks). The coefficient of variation of

biological replicates ($n = 11$) was <6% (calculated as standard error / sample mean × 100%).

### 2.3. Toxicokinetic model

Fig. 1 provides a conceptual schematic of the toxicokinetic model developed in this study. The model traces three main forms of Hg within the seal: MeHg, $Hg^{II}$, and HgSe. $Hg^{II}$ is assumed to include all forms of inorganic Hg other than HgSe, and MeHg is assumed to include all forms of organic Hg. The model is forced by dietary intake of MeHg that can be simulated either deterministically (constant exposure) or stochastically, and includes four compartments representing the blood, muscle, liver, and kidney of ringed seals. Stochastic exposure is simulated using a Markov process that is a standard numerical method for assigning probabilities to different dietary scenarios and allowing them to vary randomly across iterations. Markov processes are commonly used to represent stochastic events in models of animal behavior (Metz et al., 1983). Model compartments were chosen to represent tissues that contain a large proportion of the total body Hg burden (muscle, blood), as well as tissues hypothesized to be important for MeHg detoxification (liver, kidney). The proportion of total Hg that partitions into other tissues is small and will therefore not affect modeled concentrations in the compartments represented in the simulation.

Three previously published datasets were used to parameterize and evaluate the model that include speciated Hg measurements in muscle, liver, and kidney tissues from ringed seals harvested in Greenland. They are referred to as D1990 (Dietz et al., 1990), D1996 (Dietz et al., 1996), and D1998 (Dietz et al., 1998) (Table 1). Datasets D1990 and D1996 were used to parameterize the model and D1998 was used for model evaluation before application to interpret Labrador seal data.

**Table 1**
Summary of Greenland ringed seal datasets used for model development and evaluation.

| | D1990 (Dietz et al., 1990) | D1996 (Dietz et al., 1996) | D1998 (Dietz et al., 1998) |
|---|---|---|---|
| Sample size | $n = 12$ | $n = 9$ | $n = 456$[a] |
| Collection years | 1985–1987 | 1975–1995 | 1982–1987 |
| Hg species | Total Hg and MeHg | Total Hg | Total Hg |
| Age Cohorts[b] | YOY; adult | YOY; juvenile; adult | YOY; juvenile; adult |
| Use in study | Model development<br>Data analysis[c] | Model development | Model evaluation |

[a] Mean and standard deviation pooled by age and geographical region.
[b] YOY are <1 year, juvenile are >1 year and <5 year, adult are >5 year.
[c] Comparison of D1990 data to the Labrador seal data measured in this study.

The mass of each biological compartment was assumed to be a fixed percentage of the core body mass, following prior work (Bryden, 1971; Laws et al., 2003). The model uses allometric relationships to update the mass of each compartment daily that captures the effects of growth dilution on tissue Hg concentrations and the rapid growth of ringed seal pups (Hickie et al., 2005). Blubber is modeled separately from the core body mass to capture large seasonal fluctuations in fatty tissue (Hickie et al., 2005). $Hg^{II}$ was not included in the muscle compartment because MeHg generally accounts for >90% of the total Hg (Dietz et al., 1990; Wagemann et al., 1988; Wagemann et al., 1998).

Following previous toxicokinetic models for Hg, MeHg and $Hg^{II}$ are assumed to be readily exchanged between tissue compartments and their distribution can be adequately represented by a series of partition coefficients ($P_i$). This approach is consistent with empirical studies of the distribution of MeHg and total Hg among tissues in mink and river otter (Carrier et al., 2001a; Carrier et al., 2001b; Eccles et al., 2017;

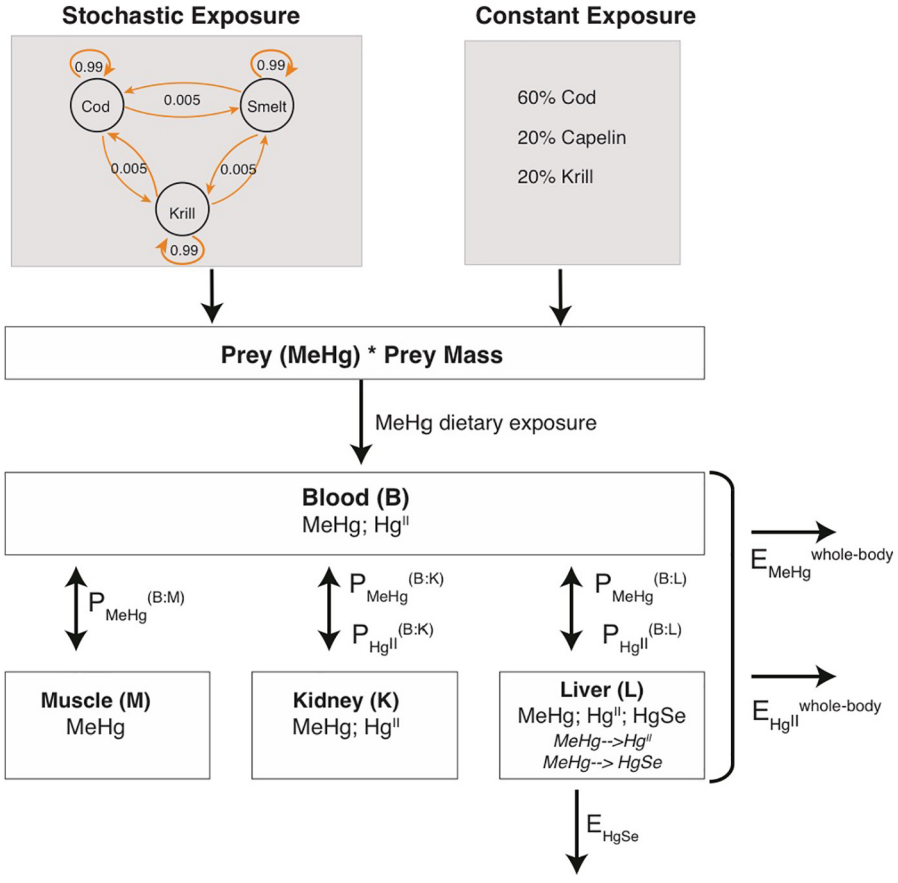


**Fig. 1.** Conceptual diagram of the toxicokinetic model developed in this study. Partition coefficients for a given Hg species (Z) between two compartments (X, Y) are denoted by $P_Z^{X:Y}$. Elimination rates for each Hg species are denoted by $E_Z$. Dietary exposure is modeled as either a stochastic (top left; using a three state Markov process with parameters in diagram) or deterministic (top right) process.

Evans et al., 2016; Young et al., 2001). Partition coefficients were parameterized for ringed seals using previously published tissue Hg measurements from Greenland (D1996 dataset described in the Supplementary materials).

Wherever possible, direct measurements from ringed seals were used to estimate rate constants for elimination and biotransformation of modeled Hg species. Where this was not feasible, rates for other mammals with similar body sizes were used (Reeves, 1998; Smith et al., 1991). For HgSe and $Hg^{II}$, elimination was determined using the previously reported HgSe and $Hg^{II}$ half-lives in ringed seals (Tillander et al., 1970). The elimination rate for MeHg is based on measured whole-body elimination rates in humans, which is driven by excretion in the urine and feces (Carrier et al., 2001a; Young et al., 2001). It does not explicitly account for elimination in hair because a recent study found that only a small proportion of the Hg body burden is deposited in hair (2% for sub-adults and 1% for adults) (Lyytikäinen et al., 2015). Slower MeHg elimination relative to $Hg^{II}$ elimination is partly driven by enterohepatic circulation that decreases the efficiency of MeHg elimination in feces (Carrier et al., 2001b; Clarkson and Magos, 2006).

Biotransformation of MeHg to $Hg^{II}$ is based on estimated rates in humans (Carrier et al., 2001a; Carrier et al., 2001b). The transformation rate of MeHg to HgSe is based on the D1990 and D1996 datasets, using methods described in the Supplementary materials (Dietz et al., 1990; Dietz et al., 1996). While HgSe has been detected in many marine mammal tissues, the liver is considered the primary site of detoxification and $Hg^{II}$ storage, possibly due to its high capacity for selenoprotein synthesis (Clarkson and Magos, 2006; Gajdosechova et al., 2016; Huggins et al., 2009; Lyytikäinen et al., 2015). Therefore, this study focuses on the impacts of HgSe formation in the liver. Due to its crystalline structure, HgSe is assumed to be non-labile and to be insignificantly partitioned into other tissues. Coupled differential equations were solved for time dependent changes in Hg species in the four compartments represented in the model using the ordinary differential equation solver ODE45 in Matlab (Tables A1 and A2).

For each prey type, ingestion needed to meet energy requirements (and associated MeHg intake) was estimated based on energy requirements to meet growth and activity levels (respiration) following the model by Hickie et al. (Hickie et al., 2005). Dietary preferences of ringed seals vary based on life stage and season (Siegstad et al., 1998; Yurkowski et al., 2016). A large-scale stomach contents analysis study from Greenland ($n = 454$) suggests that at maturity, the diet of a typical adult ringed seal consists of approximately 60% larger fish such as polar cod, 20% smaller fish such as capelin (*Mallotus villosus*), and 20% crustaceans such as North Atlantic krill (*Meganyctiphanes norvegica*), and these percentages were used in this study (Siegstad et al., 1998; Yurkowski et al., 2016). A study of the Lake Melville ecosystem found seals in this region have a similar diet to those in Greenland (Li et al., 2016).

Modeled MeHg concentrations in consumed food are based on measurements reported in the literature. Dietary $Hg^{II}$ was not included as an exposure source because of its low absorption efficiency in the gastrointestinal tract and rapid hepatic conjugation and fecal excretion (Clarkson and Magos, 2006; Clarkson et al., 2007). The deterministic model simulation uses previously published MeHg tissue concentrations for each dietary component (Dietz et al., 1996). Stochastic dietary exposure to MeHg is based on a Markov process for selecting daily prey from three states that represent high, medium, and low exposures by choosing from MeHg levels in polar cod (0.190 μg $g^{-1}$ w.w.), capelin (0.050 μg $g^{-1}$ w.w.), and krill (0.001 μg $g^{-1}$ w.w.) (Table A3) (Li et al., 2016). The parameters of the Markov process were chosen such that, on average, the seal switches primary prey type every three months. The purpose of including the stochastic dietary exposure was to show that the model still reproduces observed tissue Hg bioaccumulation patterns after accounting for changes in diet that approximate natural seasonal shifts that are driven by prey availability. Additional details on prey species and their MeHg concentrations are provided in the Supplementary materials (Table A3).

Physiological processes specific to immature ringed seals were considered in the development of the model. Transplacental transfer of MeHg from the dam during gestation are estimated using the previously published proportion of dam total Hg body burden transferred to fetus liver and muscle (Lyytikäinen et al., 2015). It is modeled as initial conditions for liver and muscle MeHg burdens. Given that the magnitude of the transferred burden depends on the maternal body burden (Lyytikäinen et al., 2015), the sensitivity of pup Hg concentrations to exposure in gestation are presented in the Supplementary materials (Table A4). Seal pups exclusively consume milk from their mothers for their first 40 days of life before switching to a diet of predominantly fish and crustacean species (Reeves, 1998). For the first 40 days, a representative range of previously measured MeHg concentrations in milk from other seal species with available data were used to model MeHg intake (Habran et al., 2011). Given the low levels of Hg in milk, the total seal Hg burden is expected to be insensitive to variability in milk Hg concentrations observed across different seal species. Stomach contents analysis indicated that immature seals consistently consume a higher proportion of amphipods and mature seals feed predominantly on fish species such as polar cod (*Boreogadus saida*) (Holst et al., 2001; Siegstad et al., 1998). The growing dietary proportion of fish is simulated with a constant linear increase in dietary Hg concentration, from milk to the estimated average adult diet, over the first five years.

## 3. Results and discussion

### 3.1. Total Hg and MeHg concentrations in ringed seal tissues

Mean and standard deviation of measured concentrations of total Hg, MeHg, and the fraction of total Hg present as MeHg (%MeHg) in the muscle, liver, and kidney in YOY ringed seals from Labrador collected in this study are shown in Table 2. Previously published measurements from YOY and adult ringed seals from Greenland (D1990) are also included for comparison (Dietz et al., 1990). Data for all individual seals are available in the Supplementary materials (Table A7). Statistically significant ($\alpha = 0.05$) differences between groups were assessed separately for each measurement (total Hg, MeHg, and %MeHg) using one-way ANOVA. Post-hoc hypothesis testing was done with Tukey's Honest Significant Differences test (adjusted $p$-value < 0.05). All statistical tests were done on log-transformed data in R. A limited number of seals ($n = 3$) sampled in Labrador had canine data definitively categorizing them as adults (>5 years of age) so were excluded from statistical comparisons.

Total Hg concentrations in the liver, kidney, and muscle of adult ringed seals are significantly enriched compared to YOY ringed seals from both locations ($p < 0.05$). Percent MeHg measured in the liver of YOY seals from Greenland (mean: 30%MeHg) and Labrador (mean: 24%MeHg) is higher than in adults from Greenland (mean: 14%MeHg) ($p < 0.05$). These results are consistent with many other studies that

**Table 2**
Summary of measured Hg concentrations (μg $g^{-1}$ w.w.).

| Tissue | Group[a] | Total Hg | | MeHg | | % MeHg | |
|---|---|---|---|---|---|---|---|
| | | μ | σ | μ | σ | μ | σ |
| Muscle | GL A | 0.62 | 0.43 | 0.55 | 0.37 | 0.89 | 0.14 |
| | GL Y | 0.12 | 0.07 | 0.11 | 0.06 | 0.97 | 0.19 |
| | LB Y | 0.07 | 0.05 | 0.08 | 0.05 | 0.82 | 0.13 |
| Liver | GL A | 9.63 | 14.12 | 0.81 | 0.78 | 0.14 | 0.11 |
| | GL Y | 0.76 | 0.50 | 0.21 | 0.13 | 0.30 | 0.05 |
| | LB Y | 0.40 | 0.66 | 0.09 | 0.12 | 0.24 | 0.19 |
| Kidney | GL A | 2.62 | 2.27 | 0.51 | 0.36 | 0.22 | 0.12 |
| | GL Y | 0.85 | 0.60 | 0.12 | 0.06 | 0.16 | 0.05 |
| | LB Y | 0.74 | 0.42 | 0.06 | 0.05 | 0.08 | 0.05 |

[a] GL = Greenland; LB = Labrador; A = adult (>5 years); Y = YOY (<1 year). Ringed seals from Greenland belong to D1990 (see Table 1), seals from Labrador were measured as a part of this study.

show higher concentrations of total Hg in the liver, kidney, and muscle tissues of adult ringed seals compared to YOY seals and a negative correlation between age and %MeHg in seal liver (Brown et al., 2016; Dietz et al., 1998; Perrot et al., 2016; Wagemann et al., 1998; Wagemann et al., 2000).

### 3.2. Toxicokinetic model evaluation

Fig. 2 compares measured total Hg concentrations for ringed seals in Greenland (from the D1998 dataset) and simulated tissue specific Hg concentrations using the toxicokinetic model based on the deterministic diet simulation. Data in D1998 ($n = 456$) span a range of life stages (pups, juveniles, and adults) and average total Hg concentrations are grouped by age and geographic location (Dietz et al., 1998). The time-dependent model simulation matches age-specific Hg concentrations predicted in muscle, kidney, and liver with age-specific observations from Greenland in Fig. 2 (Dietz et al., 1996; Dietz et al., 1998). The range of observed total Hg concentrations overlaps mean modeled values (Fig. 2a) for 89% of age-specific observations, indicating agreement between modeled and measured results. All observations are within the modeled variability of tissue total Hg concentrations (Fig. 2b).

Observed variability in total Hg concentrations across ringed seal populations and ages in Greenland is consistent with differences in dietary MeHg intake among Greenland ringed seals (Fig. 2). An extensive database of stomach contents data and measured MeHg concentrations in prey consumed by ringed seals in Greenland are used to simulate the variability in tissue Hg concentrations that can be explained by dietary differences (Siegstad et al., 1998). The highest simulated total Hg concentrations resulted from a diet that consisted exclusively of polar cod, while the lowest levels represented a diet of 70% North Atlantic krill, and 30% capelin (Fig. 2) (Siegstad et al., 1998). Variable prey Hg levels resulted in three orders of magnitude variability in modeled total Hg levels in muscle, kidney and liver, which matches the ranges of observations (Dietz et al., 2000; Holst et al., 2001; Siegstad et al., 1998). For example, the simulated range of total Hg concentrations in the liver varied between 0.61 and 24 μg $g^{-1}$ wet weight (ww), while the observed range was 0.69–30 μg $g^{-1}$ ww. This leads to the conclusion that stochastic variability in prey MeHg concentrations due to opportunistic feeding can explain the majority of variability in observed total Hg concentrations in ringed seals from Greenland.

### 3.3. Dietary MeHg intake drives variability in HgSe concentrations

The evaluated model was applied to investigate how a sudden shift in dietary MeHg intake might affect concentrations and speciation of Hg in the kidney and liver in an individual ringed seal (Fig. 3). Adult ringed seals typically exhibit high plasticity in their diet, consuming opportunistically available fish and crustaceans (Holst et al., 2001; Siegstad et al., 1998). MeHg concentrations in prey were constrained to fall within observed ranges (0.01–0.100 μg $g^{-1}$ w.w.) and variability in prey composition was based on stomach content data from the D1998 dataset (Fig. 2b).

The modeled proportion of HgSe in the liver of an adult ringed seal ranged between 26% and 79% under different stochastic dietary scenarios (Fig. 3). This result agrees well with observed ranges from 31% to 91% (means of two studies: 53% and 62 ± 29%) (Lyytikäinen et al., 2015; Wagemann et al., 2000). Model results suggest that the highest

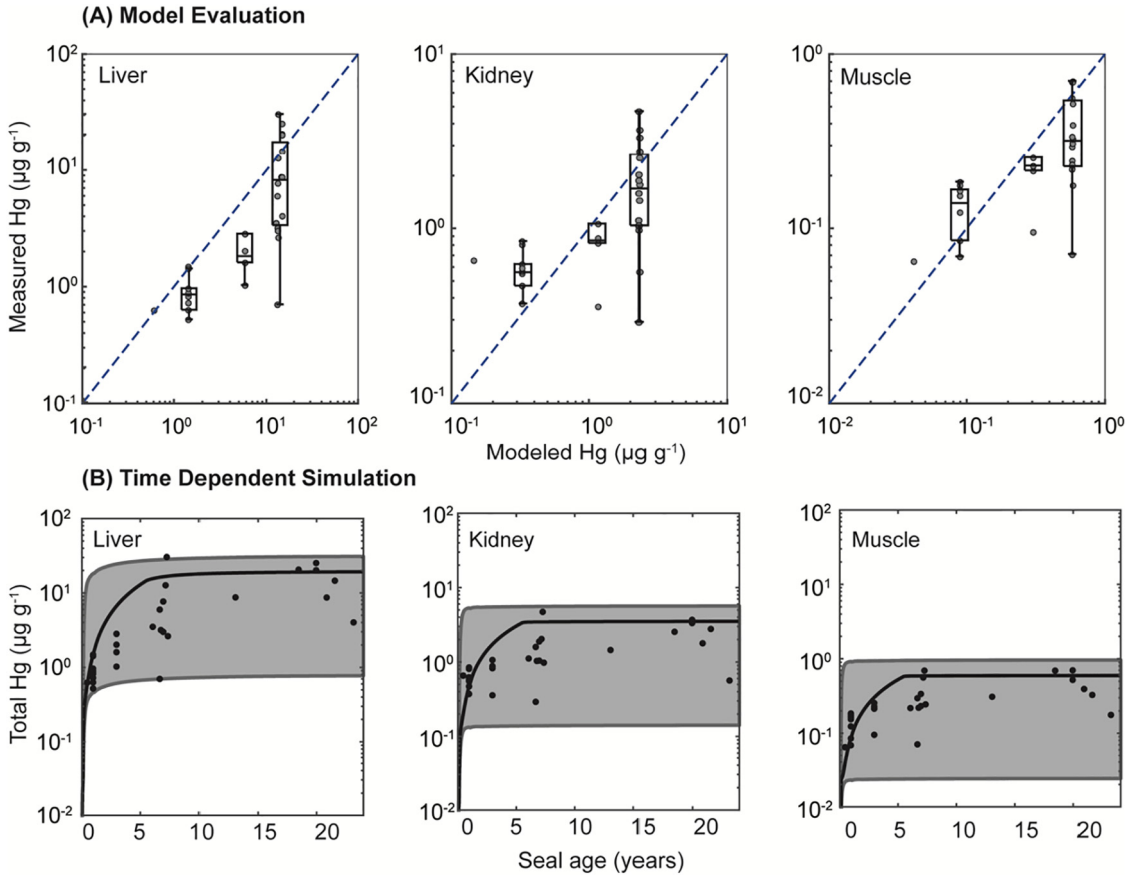


**Fig. 2.** Comparison of measured (D1998) and modeled Hg concentrations in ringed seals from Greenland. Panel (a) compares observed data for different age classes from (Dietz et al., 1998) to modeled Hg concentrations at the same age using an average dietary concentration of 0.124 μg $g^{-1}$ w.w. Panel (b) shows the modeled ranges (grey shaded region) in total Hg concentrations given inter-population differences in dietary MeHg intake derived from stomach contents analysis (Siegstad et al., 1998). The deterministic simulation under the average dietary MeHg intake scenario is shown as the solid black line and observations are indicated by circles.

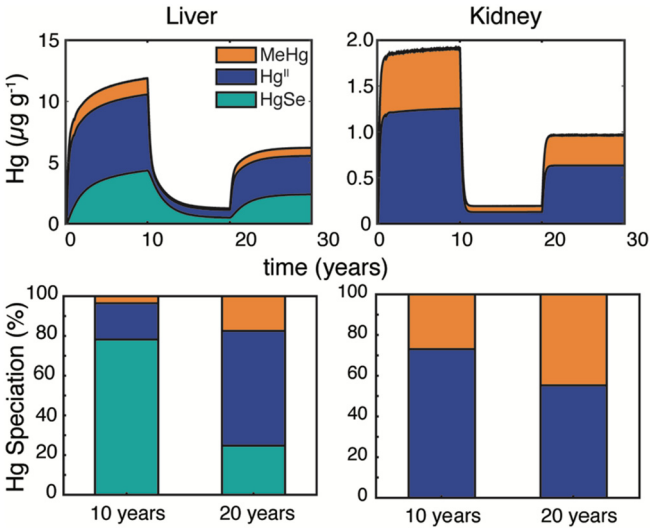


**Fig. 3.** Perturbation analysis for the effects of a stochastic shift in dietary MeHg intake for a mature ringed seal on speciated Hg concentrations in liver, kidney and muscle. The initial 10 years of the model simulation assume a dietary MeHg concentration of 0.10 μg g$^{-1}$ w.w. The following 10 years (10–20 years) assume a 10-fold decrease in dietary MeHg concentration (0.01 μg g$^{-1}$ w.w.), followed by a 5-fold increase between 20 and 30 years of 0.050 μg g$^{-1}$ w.w. MeHg.

proportion of HgSe in the liver of ringed seals occurs when dietary MeHg intake drops suddenly. Shifting the dietary intake of MeHg for an adult seal differentially alters the proportion of each Hg species in the liver. This reflects the comparatively short liver half-lives of Hg$^{II}$ (20 days) and MeHg (50 days) relative to HgSe (500 days). After changes in MeHg exposure, MeHg and Hg$^{II}$ concentrations reach equilibrium sooner than HgSe because of their faster kinetics. Despite constant internal demethylation rates, slow HgSe kinetics can result in highly variable Hg species composition in the liver of ringed seals.

Previous studies have interpreted highly variable HgSe concentrations as evidence for significant differences in inter-individual MeHg detoxification ability (Kehrig et al., 2008). The results instead suggest variability in HgSe in the liver of adult seals can reflect dietary shifts that drive changes in daily MeHg intake burdens. These findings suggest %HgSe and %MeHg in the liver are not useful proxies for the demethylation capacity of individual seals.

### 3.4. Mercury toxicokinetics vary across life stages

An early-life stage simulation of juvenile ringed seals (Table 3) shows that a high dietary MeHg exposure (0.200 μg g$^{-1}$) from a diet of 100% polar cod results in only 4% HgSe in the liver after three months of exposure, and 9% HgSe after six months, as compared to 36% at steady-state after three years. Thus, the HgSe production rate constant estimated in this study is consistent with recent findings that suggest the detoxification mechanism that produces HgSe is functional either at birth or a few months after birth (Gajdosechova et al., 2016; Lyytikäinen et al., 2015). This contrasts prior studies that have suggested a greater proportion of MeHg in the liver of young seals reflects activation of the HgSe demethylation mechanism after exceeding a threshold

**Table 3**
Simulated Hg speciation[a] in the liver of ringed seals during early-life.

| | 1 month | 3 months | 6 months | Steady-state |
|---|---|---|---|---|
| MeHg | 34% | 24% | 17% | 11% |
| HgSe | 3% | 4% | 9% | 36% |
| Hg$^{II}$ | 63% | 72% | 74% | 53% |

[a] Dietary MeHg intake based on mean prey concentrations of 0.10 μg g$^{-1}$ w.w.

Hg concentration in the liver (Caurant et al., 1996; Palmisano et al., 1995).

However, a comparison of stochastically simulated modeled concentrations and observed values indicates that physiologically-based parameters for mature seals do not adequately describe kidney and liver total Hg observations from ringed seal under 4–5 months of age (Fig. 4). While 50% ($n = 8$) of the measurements for juvenile and adult seals fell within the 95% confidence region of the model output, 97% of the measured observations from YOY seals ($n = 36$) were outside of the 95% confidence region. Lack of agreement between the measured and modeled Hg concentrations for young seals implies differences in the dynamics of organ-specific Hg accumulation between immature and mature ringed seals.

Accounting for known physiological processes that influence Hg toxicokinetics in ringed seal pups in the model does not reproduce measured total Hg concentrations in the kidney and liver of YOY ringed seals. Estimated transplacental transfer of MeHg to the ringed seal pup is included in the model as initial conditions for the simulations summarized in Fig. 4 (see the Supplementary materials). The allometric model used to estimate body mass and daily dietary consumption patterns accounts for intensive nursing during the first 40 days, rapid growth of core body mass, and decrease in blubber stores after nursing ends.

One hypothesized explanation is that the cellular composition of ringed seal liver changes as it develops, increasing the number of hepatic thiol-containing molecules and resulting in the observed increase in Hg$^{II}$ being partitioned into the liver after 4–5 months of age. Prior work shows that Hg$^{II}$ binds to erythrocytes in the blood and is able to readily dissociate and bind to thiol-containing molecules in target tissues as blood is distributed throughout the body (Cember et al., 1968; Friedman, 1957; Lau and Sarkar, 1979). Low molecular weight, thiol-containing molecule – Hg$^{II}$ complexes are thought to be transported into target cells, where some Hg$^{II}$ binds to proteins such as metallothionein and glutathione, resulting in Hg$^{II}$ accumulation in target tissues such as the kidney (Bridges and Zalups, 2010). The highest total Hg concentrations are typically found in the liver of mature marine mammals (Arai et al., 2004; Frodello et al., 2000; Woshner et al., 2002) and the kidney of terrestrial mammals (Carrier et al., 2001b; Dietz et al., 2013; Young et al., 2001). Nephrotoxicity is an endpoint of relevance to apex predators in aquatic ecosystems, for example, mature polar bear kidney

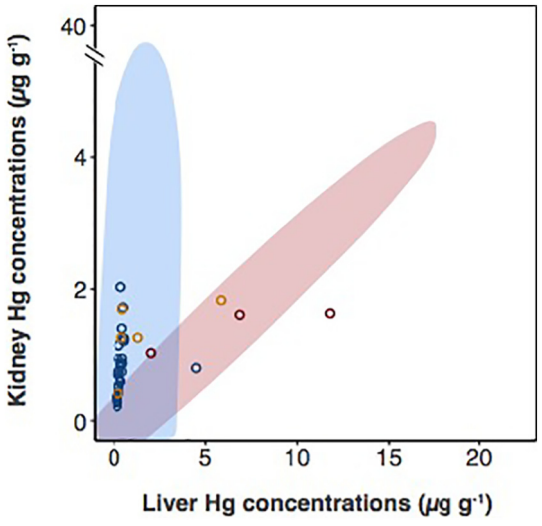


**Fig. 4.** Modeled and measured total Hg partitioning between kidney and liver compartments. Data points are from ringed seals measured as a part of this study (blue = YOY, yellow = inferred juvenile/adult, red = confirmed adult). Shaded regions are the 95% CI of model output from 1000 simulations using the stochastic dietary setting. Red corresponds to normal model parameters; blue corresponds to increased kidney: blood Hg$^{II}$ partitioning coefficient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

total Hg concentrations have been observed that exceed the established toxicity threshold for terrestrial mammals of 30 μg $g^{-1}$ w.w. (Dietz et al., 2013; Sonne et al., 2007).

Adjusting the toxicokinetic model for ringed seal pups to follow partition coefficients reported for terrestrial mammals allows it to reproduce the range of observed values (Fig. 4). The modeled total Hg levels in the kidney of adult ringed seals are found to approach the renal toxicity threshold under the median dietary MeHg intake scenario shown in Fig. 2 (0.124 μg $g^{-1}$ ww) and the partition coefficients needed to explain observed concentrations in young seals. Prior studies have suggested that greater proportional $Hg^{II}$ accumulation in the liver compared to kidney of adult seals reflect an adaptation to prevent nephrotoxicity because this lowers the Hg concentration in the kidney for a given Hg body burden (Dietz et al., 2013). Thus, one hypothesis is that Hg is differentially partitioned between the kidney and liver of adults compared to young ringed seals (<6 months) to confer protection against nephrotoxicity in mature seals. Future studies that empirically test this hypothesis would be of great interest.

### 3.5. Liver HgSe formation has limited effect on brain concentrations

Exposures of marine mammals to MeHg have been linked to neurobiochemical changes (Dietz et al., 2013). Thus, accumulation of Hg species in the brain is of particular interest. MeHg is the only Hg species in the blood able to cross the blood-brain barrier and this mainly occurs when it is complexed with -SH containing ligands (Aschner and Aschner, 1990; Hirayama, 1980; Lohren et al., 2016; Rooney, 2014). Once in the brain, MeHg can be reversibly conjugated with high molecular weight -SH containing ligands or demethylated to form inorganic Hg (Aschner and Aschner, 1990; Lohren et al., 2016; Rooney, 2014; Vahter et al., 1995). Both of these products are unable to exit the blood-brain barrier (Aschner and Aschner, 1990; Lohren et al., 2016; Rooney, 2014; Sugita, 1978), leading to an estimated half-life in the brain of humans of up to several weeks for MeHg and up to 22 years for $Hg^{II}$ (Aschner and Aschner, 1990; Sugita, 1978).

Model results suggest HgSe formation results in only a 6% decline in MeHg concentrations in the blood of ringed seals due to its slow kinetics of formation. Only 3% of the modeled MeHg intake by an adult seal is eliminated from the body as HgSe. Thus, HgSe formation in the liver of ringed seals is hypothesized to have limited effects on concentrations of MeHg in the brain. Further data on speciated Hg concentrations in the brain are needed to confirm this hypothesis.

## 4. Conclusions

Results of this study suggest that observed variability in %MeHg in the liver of ringed seals across life stages can be explained by the slow kinetics of HgSe formation and elimination and variability in dietary MeHg intake. The observed enrichment of total Hg in the kidney compared to liver of YOY ringed seals can be reproduced in the toxicokinetic model by partitioning of Hg species in a manner more similar to terrestrial mammals that tend to have highest concentrations in their kidneys. This may confer greater vulnerability of young seals to nephrotoxicity when exposed to high levels of dietary MeHg intake compared to mature individuals.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.09.299.

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