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Selenium Health Benefit Values: Updated Criteria for Mercury Risk Assessments

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Abstract Selenium (Se)-dependent enzymes (selenoenzymes) protect brain tissues against oxidative damage and perform other vital functions, but their synthesis requires a steady supply of Se. High methylmercury (CH_3Hg) exposures can severely diminish Se transport across the placenta and irreversibly inhibit fetal brain selenoenzymes. However, supplemental dietary Se preserves their activities and thus prevents pathological consequences. The modified Se health benefit value (HBV_{Se}) is a risk assessment criterion based on the molar concentrations of CH_3Hg and Se present in a fish or seafood. It was developed to reflect the contrasting effects of maternal CH_3Hg and Se intakes on fetal brain selenoenzyme activities. However, the original equation was prone to divide-by-zero-type errors whereby the calculated values increased exponentially in samples with low CH_3Hg contents. The equation was refined to provide an improved index to better reflect the risks of CH_3Hg exposures and the benefits provided by dietary Se. The HBV_{Se} provides a biochemically based perspective that confirms and supports the FDA/EPA advice for pregnant and breast-feeding women regarding seafoods that should be avoided vs. those that are beneficial to consume. Since Se can be highly variable between watersheds, further evaluation of freshwater fish is needed to identify locations where fish with negative HBV_{Se} may arise and be consumed by vulnerable subpopulation groups.

Keywords Selenium · Selenoenzymes · Methylmercury · Brain · Seafood · Fish

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Introduction

Selenium (Se)-dependent protection against otherwise lethal effects of high mercury (Hg) exposures was first described in 1967 [1], and soon afterwards, it was shown that high Hg or methyl-Hg (CH_3Hg) exposures severely diminished Se transport across the placenta [2, 3]. Although the nutritional essentiality of Se has been known since 1957 [4], the importance of tissue Hg:Se molar ratios in relation to Hg toxicity was not described until it was recognized that Se-dependent enzymes (selenoenzymes) were inhibited by Hg [5]. It was subsequently noted that when Se and Hg are coadministered, insoluble and biologically unavailable HgSe complexes formed in blood and tissues [6, 7]. Although this mechanism was initially misinterpreted as Se sequestering Hg, thereby rendering Hg unable to impose harm, numerous studies have since confirmed that Hg sequesters Se [8–11] and thereby inhibits the activities of selenoenzymes, which are vitally important for brain health and functions [12–14]. Animal studies of maternal CH_3Hg exposures have revealed that fetal brain selenoenzyme activities are far more sensitive to CH_3Hg inhibition than those of adults [15, 16], and once fetal brain selenoenzyme activities are inhibited, they are not readily restored [17]. Irreversible inhibition of selenoenzyme activities and its biochemical sequelae are well characterized [14, 18, 19] and appear to be the primary mechanism of CH_3Hg toxicity [14, 20].

The Se health benefit value, or Se-HBV [21], is a recently developed risk assessment criterion that was developed to enable concurrent consideration of CH_3Hg exposures and dietary Se intakes, particularly in regard to maternal consumption during pregnancy. Dietary Se and Hg have opposing effects on Se status and brain selenoenzyme activities. Therefore, this equation is used to provide an index (Se-HBV) to predict effects of maternal CH_3Hg exposures from seafood consumption [22]. The equation was modified to reflect variances in CH_3Hg and Se concentrations and eliminate disproportionality otherwise encountered in samples with low Hg levels. Because the equation employs Se:Hg molar ratios, the Se-HBV can become disproportionate when Hg concentrations are very low in relation to Se. The modified equation has the virtue of accurately indicating the amount of Se in excess of CH_3Hg present in that food and is designated HBV_{Se} to distinguish it from the original equation. Since Hg does not quantitatively sequester Se, the HBV_{Se} provides a highly conservative index for establishing food safety considerations. This article details the enhanced reliability of the updated HBV_{Se} index and compares the Se-HBV and HBV_{Se} of ocean fish and other seafoods for reference purposes.

Methods

Modification of the Selenium Health Benefit Value Equation

Neurological effects in children have been associated with CH_3Hg exposures from maternal consumption of seafoods that contain CH_3Hg in sufficient excess to induce a conditioned Se deficiency in placental and fetal tissues. This does not occur when adequate amounts of maternal Se are available for transport to the fetus. Assessments based only on CH_3Hg exposures [23] may indicate risks in situations where they do not exist and do not indicate risks that are accentuated by poor dietary Se intakes. The Se-HBV was developed as a more accurate index of the relative risks or benefits expected in association with seafood or freshwater fish consumption because it considers the absolute and relative molar amounts of CH_3Hg and Se that are present [21]:

$$\text{Se-HBV} = (\text{Se} \times [\text{Se}/\text{Hg}]) - (\text{Hg} \times [\text{Hg}/\text{Se}]) \quad (1)$$

This equation yields positive values when the amount of Se present in the fish is in excess of Hg, thereby indicating health risks that might otherwise accompany CH_3Hg exposures are negated. Negative values indicate the seafood's CH_3Hg concentrations are in excess of Se; thus, maternal consumption of that food does not offer protection from its CH_3Hg content but could instead induce a temporary interruption or decrease in Se transport to the fetus. However, assessing the Se-HBV becomes problematic when the Hg content of the sample is at or below the detection limit. In such cases, the Se:Hg molar ratio approaches infinity and the Hg:Se ratio approaches zero, resulting in an erroneously high value that exaggerates the health benefits of increased dietary Se. Furthermore, since excessive Se intakes can be associated with health consequences, it is essential to have an index that appropriately reflects the amounts of dietary Se provided. The effects associated with consumption of a seafood with a negative Se-HBV or HBV_{Se} depend on the CH_3Hg in excess of Se but are also dependent on the absolute amount of Se available. For example, the adverse effects of eating seafood containing 5.5 μmol CH_3Hg/kg with 0.5 μmol Se/kg would be greater than eating seafood containing 15.5 μmol CH_3Hg/kg with 10.5 μmol Se/kg. Although both instances involve a Se deficit of 5 μmol/kg, the second example involves a higher CH_3Hg exposure albeit less associated risk due to the additional Se available for distribution to fetal tissues. In certain circumstances, continual high intakes of Se might have adverse effects, so an index that reflects the amount of Se that is biologically available also needs to be reflected by the HBV_{Se} of the fish being consumed. Thus, both the CH_3Hg and the Se concentration are crucial aspects of this index. For that reason, the equation for calculating the index was refined in order to (1) incorporate relative and absolute amounts of Hg and Se, while eliminating the molar ratios that can result in disproportionately high values as a consequence of very low Hg concentrations, and (2) provide an indication of the net Se surplus or deficit. This approach provides a straightforward assessment of Se availability and provides a value that indicates the magnitude of the relative Se deficit or surplus for such seafoods or fish.

To determine whether the amounts of CH_3Hg and Se present in the seafood would potentially result in a Se deficit or a net surplus, it is necessary to incorporate the difference in their molar concentrations. Through the use of Se in the denominator, the absolute molar concentration present in the food is recognized, while the result also provides an indication of the relative amount of Se available:

$$\text{Relative Se availability} = ([\text{Se}-\text{Hg}]/\text{Se}) \quad (2)$$

However, in order to reflect the amount of physiological Se that is potentially provided or lost in respect to sequestration by the associated Hg, the relative amount of Se available is multiplied by the total amount of Hg and Se present in the food. To differentiate this index from that provided by the original Se-HBV equation, the improved criterion is designated as HBV_{Se} [24]:

$$HBV_{Se} = ([\text{Se}-\text{Hg}]/\text{Se}) \times (\text{Se} + \text{Hg}) \quad (3)$$

The sign indicates whether the food would improve or diminish Se status while the scale of the value proportionately reflects the Se surplus or deficit associated with eating that seafood.

To demonstrate how these indices are affected by CH_3Hg molar concentrations, a comparison of the calculated Se-HBV vs. HBV_{Se} was performed using the range of CH_3Hg concentrations that have been observed in various types of seafood. For purposes of this comparison, Se contents were maintained constant at 10.0 μmol Se/kg (approximating the average Se content of ocean fish) in relation to a range of CH_3Hg increasing from 0.125 to 9.971 μmol/kg (0.025 to 2.0 mg/kg), shown in the log scale of Fig. 1a, and from 9.971 to 34.9 μmol Hg/kg (2.0 to 7.0 mg/kg), as shown in the linear scale of Fig. 1b.

Comparative Evaluation of Selenium Health Benefit Values of Seafoods

The Se and CH_3Hg contents of various types of seafood were used to calculate the Se-HBV and HBV_{Se} for each sample, along with their means and standard deviations. The molar concentrations of CH_3Hg and Se present in yellowfin tuna (*Thunnus albacares*), bigeye tuna (*Thunnus obesus*), blue marlin (*Makaira mazara*), albacore (*Thunnus alalunga*), swordfish (*Xiphias gladius*), thresher shark (*Alopias vulpinus*), mako shark (*Isurus oxyrinchus*), and pilot whale (*Globicephala melas*) were used to perform side-by-side comparisons of the Se-HBV vs. HBV_{Se}. The data for the ocean fish samples were originally reported in Kaneko and Ralston [21], but the results of additional repeat analyses are included in this assessment. The pilot whale data for samples collected in 1977 and 1978 were reported by Juhlshamn et al. [25]. The 1978 data were selected by Grandjean et al. as reflective of pilot whale Hg exposures by the Faroese mothers during their study [26]. The Se-HBV vs. HBV_{Se} results for these seafoods are graphically compared in Fig. 2 and shown in Table 1.

Results

Comparison of Se-HBV and HBV_{Se}

At low CH_3Hg concentrations, the Se-HBV increases exponentially as Hg diminishes (Fig. 1a). This increases bias as Se:Hg molar ratios asymptotically approach infinity when CH_3Hg concentrations approach zero. For that reason, the Se-HBV fails to accurately reflect the moderate nutritional benefits associated with excess Se. In contrast, the calculated HBV_{Se} asymptotically approaches the actual Se concentration of the seafood as Hg contents diminish toward zero; thus, it accurately reflects the net amount of Se available. The outcomes calculated for seafoods with negative Se-HBV or HBV_{Se} similarly reflect the diminishment in Se status potentially associated with excess of maternal CH_3Hg intakes (Fig. 1b).

Comparison of Se-HBV and HBV_{Se} of Seafoods

Although the Hg contents of ocean fish species such as yellowfin tuna, bigeye tuna, blue marlin, albacore tuna, and thresher shark vary dramatically (Table 1), their HBV_{Se} indicates they are all a net source of surplus Se and are thus predicted to protect against risks associated with CH_3Hg exposures. However, swordfish do not consistently provide Se in excess of CH_3Hg and therefore are not advised for mothers to consume during pregnancy. The negative HBV_{Se} consistently observed for mako shark and pilot whale meats indicates that their consumption could compromise fetal Se supply. Thus, consumption of these seafoods should be limited during pregnancy.

The standard deviations of the Se-HBV and HBV_{Se} for the seafood examples shown in Table 1 and Fig. 2 indicate a much higher variability of Se-HBVs in comparison to HBV_{Se} results. Variability between the two indices was primarily driven by disproportionately high Se-HBVs calculated for seafoods that had low CH_3Hg contents relative to Se (Table 1). For example, the Se-HBV of the bigeye tuna samples was uniformly positive but had a standard deviation that was greater than their sample mean and a coefficient of variability (CV) of 122 % (ranging from 8.6 to 594). In contrast, the HBV_{Se} for these same samples ranged from 2.4 to 36.5, with a CV of 33 %. Since the ocean food web is rich in Se and tissue Se contents are homeostatically regulated, few seafoods have Se concentrations below 2 μmol Se/kg. For that reason, negative Se-HBVs are not prone to the exponential increases due to divide-by-zero-type errors such as those that occurred for certain seafoods with positive Se-HBVs. Thus, seafoods that contain more Se than CH_3Hg tend to have negative Se-HBV and HBV_{Se} values that are more or less equivalent. To summarize the comparisons of these seafoods, the differences

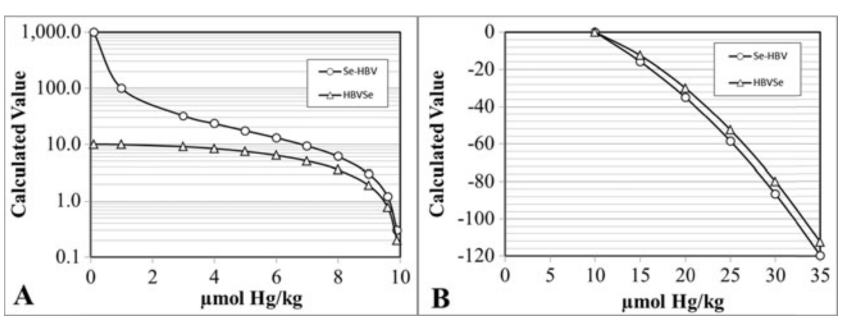

Fig. 1 Comparison of the effects of Hg concentrations on calculated Se-HBV and HBV_{Se} in a sample with 10.0 μmol Se/kg. **a** The divergent effects that occur when Hg is at low to near equimolar stoichiometry (shown in log scale). **b** The near equivalence of the two indices when Hg concentrations exceed equimolar stoichiometry with Se

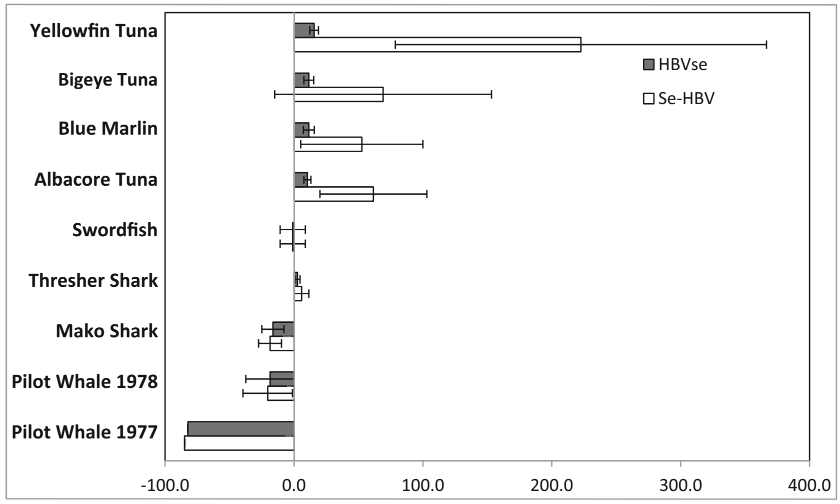

Fig. 2 Comparison of the calculated Se-HBV and HBV_{Se} of selected seafoods. Ocean fish data compared in this figure are from Kaneko and Ralston [21], while pilot whale data originate from Julshamn et al. [25]

between Se-HBV and HBV_{Se} were greatest for samples with highly positive values, but differences decreased as the magnitude of their calculated values diminished and were negligible for seafoods with negative values (Fig. 1). The Se-HBV and HBV_{Se} for the pilot whale data from 1977 shown in Table 1 and Fig. 2 reflect the results based on the mean CH_3Hg and Se contents that were reported for these samples. For that reason, the standard deviations for those samples were not established.

The HBV_{Se} results were uniformly positive for all ocean fish other than mako shark and swordfish. Because Se is homeostatically regulated in vertebrates while Hg bioaccumulates in relation to increasing age and weight, the HBV_{Se} of most varieties of fish and other forms of aquatic life tend to diminish as they grow larger. Blue marlin was a unique exception. The amount of Se in its fillets remained in excess of CH_3Hg at a near-constant amount, and their HBV_{Se} remained consistent (11.46±4.18) even though their CH_3Hg contents ranged from <1.0 μmol/kg to more than 60 μmol/kg. The concentration of CH_3Hg in the fillets approached equimolar stoichiometries with Se (~10 μmol/kg), but the Se concentrations consistently remained in excess of CH_3Hg by 6.00± 4.05 μmol/kg. The HBV_{Se} of mako shark samples were uniformly negative but demonstrated a downtrend in HBV_{Se} that accompanied increasing CH_3Hg bioaccumulation. The HBV_{Se} of swordfish diminished with increasing body weight and particularly with increasing CH_3Hg ($F=199$, $p=9.8\times10^{-19}$). However, the highest HBV_{Se} was not observed in the smallest swordfish, nor were the most negative values observed in the largest specimens.

Among pilot whales, only calves had positive values, while the HBV_{Se} of meats from adults were uniformly negative. CH_3Hg concentrations tended to increase in relation to body weight while tissue Se concentrations remained constant or diminished slightly. Therefore, the Se deficit potentially associated with pilot whale meats were significantly ($F=9.1$,

Table 1 Seafood Hg and Se contents, and HBV_{Se}

Common name of seafood[a]	Number	μmol Hg/kg Mean±SD	μmol Se/kg Mean±SD	HBV_{Se} Mean±SD
Yellowfin	50	1.51±0.88	15.80±3.44	15.6±3.4
Bigeye	50	3.00±1.23	12.38±3.48	10.0±5.3
Blue marlin	50	11.88±14.96	20.17±14.78	11.5±4.2
Albacore	20	2.49±1.18	11.11±2.40	10.4±2.7
Thresher shark	10	4.86±1.60	6.55±1.51	2.7±2.0
Swordfish	50	5.32±2.98	5.43±1.48	0.0±11.5
Mako shark	10	9.01±1.99	4.07±0.48	–16.4±8.6
Pilot whale 1978	15	8.91±2.61	4.45±1.69	–18.6±18.8
Pilot whale 1977	10	16.45±8.47	3.17±1.39	–82.3[b]

[a] Ocean fish data are from Kaneko and Ralston [21]; pilot whale data are from Julshamn et al. [25]

[b] Since only the means±standard deviations (SD) were available for Hg and Se of the 1977 pilot whale data, the approximate Se-HBV and HBV_{Se} for those samples were calculated based on mean values

$p<0.01$) related to the weight of the animal. Therefore, increasing CH_3Hg contents resulted in increasingly negative HBV_{Se} ($F=31.9$, $p<0.0001$).

Discussion

Epidemiological and toxicological studies of CH_3Hg exposures omit consideration of Se as the biochemical "target" of Hg, thus introducing statistical bias, confounding, and imprecision to their assessments. Beneficial effects of improved intakes of nutrients that counteract the adverse effects of maternal CH_3Hg exposures on fetal outcomes are well recognized [27, 28]. However, the pivotal importance of dietary Se's biochemical role in the mechanism of CH_3Hg toxicity [14, 19] was generally misunderstood and often overlooked.

Predictions of risk based only on CH_3Hg exposures are inaccurate. The HBV_{Se} reflects the Se surplus or deficit in a seafood compared to its CH_3Hg contents, providing a more reliable index for assessing CH_3Hg exposure risks. This was evident in a recent animal study that found predictions based on Se-HBV were far more consistent with observed effects than predictions based only on CH_3Hg exposures [23]. In that study, Se-HBV's relation to toxic effects of CH_3Hg exposures was highly significant ($F=161.0$, $p<0.0001$) and consistent (adjusted $R^2=0.735$). Predictions based only on CH_3Hg exposures were less consistent (adjusted $R^2=0.158$), and their statistical significance was less robust ($F=10.9$, $p<0.001$). The crucial difference was the ability of the Se-HBV index to differentially recognize CH_3Hg exposures that would induce Se deficits potentially severe enough to impair brain selenoenzyme activities from those that would not. In another animal study, HBV_{Se}, Se-HBV, and CH_3Hg exposures were compared as indices of risk. The statistical strength of HBV_{Se} and Se-HBV regressors were virtually identical, and both indexes identified adverse effects of CH_3Hg exposures sooner and with higher p values than assessments performed using only the CH_3Hg regressor [24].

Role of Background Diet

Differences in Hg exposure levels or dietary Se intakes that minimally affect physiological Se status are unlikely to have clinical consequences. However, individuals with poor dietary Se status are more susceptible to the adverse effects from consuming foods with negative HBV_{Se} than Se-rich populations. This can explain why studies have reported negative effects from high CH_3Hg exposures in populations with low dietary Se intakes. For example, a study in New Zealand reported that high CH_3Hg exposures from maternal consumption of seafoods during pregnancy resulted in negative effects in children [29]. However, this population was known to have an extremely poor Se status [30] making it especially vulnerable to adverse effects from eating foods with a negative HBV_{Se}. The study indicated that shark fillets with CH_3Hg contents as high as 4.4 mg/kg (~22 μmol/kg) and an estimated HBV_{Se} as low as −120 were frequently consumed in the form of fish-and-chips [31]. Eating such high-CH_3Hg fillets would not be recommended for any population, but the reported adverse effects were especially predictable since Se availability to fetal tissue was already compromised by the mothers' extremely low Se status. Conversely, the adverse effects of high CH_3Hg exposures have been shown to be alleviated or eliminated when diets containing seafoods with a negative HBV_{Se} are complemented by Se-rich diets (e.g., from consuming Se-rich ocean fish) [32, 33].

The Contrast Between Hg Exposures from Ocean vs. Freshwater Fish

Although most ocean fish contain excess Se over their CH_3Hg contents [21, 34], top predators in freshwater with particularly poor Se availability have been shown to accumulate more CH_3Hg than fish of the same species and size from Se-rich watersheds [35]. This situation is especially notable in areas with high Hg inputs from local point sources or with inputs of acidic material, which greatly decrease Se bioavailability. Therefore, the fish that have the least amount of Se tend to bioaccumulate the most CH_3Hg. Likewise, increases in amounts of bioavailable Se have been shown to increase CH_3Hg efflux from fish [36–44] and rapidly diminish their CH_3Hg body burdens. This mechanism of depuration is augmented by production of insoluble HgSe in tissues of prey animals at each level of the food web. Because HgSe is highly stable, it passes through the digestive tract unabsorbed and is eliminated, resulting in essentially permanent retirement in the sediments.

Watersheds with low-Se fish occur in various regions of the world. This arises due to Se's poor bioavailability at low pH [45], poor geological abundance in soils from igneous parent rock materials, or extensive leaching of porous soils by high rainfalls [46]. Since increased CH_3Hg burdens are associated with lower Se contents in fish [34], regions with freshwater fish potentially having negative HBV_{Se} need to be identified. Fish from low-Se watersheds that are concurrently exposed to high CH_3Hg inputs and acidic waste drainage are therefore expected to have negative HBV_{Se}. Eating fish from such areas would pose greater risks than consuming Se-rich fish that contain the same amount of CH_3Hg. Because the reference dose and fish consumption advisories are based on CH_3Hg levels alone, the extent of risk associated with high CH_3Hg exposures due to eating fish from Se-poor watersheds is currently overlooked. In the absence of dietary Se intakes sufficient to compensate for losses due to Hg sequestration, high CH_3Hg exposures are more likely to diminish maternal and fetal Se status. Therefore, consumption of fish with high

CH_3Hg contents that arise in areas with poor Se availability is an issue that deserves further study. Fortunately, restoring fish Se concentrations to optimal levels comes with the added benefit of diminishing their CH_3Hg contents [37–39]. The combined effects of diminishing CH_3Hg contents while improving the Se status of the aquatic ecosystem would improve the HBV_{Se} of the fish. In Se-deficient areas, CH_3Hg remediation can easily be achieved by augmenting environmental Se to adequate levels.

Conclusions

Since the HBV_{Se} is based on the biochemical mechanism of CH_3Hg toxicity, it provides an objective index for assessing the relative effects of CH_3Hg exposures and dietary Se intakes on Se status. Seafoods with negative values (i.e., pilot whale, certain types of shark, some individual swordfish) are differentiated from ocean fish varieties with positive values. Consumption of seafoods with positive HBV_{Se} would negate risks otherwise associated with CH_3Hg exposures. It is important to note that intermittent CH_3Hg exposures are unlikely to compromise maternal/fetal Se status, but consistent consumption of negative HBV_{Se} seafoods could pose this risk, especially among mothers with poor Se intakes. The HBV_{Se} provides a biochemically based perspective that confirms and supports the FDA/EPA advice for pregnant and breast-feeding women regarding seafoods that should be limited vs. those that are beneficial to consume. Since maternal consumption of seafoods has repeatedly been shown to benefit child neurodevelopment, the use of the HBV_{Se} provides a reliable, easily understood, and consistent index for identifying healthy seafood choices.

While erring on the side of caution is entirely appropriate when protecting public health, the HBV_{Se} may be overly cautious regarding the potential risks of CH_3Hg exposures from fish consumption. The HBV_{Se} conservatively considers only the Se from the fish itself, but dietary CH_3Hg would also interact with Se from all other dietary sources as well as from host tissue Se reserves. Furthermore, the equation presumes that CH_3Hg from fish consumption will unfailingly sequester an equivalent amount of Se, but the majority of the Hg that enters the body will remain bound to thiomolecules during its entire time of residence in the body without encountering or binding cellular Se. This fundamental aspect of CH_3Hg biochemistry contributes to the prolonged latency between acquiring a toxic dose and the initial onset of signs and symptoms of toxicity [47]. The HBV_{Se} is unique in being applicable for assessing risks associated with high exposures to CH_3Hg as well as in rare circumstances when excessive Se contents of fish is a concern.

The reference dose established for assessing risks associated with CH_3Hg exposures omits consideration of Se and is based on effects that were observed in a population which consumed Se-rich diets. Therefore, the reference dose may not be applicable to health consequences that may be associated with elevated CH_3Hg exposures in Se-poor populations. For that reason, the HBV_{Se} of freshwater fish in Se-poor regions warrants study to help identify populations that may experience accentuated risk from consistently consuming fish with negative HBV_{Se}. A thorough evaluation of HBV_{Se} of freshwater fish will enable recognition of locales with varieties that should be avoided or whose consumption should be limited among susceptible subpopulations. Such studies would also indicate where Se augmentation to accomplish CH_3Hg remediation and restore Se to optimal concentrations would be appropriate.

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Compliance with Ethical Standards The work described in this manuscript did not involve studies of humans or live animals.

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