New Insights into Traditional Health Risk Assessments of Mercury Exposure: Implications of Selenium

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ABSTRACT: There is increasing evidence that selenium (Se) has a significant effect on mercury (Hg) toxicology; however, Hg exposure risk assessments usually consider only the amount of Hg present in the environment or in food. On the basis of the present understanding of mechanisms of interaction between Se and Hg, the physiology/toxicology of Se, and the toxicology of Hg, we propose a new criterion for Se/Hg exposure assessment. This criterion, which is based on Se−Hg interactions, considers not only the toxicological consequences of Hg exposure but also the benefits and/or adverse effects of Se intake, especially the adverse effects related to a Se deficiency/excess. According to an illustrative assessment based on the new criterion and nine existing criteria, large knowledge gaps in the traditional assessments of exposure to Hg and/or Se were found, including those that assessed the interactions between Hg and Se. These results suggest that future assessments of Hg exposure (or Se intake) should include both Se and Hg.

INTRODUCTION

Mercury (Hg) is an exogenous, toxic, and ubiquitous trace element that is nonessential to humans and animals. Methyl-Hg (MeHg), one of its most toxic organic forms, can easily cross the blood-brain and placental barriers; high exposure may cause severe and irreversible damage, particularly to the fetal central nervous system.1 The MeHg concentrations in water, soil, and sediments are usually negligible when compared to its less toxic inorganic form;2,3 however, MeHg can bioaccumulate and be biomagnified in aquatic food webs and even some terrestrial plants (e.g., rice3), eventually posing a serious threat to humans through the consumption of fish and/or rice.2 At present, the consequences of long-term, chronic exposure to MeHg remain poorly understood; however, recent epidemiological studies have shown a dose-response relationship at much lower levels of MeHg exposure than those previously recognized as hazardous.4

Selenium (Se) is an essential trace element and nutrient that is of vital importance to human health.5,6 Se exists in human and animal selenoproteins as selenocysteine (Sec) and selenomethionine (SeMet) and is incorporated into the active sites of antioxidant selenoenzymes (gluthathione peroxidase and thioredoxin reducates).7,8 The human selenoproteome includes 25 genetically encoded selenoproteins (including multiple forms of glutathione peroxidases and thioredoxin reductases).5 Through its incorporation into selenoenzymes (primarily via Sec in mammals), Se exerts important biological functions that affect processes such as free radical metabolism, immune function, reproductive function, and apoptosis.8,9 Se is particularly fundamental for the redox-mediated prevention and repair of oxidative damage in the brain and neuroendocrine tissues.10 Epidemiological studies indicate that Se deficiency is necessary for the occurrence of a well-known cardiomyopathy endemic to China (Keshan disease), which is associated with >90% mortality and affects many young children in areas of China where the Se intake is lower than 10 μg/day.11 Other effects of Se deficiency include muscular dystrophy, reproductive disorders, dental caries, necrosis of the liver/kidney/heart, and cancer.7,8 Therefore, an adequate intake of Se is important for maintaining the normal physiological synthesis and activity of essential selenoproteins.

The recommended dietary allowance (RDA) of Se for adults in the US is 55 μg/day (the same as that set by the World Health Organization (WHO), equivalent to 0.79 μg/kg body weight [bw]/day, assuming a 70-kg bw for US residents12,13). In general, humans obtain Se through dietary intake alone, and many common foods such as fish meals, seafood, seaweeds, meat, cereals, and eggs are important sources of Se.14,15 However, Se can also be harmful to humans and animals at high exposures due to the narrow margins between the amount that is essential and the levels associated with deficiency or toxicity.8 Long-term exposure to high levels of Se in food and water may result in health problems, including loss of nails and hair, tooth decay and discoloration, skin lesions, nervous system disorders,
paralysis, and death.\(^8\) The tolerable upper limit (UL) of Se intake for an adult set by the U.S. Food and Drug Administration (US FDA) and the WHO is 400 \(\mu g/\text{day}\) (equivalent to 5.71 \(\mu g/\text{kg bw/day, assuming a 70-kg bw for US residents.}\)\(^2,13\) However, the UL of 400 \(\mu g/\text{day}\) has been considered to be too conservative considering it was derived arbitrarily by defining one-half the estimate made by Yang et al.\(^16\) Using the same study conducted in Enshi China by Yang et al.\(^16\) as the reference case, Poirier\(^17\) pointed out that no adverse effects were observed with the Se intake for an adult as great as 853 \(\mu g/\text{day}\).

The coexistence of Se and Hg in animal tissues and protective effect of Se against inorganic Hg toxicity has been recognized for nearly half a century, since 1967.\(^18−24\) For a number of years, the protective roles of Se against MeHg have inconsistent.\(^6\) Only recently, the protective effects of organic Se against MeHg toxicity in fetal brain and development have been confirmed by a series of animal studies.\(^25,26\)

MeHg can pass the blood brain barrier and placenta to exert toxic effects on the central nervous system of adults and fetuses.\(^7\) MeHg can exert its neurotoxicity by altering the activity of Na+/K+-ATPase, disrupting intracellular calcium homeostasis, and causing oxidative stress, and disrupting neurotransmission.\(^27\) Besides, MeHg toxicity has been considered to be linked to its reactivity to the thiol ligands (SH) of the proteins in the organisms.\(^28\) Previous study revealed that the biologically active MeHg may predominantly bind to cysteine thiols as MeHg−cysteine complex (MeHg−Cys).\(^29\) The MeHg−Cys complex is molecularly similar with SeMet, which thus can readily cross the placental and the blood-brain barrier.\(^30\) When MeHg−Cys reaches at the active sites of selenoenzyme, the S atom of MeHg−Cys can be directly replaced by the ionized Se of Sec and form the unavailable MeHg−Sec complex owing to the extremely high binding affinity between Se and Hg than that between S and Hg.\(^31\) The formation of the unavailable MeHg−Sec complex thereby inhibits the bioavailability of MeHg yet simultaneously results in efficient sequestration of the biologically required Se in intracellular cycles of Sec synthesis that maintain normal selenoenzyme metabolism in these otherwise protected tissues. Therefore, MeHg has been considered to be a highly specific, irreversible selenoenzyme inhibitor,\(^32\) which implies that impairing selenoenzyme activity and synthesis is one of the possible mechanism of MeHg toxicity especially when the organism is in a Se-deficient state.

Although several physiologic/biochemical mechanisms have been proposed to explain the antagonism between Hg and Se (well summarized by e.g., Yang, et al.\(^25\) and Khan and Wang\(^24\)), the molecular mechanism likely involves the formation of insoluble, equimolar, and biologically unavailable mercury selenide (HgSe) precipitates. Approximately 1:1 molar ratios of Se:Hg have been commonly observed in various species, for example, marine mammals (plasma, erythrocyte, liver) and sea birds and in human (Hg miners, brain, kidney, liver, muscle tissue and urine; and residents, urine) of Hg-mining areas.\(^24,33,34\) The binding affinity between Hg and Se is exceptionally high (with a constant of \(10^{65}\)); in particular, it is one-million-fold higher than the binding affinity (\(10^{49}\)) between Hg and sulfur in the production of mercury sulfide (HgS). Thus, an interaction between Se and Hg should readily result in the formation of metabolically inert HgSe precipitates, which have an extremely low solubility (\(10^{-58}\) to \(10^{-65}\)) compared to that of HgS precipitates (\(10^{-32}\)).\(^35\) It has been proposed that the Hg and Se bind to plasma protein to form high molecular weight complexes, which was described as (Hg−Se)−selenoprotein P (or (Hg−Se)n-SelP).\(^23,24\) The (Hg−Se)n-SelP was considered to be the precursor of the HgSe(s).\(^24\) Recently, the existence of inert HgSe(s) granules in vivo was unambiguously confirmed using X-ray absorption near edge structure (XANES).\(^24\)

As mentioned earlier, the extensive formation of inert Hg−Se would consequently compromise the biological availability of both Hg and Se, which is consistent with the results of numerous studies reporting alleviation of acute toxicity after simultaneous exposure to Hg and Se in doses higher than their threshold limit values.\(^20,23,24\) Another possible mechanism of the Se protective effect is antioxidation. MeHg disrupts the glutathione (GSH) system maturation resulting in a decrease of GSH-Px in the developing brain, but this toxic effect can be protected by Se as Se can decrease the overall oxidative stress induced by MeHg.\(^26\)

Because Se plays important physiological and biochemical roles in humans and animals, the formation of HgSe precipitates may result in Se deficiency and a corresponding impairment of selenoenzyme activity and synthesis,\(^7,8\) with consequent adverse effects. However, the observed toxicity may be affected by both MeHg toxicity and Se deficiency, especially when there is a greater exposure to MeHg than to Se. After reviewing a large number of studies on this subject, Khan and Wang\(^24\) proposed that Hg toxicity is caused, at least in part, by Hg-induced Se deficiency. In other words, the antitodal effect of Se for counteracting Hg occurs by ensuring that normal selenoenzyme activity and synthesis is maintained. Hence, some of the adverse effects of Hg exposure may be prevented by consuming sufficient Se to result in a greater than 1:1 molar ratio of Se/Hg,\(^36\) while attempting to maintain the Se intake in the physiologically appropriate range. One good example is the study recently conducted in Wanshan Hg mining area in China by Li et al.\(^34\) In their study, supplementation of organic selenium significantly increases Hg excretion and protects against the oxidative damage of long-term Hg exposed local residents.

Despite the decades-long establishment of protection against Hg toxicity by Se in general\(^18\) and by an Se/Hg molar ratio of >1:1 in particular,\(^58\) the current criteria for safe levels of Hg exposure do not consider Se, primarily because the exact Se/Hg ratio that confers protection is unclear. Nonetheless, Se/Hg molar ratios have been commonly used in research and/or assessments of Hg exposure to simplify assessments of the nutritional benefits of Se intake and the risks of MeHg exposure from the consumption of fish and ocean-sourced foods. For instance, a recent animal study indicated that MeHg toxicity could not be explained by MeHg alone but could be explained by considering Hg and Se together (based on Se/Hg molar ratios).\(^37\)

Recently, Kaneko and Ralston\(^38\) proposed a new safety criterion for Hg exposure assessment, the Se-Health Benefit Value (Se-HBV), which is calculated as Se-HBV = Se × (Se/Hg) − Hg × (Hg/Se). This equation includes both the absolute molar concentrations and the relative molar ratios of Se and Hg. The Se-HBV indicates the health benefits (if positive) or health risks (if negative) of Se in terms of Hg exposure. At first glance, the Se-HBV appears more elegant than the molar ratio alone, and it has also been commonly cited in many studies to assess Hg exposure from seafood. Unfortunately, however, the Se-HBV and the traditional Se/
Hg molar ratio both have a serious limitation: in certain extreme cases, although the safety requirement (Se/Hg molar ratio > 1 or Se-HBV > 0) is met, the Se intake may be either below the level required for normal selenoenzyme activity and synthesis (deficiency) or above the safe range (poisoning). Although the Se-HBV and Se/Hg molar ratio may both appear ideal, these are associated with hidden risks. Therefore, an assessment based on either criterion may be misleading. Besides, we noticed that the criterion of Se-HBV=Se(Se/Hg)−Hg(Hg/Se) was recently “updated” as HBVSe=(Se−Hg)/Se5 (Se + Hg) by Ralston and Raymond.39 Unfortunately, it still has a similar limitation: for example, when we assume Hg exposure is zero and Se intake is 10<sup>5</sup> nmol/kg/day (far greater than 170 nmol/kg/day, the threshold value for Se poisoning4,12,15), then the calculated HBVSe should be 105 (indicates great health benefit). However, this value is actually associated with hidden risks of Se poisoning and thus misleading.

Our main objectives of this study were (1) to develop a new criterion for Se/Hg exposure assessment, which is based on Se−Hg interactions and considers not only the toxicological consequences of Hg exposure but also the beneficial effects and/or adverse effects of Se intake, especially the adverse effects related to a Se deficiency/excess, as mentioned above; (2) to examine the knowledge gaps in previous studies that considered Hg or Se alone versus those that considered Se−Hg interactions (using the new criterion and other existing criteria).

### MATERIALS AND METHODS

#### Proposal for a New Criterion
On the basis of the present understanding of Se−Hg interactions, the physiology/toxicology of Se, and the toxicology of Hg, we propose a new criterion for assessing Hg exposure and Se intake, as shown below:

\[
\text{BRV} = \frac{\text{PDI}_{\text{Se}} - \Delta_{\text{Se}} - \text{PDI}_{\text{Hg}}}{\text{PDI}_{\text{Hg}}} \tag{1}
\]

\[
\text{PDI} = \frac{\Sigma(C^1 \times I^2)}{\text{bw}} \tag{2}
\]

where BRV represents the benefit-risk value, which indicates either health benefits (if 0 < BRV < \text{BRV}_{\text{safe}}) or health risks (if BRV < 0 or BRV > \text{BRV}_{\text{safe}}); \Delta_{\text{Se}} represents the minimal Se amount required for normal biological function when Hg exposure is zero; \text{BRV}_{\text{safe}} represents a threshold value for Se poisoning which considered the protective effects from Hg exposure; PDI represents the probable daily intake of Se (PDI<sub>Se</sub>, Hg (PDI<sub>Hg</sub>), or MeHg (PDI<sub>MeHg</sub>); C is the concentration of the exposed medium; IR is the intake rate (the rate of ingestion or inhalation); and i is the intake of a potentially Hg-contaminated substance such as water, rice, fish, vegetable, corn, meat, or poultry. All of the above calculations are based on units of molar concentrations; for example, PDI is measured in nmol/kg bw/day.

Some researchers may prefer a format that directly reflects the molar ratio of Se/Hg. The BRV mentioned above can also be expressed as a molar ratio, that is, a benefit-risk ratio (BRR), as shown below:

\[
\text{BRR} = \frac{\text{PDI}_{\text{Se}} - \Delta_{\text{Se}}}{\text{PDI}_{\text{Hg}}} \tag{3}
\]

where \text{BRV}_{\text{safe}} temporarily represents the lowest safe intake of Se for a human, which is 11 nmol/kg/day (equivalent to 50 μg/day recommended by the Chinese Nutrient Society (CNS)14,15 or 0.83 μg/kg bw/day if bw is assumed to be 60 kg for Chinese residents; or equivalent to 55 μg/day recommended by the US FDA and the WHO or 0.79 μg/kg bw/day if bw is assumed to be 70 kg for US residents). Similarly, the value of \text{BRV}_{\text{safe}} temporarily represents the threshold value for Se poisoning set by the CNS14,15 which is 170 nmol/kg/day (equivalent to 800 μg/day, or 13.3 and 11.4 μg/kg bw/day, respectively, for Chinese residents and US residents). The dietary Se intake in most populations is far below this threshold value15 but it should still be assessed. The intention of the proposed criterion is to examine the use of alternate indices.

### Table 1. Probable Daily Intake of Se versus Hg by Adults (60 kg bw) for Rice-Based Rural Population Living around the Wanshan Hg Mined Area, Including Values Assessed Using Different Criteria and the Corresponding Percentages of Sites with Health Risks and Benefits<sup>a</sup>

<table>
<thead>
<tr>
<th>No.</th>
<th>mean ± SD</th>
<th>range</th>
<th>percentage of sites with risks</th>
<th>percentage of sites with benefits</th>
<th>assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>1.9 ± 1.5</td>
<td>1.2—6.1</td>
<td>100%</td>
<td>0%</td>
<td>[PTWI\text{MeHg} (&lt;0.57 μg/kg bw/day)]&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(2)</td>
<td>0.096 ± 0.17</td>
<td>0.015—0.46</td>
<td>34%</td>
<td>0%</td>
<td>[RD\text{MeHg}(&lt;0.10 μg/kg bw/day)]&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>(3)</td>
<td>2.1 ± 1.5</td>
<td>1.4—8.0</td>
<td>12%</td>
<td>88%</td>
<td>[SIR\text{Se}(0.83—3.33 μg/kg bw/day)]&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>(4)</td>
<td>0.99 ± 0.41</td>
<td>0.10—2.2</td>
<td>59%</td>
<td>41%</td>
<td>[RD\text{MeHg} and SIR\text{Se}]&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>(5)</td>
<td>150 ± 260</td>
<td>−55—1700</td>
<td>9%</td>
<td>91%</td>
<td>[Se(Se/THg) − THg(THg/Se) &gt; 0]&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>(6)</td>
<td>2200 ± 12400</td>
<td>140—88000</td>
<td>0%</td>
<td>100%</td>
<td>[Se(Se/MeHg) − MeHg(MeHg/Se) &gt; 0]&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>(7)</td>
<td>3.0 ± 2.6</td>
<td>0.58—16</td>
<td>9%</td>
<td>91%</td>
<td>[Se/THg &gt;1]&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>(8)</td>
<td>80 ± 150</td>
<td>6.1—860</td>
<td>0%</td>
<td>100%</td>
<td>[Se/MeHg &gt;1]&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>(9)</td>
<td>9.1 ± 21</td>
<td>−28—84</td>
<td>25%</td>
<td>75%</td>
<td>[0 &lt; PDI_{\text{Se}} − V_{\text{Se}} − PDI_{\text{Hg}}(\nabla \text{Se})]&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>(10)</td>
<td>45 ± 120</td>
<td>3.2—770</td>
<td>0%</td>
<td>100%</td>
<td>[0 &lt; PDI_{\text{Se}} − V_{\text{Se}} − PDI_{\text{MeHg}}(\nabla \text{Se})]&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Abbreviations: BRV, benefit-risk value; PDI, probable daily intake; PTWI, provisional tolerable weekly intake; RD, reference dose; Se-HBV, Se-Health Benefit Value; SIR, safe intake range.  
<sup>b</sup>Equivalent to 4 μg/kg bw/week.40  
<sup>c</sup>Equivalent to 0.7 μg/kg bw/week.41  
<sup>d</sup>Equivalent to 50—200 μg/kg bw/week.14,15  
<sup>e</sup>Concurrently meet criterion (2) and (3), i.e., PDI_{\text{MeHg}} < RD_{\text{MeHg}} (0.10 μg/kg bw/day) and PDI_{\text{Se}} within the SIR\text{Se}(0.83—3.33 μg/kg bw/day).  
<sup>f</sup>Kaneko and Ralston.38  
<sup>g</sup>Ganter et al.36  
<sup>h</sup>Present study.
that may more accurately reflect health risks and benefits for use in future studies.

Comparison of Different Criteria. We used the new criterion (BRV) proposed above together with existing criteria (PDI, Se-HBV, and Se/Hg molar ratio; Table 1) to assess the health benefits and/or risks of combined Hg and Se exposure through dietary sources (e.g., rice, fish, meat, poultry, vegetable, and drinking water) for residents of 59 locations around a heavily Hg-contaminated area of China covering over 700 km² (Wanshan, the largest Hg mining region in Asia). Detailed information about the local settings were provided in our recently published articles.2,3,33

The design of this illustrative assessment included four different scenarios: (I) considering only Hg levels using the criteria established by the US Environmental Protection Agency (USEPA) and the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA); (II) considering only Se levels using the criteria established by the CNS; (III) considering both Se and Hg independently using the criteria established by the USEPA, JECFA, and CNS; and (IV) considering Se–Hg interactions based on their molar concentrations.

The assessments for the four different scenarios were based on each of the 10 criteria (i.e., PDIHg, PDISe, PDISe, and PDISe, Se-HBV, Se-HBV, Se-HBV, molar ratio of Se/THg, molar ratio of Se/MeHg, BRVHg, and BRVMeHg), as shown in Table 1 and Figure 1. It should be mentioned here that all of

![Figure 1. Percentages of sites with health benefits or risks using different criteria.](Image)

Results and Discussion

Differences observed among the results of the assessments using each of the 10 criteria mentioned above were shown in Figure 1 and Table 1.

Scenario I. Criteria Considering only Hg. As reported in our previous study,2 all the sites in Wanshan exhibited levels of Hg exposure associated with health risks if they were assessed using the PDIHg criterion alone based on the provisional tolerable weekly intake (PTWI) of 4 μg/kg bw/week (equivalent to 0.57 μg/kg bw/day).46 In that study, however, we concluded that PDIHg should not be used to evaluate Hg exposure in the Wanshan area because 95% of the Hg to which the local residents were exposed was inorganic Hg (Table 2), which is much less toxic than MeHg and has a low (only 7%) absorption rate compared to that of MeHg (95%). Alternatively, if assessed using the reference dose (RfD) of 0.1 μg/kg bw/day recommended by the USEPA,41 the proportion of Wanshan sites with risky levels of Hg exposure was greatly reduced (to 34%). The main reason for this large difference is that rice consumption accounts for ~95% of the total MeHg exposure among the local residents, whereas fish accounts for only 1% (the local residents rarely eat fish).2

The development of the PTWIHg by the JECFA was based on a fish-eating population (derived from toxicity data from poisoning incidents at Minamata and Niigata in Japan) that was primarily exposed to MeHg. The PTWIHg was originally set at 5 μg/kg bw/week (equivalent to 0.7 μg/kg bw/day).42 More recently, this value was adjusted to the present level of 4 μg/kg bw/week (equivalent to 0.57 μg/kg bw/day).47 The PTWIHg of 0.57 μg/kg bw/day may be acceptable for fish-eating populations in regions where MeHg is the primary Hg species (i.e., at least more than 40% of THg; see Results and Discussion in what follows) and where MeHg data are unavailable, because inorganic Hg is much less toxic than MeHg and its absorption rate by human body through dietary intake has been estimated to be only 7% while the absorption rate for MeHg is about 95%. As there are great variations in the MeHg/THg ratios among fish species or geographic regions,43 MeHg concentrations should be measured based on the PTWIHg or the RfDMeHg to better provide health guidelines for fish-eating populations.

Similar with PTWIHg, the PTWISeHg has also been adjusted, from 3.3 μg/kg bw/week (equivalent to 0.47 μg/kg bw/day)42 to the present level of 1.6 μg/kg bw/week (equivalent to 0.23 μg/kg bw/day).4 This adjustment reduced the ratio of MeHg/THg from 66% to approximately 40%. USEPA recommended a more conservative RfD (MeHg) of 0.1 μg/kg bw/day (equivalent to 0.7 μg/kg bw/week),41 compared to the PTWISeHg (1.6 μg/kg bw/week).

However, for rice-eating populations in inland China (e.g., Wanshan in the present study) or other regions where Hg exposure is dominated by inorganic Hg (exceeding 90% of THg2), the JECFA PTWI (THg and MeHg) and the USEPA RfD (MeHg) may both inadequately reflect the level of health risk because rice does not contain several important neurologic development-enhancing micronutrients found in fish, such as docosahexaenoic acid (DHA, an omega-3 long-chain polyunsaturated fatty acid), arachidonic acid (an omega-6 fatty acid), and iodine.43

Fortunately, Se, another important micronutrient for human health and a well-known efficient antidote to Hg exposure as mentioned earlier, can be absorbed and significantly bio-

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accumulated in many foods, including rice. Rice is a staple food in most of Asian countries. Indeed, rice consumption has been observed to be the primary route (70%) of Se intake among rice-based rural populations in inland China. Because they rarely eat fish and ocean-sourced foods, the general populations of rice-based areas of inland China, except heavily Hg-contaminated areas (e.g., Wanshan), have Hg exposure levels well below the MeHg RfD of 0.1 μg/kg bw/day. In such populations, it may be more beneficial to assess the local residents’ Se intake status rather than their Hg exposure because either excessive or inadequate Se intake is associated with serious health risks.

**Scenario II. Criteria Considering only Se.** According to our estimates from the present illustrative assessment, most (88%) of the sites in the Wanshan area exhibited PDIse values well within the safe intake range of Se (SIRSe) of 50–200 μg/kg (equivalent to 0.83–3.33 μg/kg bw/day for a bw of 60 kg) established by the CNS. Approximately 12% of the Wanshan sites had PDIse values higher than the UL of the SIRSe (3.33 μg/kg bw/day). However, the highest PDIse in Wanshan, 8 μg/kg bw/day, was still below the threshold value for Se poisoning (13.33 μg/kg bw/day; equivalent to 800 μg/kg; Table 1). No sites had PDIse values below the lowest limit of the SIRSe.

The PDIse range in Wanshan (85–478 μg/day) was comparable to that in countries with adequate Se intake levels (e.g., the US range of 71–152 μg/kg); however, the average PDIse in Wanshan (128 μg/day) was 6–18 times greater than that in regions with high rates of Se deficiency (e.g., 7 μg/day in an endemic Keshan disease area of China and 17 μg/day in Burundi) and 3–4 times greater than in regions with moderate rates of Se deficiency (e.g., 34 μg/day in the UK, 39 μg/day in Greece, and 44 μg/day in Suzhou, China). The Se levels in food are mainly determined by the Se levels in the soils where the plants are grown. In our recent study, the average soil Se levels in Wanshan (2.1 mg/kg) were elevated compared to the background concentrations in Guizhou (0.38 mg/kg) and China as a whole (0.24 mg/kg), reaching levels comparable to those in the Enshi seleniferous region (4.1 mg/kg). Therefore, the high Se levels in the local soils produced high Se levels in foods such as rice, vegetables, meat, fish, and poultry (Table 2). For instance, the total Se levels in the local rice averaged 98 μg/kg, which was 3–4 times greater than in China as a whole (32 μg/kg) and similar to the average Se levels in rice (81 μg/kg) from the Se-rich Kaiyang region in Guizhou Province. According to the results, rice (43%), meat (40%), and vegetables (8%) were the main routes of Se intake for residents in Wanshan, whereas a combination of fish, poultry, and other foods accounted for only 9% of the total PDIse (Table 2).

**Scenario III. Criteria Considering Hg and Se Independently.** When Hg and Se were considered independently, few sites (approximately 5%) showed an additive risk. Approximately 36% of the sites showed a single type of risk, e.g., 29% of the sites had an PDIse higher than 0.1 μg/kg bw/day but an Se intake in the safe range, and 7% of the sites had an PDIse exceeding the safe range but an MeHg intake below the RfDMeHg. Approximately 59% of the sites showed a complete absence of risk; that is, neither MeHg nor Se was in excess of the acceptable limits (Table 1). Overall, approximately 41% of the sites had some health risk (either a single risk or double risks) when Hg and Se were considered independently. This number was higher than those found when MeHg (34%) or Se (12%) was assessed alone.

Compared to Hg exposure, the health problems associated with the incorrect intake of Se are seriously overlooked by the general population. Most people are familiar with the health risks of MeHg toxicity, but few are aware of the physiological importance of Se. Similarly, researchers often consider the ability of Se to inhibit the toxicity of Hg, but we rarely consider that Hg can also inhibit the toxicity of Se. Therefore, a criterion that considers Se–Hg interactions is fundamental to the appropriate evaluation of risk from exposure to both Hg and Se.

**Scenario IV. Criteria Considering Se–Hg Interactions.** We found that all the sites showed health benefits rather than health risks when assessed using criteria that considered the protective interactions between Se–MeHg based on their molar concentrations. All of the three methods, that is, Se/Hg molar ratios, Se-HBV, and BRV (the present study) (Table 1) indicated that the health risks of MeHg exposure were offset by Se intake. The reverse was also true: the health risks of excessive Se intake were neutralized by moderate MeHg exposure. Hence, the 41% of sites with health risk of Se and MeHg exposure under scenario III above exhibited little or no health risk. These results indicate that our previous study considering only the Hg in the environment and foods in this area may have overestimated the level of risk for the local residents. This may be ubiquitous for the previous Hg exposure assessment for fish-eating population as molar ratios of Se/Hg > 1:1 are commonly observed in most marine fish, similar with that in rice, except for pilot whale which contains much more Hg than Se. 

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**Table 2. Average Concentrations of Hg versus Se and the Average Estimated Daily Intake of Se versus Hg by Adults (60 kg bw)**

<table>
<thead>
<tr>
<th>source</th>
<th>unit</th>
<th>Hg</th>
<th>Se</th>
<th>MeHg intake</th>
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<td></td>
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<td>rice</td>
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<td>98b</td>
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</tr>
<tr>
<td>vegetables</td>
<td>(μg/kg, WW)</td>
<td>130c</td>
<td>29d</td>
<td>0.097c</td>
</tr>
<tr>
<td>meat</td>
<td>(μg/kg, WW)</td>
<td>220e</td>
<td>690f</td>
<td>0.85e</td>
</tr>
<tr>
<td>poultry</td>
<td>(μg/kg, WW)</td>
<td>160g</td>
<td>1500h</td>
<td>2.4g</td>
</tr>
<tr>
<td>fish</td>
<td>(μg/kg, WW)</td>
<td>290i</td>
<td>3000j</td>
<td>60i</td>
</tr>
<tr>
<td>water</td>
<td>(ng/L)</td>
<td>50k</td>
<td>1010l</td>
<td>0.064k</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DW, dry weight; PDI, probably daily intake; WW, wet weight. 
Zhang et al., Zhang et al., Li et al., Gou et al., Ji et al., Zhang et al.
Estimated based on 65% water content.

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Source: Environmental Science & Technology
Although THg was not used in this assessment, the results based on Se and THg using the three corresponding criteria (Table 1) are shown to elucidate the differences among the three criteria based on the aforementioned molar concentrations above. The results revealed that there was no difference between the results using the Se/Hg molar ratios criterion and the Se-HBV criterion, both of which indicated that 9% of the sites may be associated with health risks. This observation is not surprising because there is no difference in the underlying mechanisms. However, the use of the BRV criterion proposed in the present study increased the proportion of sites with health risks from 9% to 25%, likely because the BRV criterion considers both the health risks of Se excess/deficiency and the Se amount (\( V_{Se} \)) required for normal biological function.

**IMPLICATIONS**

On the basis of the present study, the traditional method of assessing the health risks of Hg exposure clearly does not fully reveal the actual health risk because this method neglects the contribution of Se. Dietary Se intake may have an important impact on the toxicological consequences of Hg exposure; similarly, assessments of Se intake alone may inadequately reflect the health risk/benefit of Se if its interactions with Hg are not considered. Recently, Laird et al.\(^46\) emphasized the importance of including the benefits of nutrients when issuing dietary advice on Inuit traditional food in Canada. The proposed assessment criteria can potentially be applied as the sources of Se and Hg were reported coming from the same food items.

The most noteworthy finding of the present study is that assessment criteria that consider Se–Hg interactions should also take into account the Se amount (\( \Delta_{Se} \)) required for normal selenoenzyme synthesis and activities that is critical for human health (e.g., peroxide detoxification) as well as the threshold value (\( V_{Se} \)) for Se poisoning, considered the modulation effects from Hg exposure, although the specific values may require further validation. These factors, which have commonly been omitted by previous studies, may be critical for understanding the “paradox” in previous epidemiological studies, that is, higher exposures to MeHg producing lower toxicological consequence (e.g., studies conducted in the Seychelles and the Faroe Islands and other regions\(^5,47,48\)).

The BRV criterion proposed in the present study is concise and intuitive, and its use can help deepen our understanding of previous assessments. More importantly, this criterion has potential for broad applications in future research. Although the illustrative evaluation in the present study was conducted for the rice-based population, it is also appropriate in application for the fish-eating population. As all calculations in the BRV criterion are based on molar concentrations, Hg and Se can be viewed as a molar relationship: the number of Se atoms versus Hg atoms present or consumed. Thus, essentially, there is no real distinction of applications of this criterion between the two populations regarding the interactions between the two elements. Furthermore, this criterion may be sufficient to protect the fish-eating population against the toxicity of Hg exposure, or at least its evaluated result may be “safer” than that of rice-based populations (given their Hg and Se exposure status are equal) considering fish contains other important nutrients (e.g., n-3 polyunsaturated fatty acids) while rice does not.\(^5,6,43\) Despite this, it should be noted here that, until substantial epidemiological evidence is collected, the application of such novel criteria should be limited to scientific inquiry and research rather than prematurely replacing the traditional means of assessing risks/benefits in actual populations.

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**Notes**

The authors declare no competing financial interest.

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